

Pharmacokinetic analysis of antibody localization in human colon cancer: comparison with immunoscintigraphy

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The biodistribution and imaging characteristics of the ^{111}In -labeled anti CEA monoclonal antibody ZCE-025 were studied in five patients with suspicion of colorectal carcinoma. Evaluation included antibody pharmacokinetics and assessment of antibody distribution in surgical specimen, making a comparison with whole-body imaging with a gamma camera. ZCE-025 localization in tumors was demonstrated by gamma-camera imaging in 4 of the 5 patients, corresponding to surgical findings. Persistent accumulation of ^{111}In in the lymph nodes was observed in one patient, whereas surgical exploration of these lymph nodes showed no gross or microscopic evidence of metastases of colon carcinoma. Analysis of individual plasma by size exclusion HPLC showed two radioactivity peaks, labeled antibody and free DTPA. No transchelation of ^{111}In to circulating transferrin was observed. The blood clearance was fitted to a two-compartment equation and its half-lives were found to be 10.8 ± 8.7 h and 69.5 ± 21.8 h for $t_{1/2\alpha}$ and $t_{1/2\beta}$, respectively. Total urinary excretion averaged 0.3% of the injected dose/h with a small patient to patient variation. At 24 hrs postadministration the predominant radiolabeled species in urine was free DTPA. Thereafter, radioactivity in urine was partly present as a low molecular weight catabolic product. No apparent correlation between CEA content and uptake of ^{111}In -ZCE-025 in tumors resected by surgery could be found. How ^{111}In -labeled antibody is accumulated into tumors as well as into some non-tumor tissues needs further study.

Key words: monoclonal antibody, colon cancer, immunoscintigraphy, pharmacokinetics

INTRODUCTION

THE USE OF ANTIBODIES as targeting agents for cancer continues to attract much attention despite the many technical challenges that confront its successful clinical application.

ZCE-025 is one of the murine monoclonal antibodies (MoAbs) which have shown promise for the immunoscintigraphy and radioimmunotherapy of colon cancer. ZCE-025 is of the IgG₁ subclass and is derived from the same clone as MAb-35.¹ It reacts with approximately 95% colorectal tumors including

cultured cell lines and primary and metastatic tissues obtained by biopsy. The antibody was provided by Hybritech, Inc. (San Diego) in the U.S.A., and the immunoscintigraphy of colorectal cancer with ^{111}In -labeled ZCE-025 has been exclusively evaluated in the U.S.A.²⁻⁴ Few papers have, however, dealt with its pharmacokinetic characterizations.⁵ It is important to know how injected antibody is metabolized in humans from the point of antibody-guided targeting studies.

In this report we described the pharmacokinetic behavior of ^{111}In -ZCE-025 injected into patients, comparing it with their immunoscintigraphic results.

MATERIALS AND METHODS

Radiolabeling of monoclonal antibody

The anti-CEA monoclonal antibody (MoAb), ZCE-

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025 was of murine origin. ZCE-025-DTPA conjugates, prepared and characterized as described in a previous paper,⁶ were supplied by Hybritech, Inc. through Teijin Limited as a sterile, apyrogenic freeze-dried powder. The conjugated antibody was labeled with 75 MBq of ¹¹¹In in 0.26 M citrate buffer solution (pH 1.5) followed by the addition of 0.13 M citrate buffer solution (pH 8.5) to neutralize the solution. Labeling efficiency higher than 90% was achieved without loss of immunoreactivity, which was confirmed by the cell binding assay.

The labeled antibody preparation was assayed by size exclusion HPLC using a single 7.5×300-mm Hitachi Gel Pack W-530 column with the UV 280-nm detector and 0.1 M phosphate buffer (pH 7.5) containing 0.2 M KCl as the eluant. Ten μ l of the sample was analyzed with an automatic injector and fraction collector. Fractions were then counted in an automatic well gamma counter.

Patient selection and administration of ¹¹¹In-labeled antibody

Patients in this study had suspected colorectal carcinoma. In each case, the patient had been scheduled for surgical procedures. Informed consent was obtained and the consent forms were approved by the Review Board of Keio University, School of Medicine.

An intradermal skin test with 0.1 μ g of ZCE-025 was performed 15 minutes prior to antibody administration to detect immediate-type hypersensitivity reactions. No positive skin tests were observed. Each patient received 42 mg of ZCE-025 labeled with

74 MBq of ¹¹¹In (2 mg of ¹¹¹In-ZCE-025 mixed with 40 mg of unmodified MoAb) in 100 ml of normal saline containing 30% human serum albumin by intravenous injection over a period of 60 min. One and three days after the administration, planar and SPECT images were obtained. The gamma camera used was a Toshiba GCA-90B with a medium energy parallel collimator.

Specimens resected, blood, and urine samples

In all patients, blood was drawn just after and 1, 3, 24, 48, 72 and 120 minutes after the injection. The clearance and half-life of ¹¹¹In in blood were calculated with a nonlinear regression analysis computer program. For all patients, plasma samples were analyzed by size-exclusion HPLC under the same conditions as for the labeled antibody.

In order to monitor ¹¹¹In excretion, urine samples were collected as 24 hours aliquots for 72 hours following injection of the antibody. The 72 hour cumulative excretion radioactivity in urine was expressed as % of the total dose administered. Urine samples were analyzed by size-exclusion HPLC under the same conditions as for the labeled antibody.

Surgical procedures were planned for performance between 7 and 10 days after ¹¹¹In-ZCE-025 injection. Tumor, the adjacent colon tissue and regional lymph nodes resected at exploration were examined so that the imaging results could be compared with the surgical findings. Excised tumor or non-tumor specimens were examined for the presence of CEA from snap-frozen samples with ZCE-025 by the avidin-biotin-immunoperoxidase procedure.⁷ In addition,

Table 1 Characterization of resected specimens from patients received ¹¹¹In-ZCE-025

Patient No.	Sex	Age	Plasma CEA (ng/ml)	Specimens resected	CEA contents (ng/mg prot.)	¹¹¹ In uptake* (%ID/g)	Staining with ZCE-025
1	M	45	3.0	primary tumor	187	0.018 (a)	+
				normal colon	9	0.0032 (a)	+ ?
2	F	64	3.1	primary tumor	656	0.014 (b)	+
				normal colon	55	0.0021 (b)	—
3	M	46	5.5	benign stenosis	69	0.0011 (c)	—
				normal colon	17	0.0017 (c)	—
4	F	68	10.5	primary tumor	771	0.0116 (b)	+
				lymph node (12b ₁)	86	0.405 (b)	— ?
				lymph node (12b ₂)	37	0.0289 (b)	— ?
				lymph node (normal)	n.d.	0.0133 (b)	—
				normal colon	n.d.	0.0008 (b)	—
				liver metastasis	862	0.033 (b)	+
				normal liver	19	0.0055 (b)	—
5	M	70	3.0	primary tumor	117	0.0284 (a)	+
				normal colon	90	0.0101 (a)	+
				liver metastasis	8	0.0120 (a)	+
				normal liver	n.d.	0.0012 (a)	+ ?

*Operations were performed 7 (a), 9 (b), or 10 (c) days after the injection of antibody.

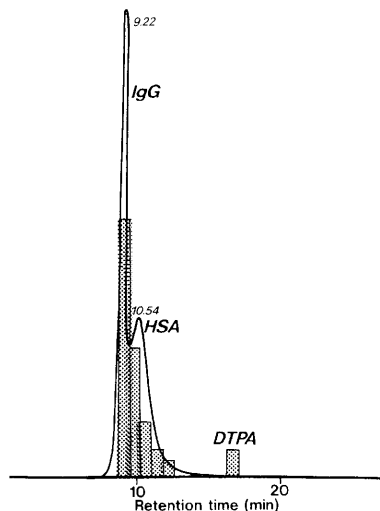


Fig. 1 HPLC profile of ^{111}In -ZCE-025 injected into patients —: OD₂₈₀, ■: ^{111}In activity, IgG, human serum albumin and DTPA should appear at 9.2, 10.6, and 18.2 min of retention time, respectively.

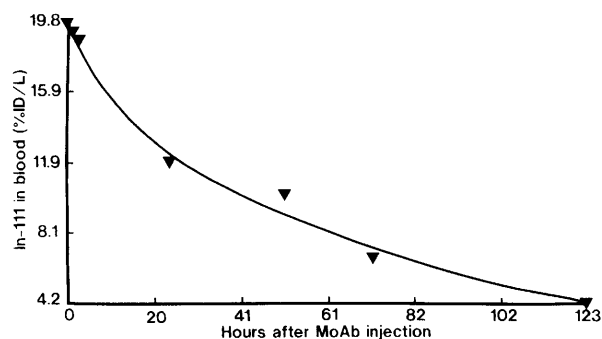


Fig. 2 Representative blood clearance of ^{111}In -ZCE-025 in patient No. 3.

Table 2 Blood clearance of ^{111}In -ZCE-025

Patient No.	Mean-peak blood level (%ID/L)	Blood clearance ($T_{1/2}$ hrs)	
		α	β
1	19.9	2.5	77.6
2	28.4	19.1	73.0
3	19.6	6.8	64.2
4	28.4	4.3	32.8
5	20.5	21.2	100.0

α : half-life of the fast compartment

β : half-life of the slow compartment

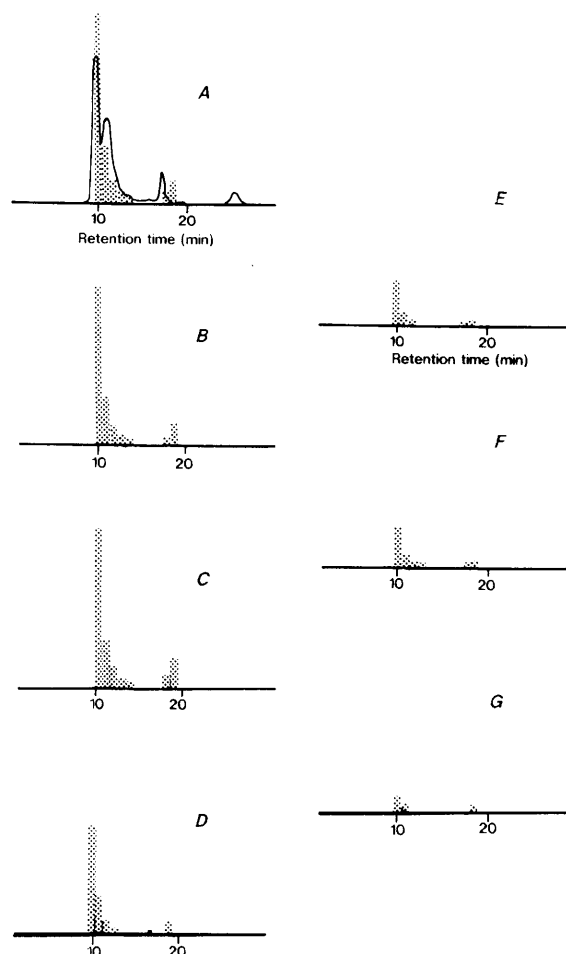


Fig. 3 HPLC profiles of plasma samples obtained from patient No. 5 after i.v. injection of ^{111}In -ZCE-025. —: OD₂₈₀, ■: ^{111}In activity, A: immediately, B: 1 hr, C: 3 hrs, D: 24 hrs, E: 48 hrs, F: 72 hrs and G: 120 hrs after injection

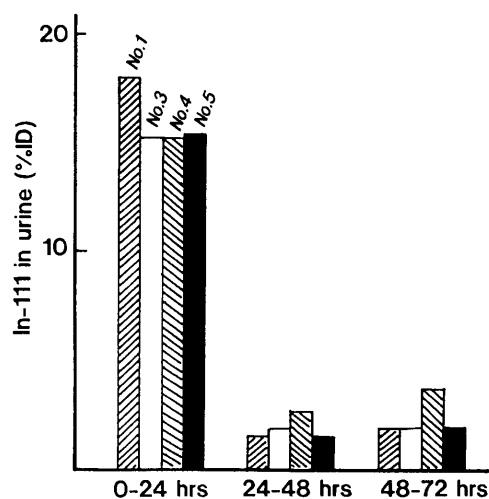


Fig. 4 Cumulative urinary excretion of ^{111}In .

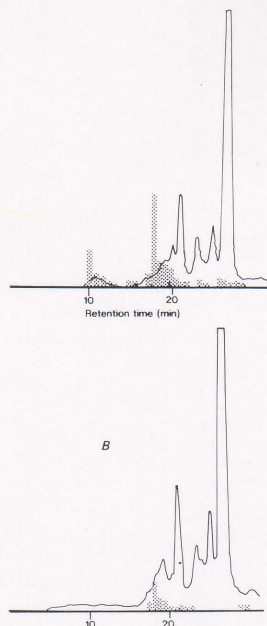


Fig. 5 HPLC profiles of urine samples from patient No. 4. —: OD₂₈₀, ▨: ¹¹¹In activity, A: 0–24 hr and B: 24–48 hr cumulative urine

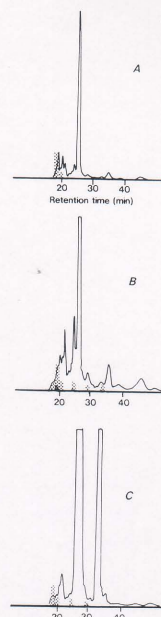


Fig. 6 HPLC profiles of urine samples from patient No. 5. —: OD₂₈₀, ▨: ¹¹¹In activity, A: 0–24 hr, B: 24–48 hr, and C: 48–72 hr cumulative urine

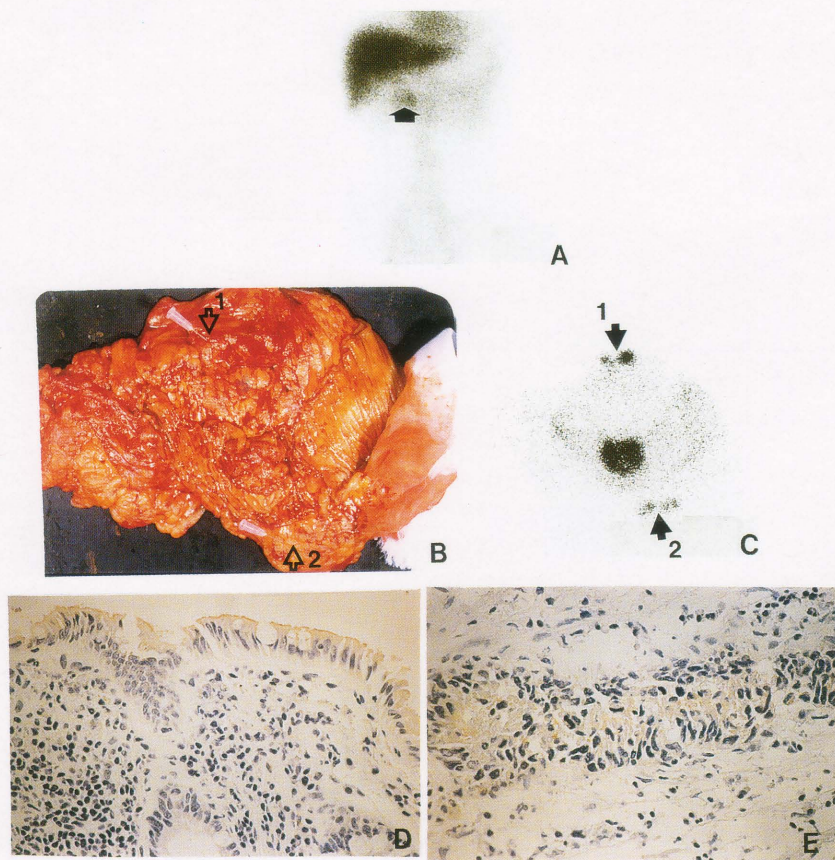


Fig. 7 Immunoscintigram (A), specimen resected (B), gamma-camera image of specimen resected (C), and sections of normal colon (D) and primary colon tumor (E) stained with ZCE-025 (patient No. 1). Increased uptake (A, arrow) can be seen in the transverse colon. Abnormal uptakes in *ex vivo* scan (C, arrows 1 and 2) correspond to spots (B, white arrows 1 and 2). CEA immunoreactivity is localized in the section of non-tumorous mucosa, with staining seen in the epithelium in the mucosa (D).

the gamma camera images of specimens resected were obtained immediately after the surgery.

Aliquots of tissues in excess of that required for histopathological analysis were weighed and analyzed quantitatively for CEA and ^{111}In content. Specimens resected were homogenized with PBS (9.6 mM phosphate buffer solution (pH 7.3) plus saline) by the procedure described in our previous paper,⁸ and their CEA content and protein concentration were determined by means of the enzyme-linked immunoassay with anti-CEA monoclonal antibody⁹ and by the Lowry method,¹⁰ respectively.

RESULTS

Patient characteristics

Characteristics of all 5 assessable patients are shown in Table 1. Two patients (No. 4 and 5) had liver metastases confirmed by surgery. Three patients (No. 1, 2, and 5) had well or moderately differentiated carcinoma with normal plasma CEA levels. One patient (No. 4) had moderately differentiated carcinoma with increased plasma CEA. Patient No. 4 had metastases in the liver and a paracolic lymph node. One patient (No. 3) had a history of rectosigmoid adenocarcinoma resected previously. No recurrence was confirmed by surgery, though a severe structure was seen in the rectum in a Ba enema.

Following radiolabeling, in analysis by size exclusion HPLC a small amount of free ^{111}In non-attached to antibody was detected, leading the labeling efficiency with higher than 90% (Fig. 1).

Pharmacokinetics of ^{111}In -ZCE-025

In all patients documented with colorectal carcinoma, the mean peak blood level of ^{111}In -ZCE-025 was $24.3 \pm 4.1\%$ of the injected dose per liter of blood, at the end of the 60-min injection. A representative pattern is shown in Figure 2. Clearance of ^{111}In -ZCE-025 from the blood showed a half life, $t_{1/2\alpha}$, of 11.8 ± 8.4 hours and a $t_{1/2\beta}$ of 70.9 ± 24.2 hours (Table 2). In patient No. 3, the mean peak blood level of ^{111}In was 19.6% ID/L, with blood clearance of 6.8 h for $t_{1/2\alpha}$ and 64.2 h for $t_{1/2\beta}$.

Size exclusion HPLC was performed on a total of 35 plasma samples from the five patients. The radiochromatograms most often showed a prominent peak corresponding to that of labeled antibody and species with longer retention times. Fig. 3 shows the most pronounced examples of the radiochromatograms, which were obtained by analysis of the 1, 3, 24, 48, 72, and 120-h plasma from patient No. 5. In this case, the first peak predominated labeled antibody and was therefore at least largely due to the ^{111}In -labeled antibody still present in the plasma. The

second peak coeluted with radiolabeled DTPA. However, radiolabeled DTPA, administered as a small radiocontaminant in the injectate, may be expected to clear rapidly into the urine from plasma by glomerular filtration. Since this peak was observed in plasma collected after 120-hour post-administration, it was likely that the species responsible was not labeled DTPA but was a catabolic product with a similar retention time in size exclusion HPLC.

The radiochromatogram obtained by analysis of plasma from patient No. 4, who had increased plasma CEA, did not show a peak due to immunocomplexes resulting from high circulating CEA levels. Analysis by HPLC also indicated that there was no detectable transchelation of ^{111}In from IgG to transferrin or to some other proteins.

Urine analysis

A 72-hour cumulative urinary excretion was $20.4 \pm 1.4\%$ ID and approximately 78% of them was excreted in 24 hours after administration (Fig. 4). As in the case of blood, ^{111}In was excreted in the urine with a similar pattern regardless of the tumor burden or plasma CEA level.

Size exclusion HPLC analysis showed a slight difference between early and late urine collection in the prominent peak of 18 min-retention time which differed from patient to patient. Radiochromatograms of urine sample from patient No. 4 at 0–24 h showed two distinct peaks (Fig. 5). The first peak with 10 min retention time was found only in the 0–24 h urine sample. The second (18 min-retention time) was exclusively present in the 48-h urine sample and all urine samples from patient No. 5 (Fig. 6). At 24 hrs, radioactivity in urine was primarily due to radiolabeled free DTPA excreted into urine following its introduction into plasma as a small radiocontaminant of the injectate. This 18 min-peak was still observed in the late urines, which might possibly mean a product of antibody catabolism.

Imaging studies and surgical findings

Gamma camera images were obtained 1 and 3 days after antibody injection. Specific antibody localization was assessed by correlating immunoscintigraphy with (1) Ba enema, (2) CT scan, (3) surgical findings, (4) pathological findings, and (5) radioactivity measurements in tumor and the adjacent colon tissue.

With progressive ^{111}In -ZCE-025 clearance from the blood, metastatic foci in the liver in patient No. 4 as well as primary tumor sites in all four patients became obvious by day 3. The percentage of the injected dose per gram of primary tumors ranged from 1.2 to 2.8×10^{-2} (Table 1). There was no apparent relation of CEA content to the clarity of tumor images or the percentage of the injected dose

of antibody taken up by the tumor.

A typical case with colon carcinoma is shown in Fig. 7. In some patients, the normal colon was faintly visualized in the 24 hr-image. As significant radioactivity could be removed from the bowel as time passed, this would suggest that some ^{111}In activity is present in the feces. Furthermore, *ex-vivo* scan of species resected showed faint ^{111}In uptake in the normal colon (Fig. 7B, C). Tsutsumi et al. reported that CEA was stained on the luminal surface of normal colonic epithelium,¹¹ which was also indicated by our immunostaining findings in Fig. 7D. Two lymph nodes (12b₁ and 12b₂) in patient No. 4, which were clearly visualized in the SPECT image, were pathologically confirmed to have no tumor cells. A detailed description of the imaging results obtained in these patients has been included in other papers.^{12,13}

DISCUSSION

All five patients who enrolled in the investigation were suspected to have colorectal carcinoma from the Ba-enema and/or CT-scan, and all four primary tumors could be visualized by immunoscintigraphy. Detectability cannot be discussed here since the number of cases studied was too small. It should be highly appreciated that the tumors that produced CEA accumulated ^{111}In -labeled anti-CEA MoAb. Furthermore, it is noteworthy that the lesion, as in patient No. 3, which was confirmed to be pathologically non-malignant (a benign structure caused by previous surgery), was determined to be negative in the immunoscintigraphy, since it is very difficult to differentiate tumor recurrence from postoperative granuloma by other modalities.

The injectate contained a small amount of free ^{111}In -DTPA throughout the investigation. The free ^{111}In -DTPA was not detected in the first labeling vial before the addition of cold MoAb and the 100-m/ saline, suggesting that ^{111}In attached to MoAb partly dissociated from MoAb during dilution with MoAb and/or saline. The presence of free ^{111}In -DTPA in the injectate would not affect the image qualities because of rapid excretion of ^{111}In -DTPA in the urine.

^{111}In was still attached to MoAb in the plasma, meaning that ^{111}In -labeled MoAb was quite stable in the blood. Some reports described the presence of the immunocomplex between the antibody injected and circulating antigen.^{14,15} We experienced one patient (No. 4) with slightly increased plasma CEA, and observed no immunocomplex in the plasma in size-exclusion HPLC.

Few reports have described ^{111}In -MoAb characterization in cumulative urine excretion. Patt et al.

reported that 48 h-cumulative urine excretion from patients with colorectal cancer under a similar regime to ours was $9.9 \pm 2.2\%$, which was lower than in our results ($18.0 \pm 1.1\%$).³ The clearance rate of ^{111}In in the urine did not vary among patients, meaning that it did not depend on the tumor burden or on the plasma CEA level. What was bound with ^{111}In in the urine was different from patient to patient, suggesting that it depended on several factors including renal function. In general, ^{111}In was cleared into the urine primarily as ^{111}In -DTPA.

The uptake of ^{111}In in tumor tissues was not high, as already pointed out in other papers.^{16,17} When ^{111}In -ZCE-025 was injected into nude mice bearing human gastric cancer MKN45 producing CEA, ^{111}In -ZCE-025 was localized in the tumor with 11.5% ID/g 2 days after the injection. The reason for the discrepancy between clinical and animal experiment results remains unclear.

The uptake of ^{111}In in tissues was not correlated with their CEA content, which disagrees with Duda's report.¹⁷ The reason might be the different accessibility of each monoclonal antibody.

One regional lymph node resected by surgery, which was confirmed to be pathologically malignant, was not visualized in the immunoscintigraphy because it was located very near the primary colon tumor. On the other hand, some lymph nodes (in patient No. 4, 12b₁ and 12b₂), which were visualized in both planar and SPECT images with intensive ^{111}In uptake (0.41 and 0.03% ID/g, respectively), did not contain high CEA (86 and 37 ng CEA/mg prot., respectively), compared with primary tumor (771 ng CEA/mg prot. and 0.01% ID/g of ^{111}In uptake). Furthermore, they were histopathologically confirmed to have no tumor cells. As shown in Fig. 7, some spots showed intensive ^{111}In activity in *ex-vivo* scans of the specimens resected. They were also confirmed to be pathologically non-malignant. False-positive cases in the immunoscintigraphy were reported in several papers.^{4,19,20} They pointed out the following factors as the reasons for the false positive; (1) involvement of macrophages, (2) the presence of a blood pool, and (3) presence of shedding CEA or antigen. Actually ^{111}In -ZCE-025 was localized in the abscess containing macrophages, which were formed in nude mice with 6.03% ID/g, which was lower than that in tumor MKN45 (11.5% ID/g) grown on the same mice. The lymph nodes we discussed in patient No. 4 did not contain high shedding CEA (10.5 ng/ml) and were not stained positively with anti-CEA MoAb immunohistologically. The lymph nodes did not contain many macrophages. Our false positive result, therefore, could not be explained by any factors already described. As shown in Table 1, immunohistological findings

indicated that CEA was present in some normal colon, but ^{111}In -ZCE-025 did not concentrate at this site, possibly because of poor accessibility to the antigen. The cross reactivity of ZCE-025 or antigen accessibility in the lymph nodes might be other factors as the reasons for the false positive result.

In conclusion, immunoscintigraphy with ^{111}In -labeled ZCE-025 shows promise in detecting CEA-producing tumor and appears to be useful in distinguishing recurrent tumor from glaucoma which other imaging modalities failed to depict. The quality of our images was almost the same as those already reported, although the pharmacokinetics of ^{111}In -ZCE-025 was slightly different from them. ^{111}In are present in the blood or in the urine simply in the form of ^{111}In -MoAb or ^{111}In -DTPA. The accumulation mechanism of ^{111}In -labeled MoAb in tumors as well as in some normal tissues needs further study in order to develop MoAb targeting for the radioimmunotherapy of cancer.

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