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Re-appraisal of clinical usefulness of ^{67}Ga-citrate scintigraphy for primary colorectal carcinoma: with evaluation of scintigram obtained from resected specimens

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Clinical usefulness of ^{67}Ga-citrate scintigraphy for the diagnosis of colorectal carcinoma was reappraised at the standpoint of clinicopathological diagnosis. Fifty-eight patients with colonic carcinoma were subjected to this study. They underwent ^{67}Ga scintigraphy before surgery. Colorectal carcinomas were detected in 38 patients, 65.5% by this procedure.

Surgical specimens from thirty-seven patients underwent postoperative scanning. The scanning of the surgical specimen revealed accumulation of ^{67}Ga-citrate in all 37 patients, suggesting that ^{67}Ga-citrate accumulated in the carcinoma of the colon. The results suggested that detectability of carcinoma of the colon by ^{67}Ga scintigraphy in this series was better than generally considered.

^{67}Ga scintigraphy was considered to provide useful information in cases of severe stenosis and dolichocolon which were difficult to diagnose with a Barium enema and fiberscope. The problem is that abnormal accumulation is sometimes hard to distinguish from physiological excretion in the stools. However we believe that images should be carefully evaluated, keeping in mind the fact that ^{67}Ga-citrate could accumulate in a colorectal carcinoma, and also believe that we radiologists should actively promote Ba-enema examination in positive cases rather than to devote time to the differentiation between physiological excretion of ^{67}Ga in the stools and accumulation in a colorectal carcinoma.

Key words: colorectal carcinoma, ^{67}Ga-citrate scintigraphy

INTRODUCTION

THE DETECTABILITY OF CARCINOMA of the colon with ^{67}Ga scintigraphy has been generally reported to be as low as 20–40%, and it has been believed to not offer an advantage in evaluating colorectal carcinoma. In the beginning of our practice of nuclear medicine we also did not highly rate the usefulness of ^{67}Ga scintigraphy for colorectal carcinoma, but we often encountered patients with a high accumulation of ^{67}Ga-citrate in carcinoma of the colon.

We have since reported that the detectability of colorectal carcinoma with ^{67}Ga-scintigraphy is as high as 70%, and it has mainly attributed to the size of tumor and depth of invasion.[1] However, at times it is difficult to distinguish a true accumulation of ^{67}Ga-citrate in the tumor from the radioactivity of physiological excretion in the stools. We therefore tried to reappraise true detectability and factors contributing to the accumulation of ^{67}Ga-citrate in the tumor.

SUBJECT AND METHODS

Fifty-eight patients were subjected to this study. They underwent preoperative ^{67}Ga scintigraphy between May, 1984 and February, 1990 at Juntendo Urayasu Hospital. Thirty-seven underwent extracorporeal scanning in the morning of operation, and surgical specimens were also imaged.

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Scintigraphy was performed 72 hours after intravenous injection of 11.1×10^7 Bq (3 mCi) of ^{67}Ga-citrate with bowel preparation. In the patients who underwent scanning on the day of operation, preoperative preparations included cleaning enema and parenteral nutrition via central veins. The apparatus used was a Toshiba GCA 90-A super-jumbo gamma camera equipped with a medium-energy collimator. Three photo peaks were set over 93 KeV, 184 KeV and 296 KeV.

In order to study factors influencing ^{67}Ga accumulation in each patient, macroscopic classification of the carcinoma of the colon, location of the tumor, microscopic depth invasion of the tumor and the histological type of the tumor were described according to the General Rules for Clinical and Pathological Studies of Cancer of the Colon, Rectum and Anus (the Japanese Research Society for Cancer of the Colon and Rectum), and Dukes' classification was also employed.

Cases of advanced carcinoma of the colon were macroscopically classified as type 1: a polypoid tumor mass, type 2: localized ulceration, type 3: infiltrative ulceration and type 4: diffuse infiltration. Early carcinomas of the colon were also classified as type 0, i.e., a superficial type, type I having a polypoid appearance, type IIa with elevated lesion, type IIb with a flat lesion, type IIc with a depressed lesion, and type III with ulceration, according to the macroscopic classification of early gastric cancer. Furthermore, cases of type I (polypoid type) were subclassified as pedunculated (type Ip) or broad-based (type Is).

The location of tumor was named according to the 7 segments of the colon, i.e. (1) cecum (C), (2) ascending colon (A), (3) transverse colon (T), (4) descending colon (D), (5) sigmoid colon (S), (6) rectum (R) and (7) proctos (P).

Microscopic depth invasion of the wall of the colon was classified as follows: m: cancerous lesion confined to the mucosa without submucosal invasion; sm: cancerous lesion invading the submucosa without muscular invasion; pm: cancerous lesion invading the muscularis propria; ss: cancerous lesion invading the tunica muscularis propria but remaining within the subserosa; s: cancerous lesion invading the subserosa; and si: cancerous lesion clearly invading other adjacent tissue.

Microscopic invasion at a site without serosa was also classified into by six stages as follows: Grades m, sm, and pm were the same as the above; a_1: cancerous lesion invading the muscularis propria, without further deep invasion; a_2: cancerous lesion invading the muscularis propria with deeper invasion, but without invasion of other organs (tissue); and *ai*: cancerous lesion with invasion of outer organs.

One carcinoid case also dealt with from the viewpoint of the malignant epithelial cells was carcinoma of the colon.

RESULTS

Of 58 patients, a positive accumulation was detected in 38 cases (65.5%). In 37 patients, extracorporeal scanning was performed in the morning of operation with additional scanning of surgical specimens (*case Tables 1, 2, 3).

The scanning of surgical specimens revealed the accumulation of ^{67}Ga-citrate in accordance with the extent of the tumor in all 37 patients. Tables 2 and 3 show the macroscopic classification, size, location and histological type of the tumors. The correlation between each factor and accumulation was evaluated.

1. ^{67}Ga-citrate accumulation by depth of invasion and tumor size

Detectability of carcinoma of the colon was studied with reference to the depth of invasion and tumor size (Table 4). In all cases with accumulation of ^{67}Ga (positive cases), pathological studies showed an infiltration extent of a_1 (ss), a_2 (s) or a_1 (si).

This means that all cases showed signs of infiltration of the carcinoma beyond the muscularis propria. Extracorporeal scanning failed to detect tumors of A Dukes' classification. All tumors detected were over 8 cm in diameter.

2. ^{67}Ga-citrate accumulation by location of the tumors

Table 5 shows the correlation between the location of the tumor and the accumulation of ^{67}Ga-citrate. There was a tendency for positive accumulation to be seen in cases of carcinoma of the ascending colon and the cecum.

3. ^{67}Ga-citrate accumulation by histological type of tumors

Table 6 shows the relationship between the histological type and accumulation.

Positive accumulation was seen in 26 cases out of

Table 1 Cases of colorectal carcinoma evaluated by ^{67}Ga scintigraphy

Extracorporeal scanning		Scintigram of the resected specimen		
Positive	38 (65.5%)	23	Positive	23 (100%)
			Negative	0 (0%)
Negative	20 (34.5%)	14	Positive	14 (100%)
			Negative	0 (0%)
Total	58	37		37

Table 2 Positive ^{67}Ga-citrate scintigram in cases of primary colorectal carcinoma

Case	Age	Sex	Macroscopic type	Size (cm)	Depth of invasion		Location	Histology
1	60	F	3	12×9	s	B	Ascending colon	well diff. ad. ca.
2	48	M	4	15×4	a_1	C	Rectum (Ra)	poor. diff. ad. ca.
3	39	F	2	4.5×6	s	B	Transverse colon	well diff. ad. ca.
4	72	M	2	5×5	s	B	Sigmoid colon	mod. diff. ad. ca.
5	71	M	3	10×5	si	C	Transverse colon	poor. diff. ad. ca.
6	68	M	3	10×7	s	C	Ascending colon	mod. diff. ad. ca.
7	46	M	3	3×3	s	C	Transverse colon	well diff. ad. ca.
8	44	M	3	6×5.5	a_1	C	Rectum (Rb)	well diff. ad. ca.
9	62	M	3	10×5	s	C	Ascending colon	well diff. ad. ca.
10	44	M	2	5×4.5	s	B	Sigmoid colon	well diff. ad. ca.
11	33	F	3	16×16	si	C	Transverse colon	poor. diff. ad. ca.
12	69	F	1	11.5×7	s	B	Ascending colon	well diff. ad. ca.
13	44	M	3	9×5	a_2	C	Rectum (Ra)	well diff. ad. ca.
14	68	M	3	12×12	si	C	Cecum	well diff. ad. ca.
15	58	F	3	10×6	s	B	Transverse colon	well diff. ad. ca.
16*	67	F	1	2.1×3	a_2	C	Rectum (Rb)	mod. diff. ad. ca.
17*	76	F	3	7.5×4.5	s	C	Cecum	well diff. ad. ca.
18*	40	M	3	8×5	s	B	Sigmoid colon	mod. diff. ad. ca.
19*	70	M	2	4.5×4.5	si	B	Rectum (Rs)	well diff. ad. ca.
20*	72	F	1	4×3	ss	B	Cecum	well diff. ad. ca.
21*	58	M	2	7.5×5.3	a_2	C	Rectum (Ra)	mod. diff. ad. ca.
22*	75	M	2	3.5×2.5	a_2	C	Sigmoid colon	well diff. ad. ca.
23*	63	F	3	8×6	si	C	Rectum (Rs)	well diff. ad. ca.
24*	42	F	2	5×4.5	a_2	C	Rectum (Ra)	mod. diff. ad. ca.
25*	55	F	3	5×3	a_2	B	Ascending colon	well diff. ad. ca.
26*	72	F	2	4×3	ss	B	Sigmoid colon	well diff. ad. ca.
27*	54	M	3	7×5	si	C	Ascending colon	well diff. ad. ca.
28*	72	F	3	7×6	ai	C	Sigmoid colon	well diff. ad. ca.
29*	38	F	2	7×6	si	C	Rectum (Ra)	well diff. ad. ca.
30*	41	M	3	5×7	a_2	B	Ascending colon	poor. diff. ad. ca.
31*	63	F	3	9×5.5	si	C	Ascending colon	mod. diff. ad. ca.
32*	40	M	3	6.5	ai	B	Rectum (Rb)	well diff. ad. ca.
33*	39	F	2	5×4	a_2	B	Descending colon	well diff. ad. ca.
34*	76	M	2	4.5×3.5	ss	B	Rectum (Rb)	well diff. ad. ca.
35*	48	M	3	6×7	a_1	C	Rectum (Rb)	well diff. ad. ca.
36*	49	F	3	7×8	a_2	B	Rectum (Rb)	well diff. ad. ca.
37*	38	M	3	4×4	a_2	C	Descending colon	mucinous ca.
38*	64	M	3	7×3.5	s	C	Sigmoid colon	well diff. ad. ca.

Abbreviations: well diff. ad. ca.=well differentiated adenocarcinoma, mod. diff. ad. ca.=moderately differentiated adenocarcinoma, poor. diff. ad. ca.=poorly differentiated adenocarcinoma, *=scintigram of a surgical specimen

40 (65%) with well differentiated adenocarcinoma, in contrast to 7 of 10 cases (70%) with moderately differentiated adenocarcinoma, and all of 4 cases (100%) of a poorly differentiated type.

The following are representative cases.

Case 12. The patient was a 69-year-old female with diabetes mellitus, hypertension and cerebral infarction. ^{67}Ga scintigraphy was performed for evaluation of anemia. Abnormal accumulation was detected in the right lower abdomen. Type 1 advanced carcinoma of ascending colon was then confirmed by Ba-enema. In this case ^{67}Ga scintigraphy greatly helped in diagnosing colorectal carcinoma (Fig. 1).

Case 29. The patient was a 38-year-old female with type 2 advanced carcinoma of the rectum (localized ulceration type).

The lesion was 7.0×6.0 cm in size with infiltration to adjacent tissue (si). The histological type was well differentiated adenocarcinoma. The scanning performed in the morning of operation revealed ^{67}Ga-citrate accumulation indicating the tumor. The scanning of surgical specimens also revealed accumulation in the same site (Fig. 2).

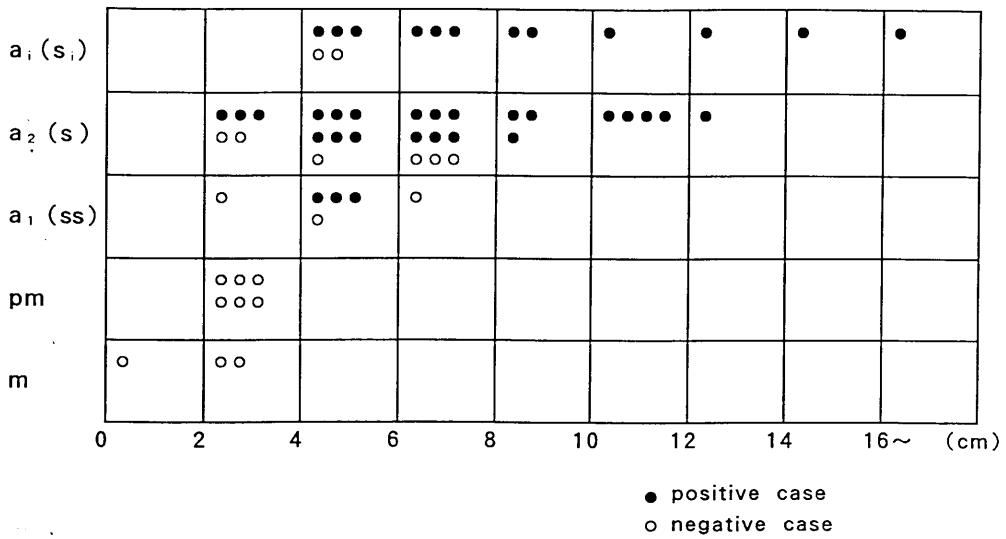
Case 30. This was a 41-year-old male patient with

Table 3 Negative ^{67}Ga-citrate scintigram for primary colorectal carcinoma

Case	Age	Sex	Macroscopic type	Size (cm)	Depth of invasion	Dukes	Location	Histology
1	57	F	2	3.5×2	pm	C	Sigmoid colon	well diff. ad. ca.
2	64	F	2	7×6	s	B	Cecum	mod. diff. ad. ca.
3	73	M	IIa	2×1.3	m	A	Sigmoid colon	well diff. ad. ca.
4	58	M	2	2×2	pm	C	Sigmoid colon	well diff. ad. ca.
5	58	M	2	3×2	pm	A	Rectum (Rb)	well diff. ad. ca.
6	60	F	3	5×3	a_1	B	Rectum (Ra)	mucinous ca.
7*	68	F	2	5.5×3.5	s	C	Cecum	mucinous ca.
8*	58	F	3	3.5×3	pm	A	Rectum (Ra)	well diff. ad. ca.
9*	67	M	1	3.7×3.2	pm	B	Sigmoid colon	mod. diff. ad. ca.
10*	80	M	2	3.5×2.5	s	B	Transavers colon	well diff. ad. ca.
11*	80	F	3	5×3	ss	B	Sigmoid colon	well diff. ad. ca.
12*	63	M	Ip	2.4×2.0	m	A	Rectum (Ra)	well diff. ad. ca.
13*	47	M	3	6×5	a_2	B	Rectum (Rb)	carcinoid.
14*	60	M	2	6×5	a_1	B	Rectum (Rb)	well diff. ad. ca.
15*	40	M	2	2×1.9	a_2	B	Rectum (Ra)	mod. diff. ad. ca.
16*	64	M	3	5×4	si	C	Sigmoid colon	well diff. ad. ca.
17*	48	F	2	6×6	a_2	B	Rectum (Ra)	well diff. ad. ca.
18*	46	F	3	3×3.5	a_1	C	Rectum (Ra)	well diff. ad. ca.
19*	62	F	IIa	1.5×1.5	m	A	Cecum	well diff. ad. ca.
20*	58	M	2	3.0×2.5	pm	A	Sigmoid colon	well diff. ad. ca.

*: Scintigram of the resected specimen

Table 4 Relationship between accumulation of ^{67}Ga-citrate in a primary colorectal carcinoma and tumor size and depth of invasion



type 3 advanced carcinoma of the ascending colon (infiltrative ulceration type) and a polyp in the transverse colon.

The main lesion was 5.0×7.0 cm in size with infiltration beyond the tunica muscularis (a_2). Histological type was poorly differentiated adenocarcinoma.

Scanning of the surgical specimens showed accumulation of ^{67}Ga-citrate. The polyp was a sessile polyp, about 10 mm in diameter, and was located 5 cm distal to the main lesion.

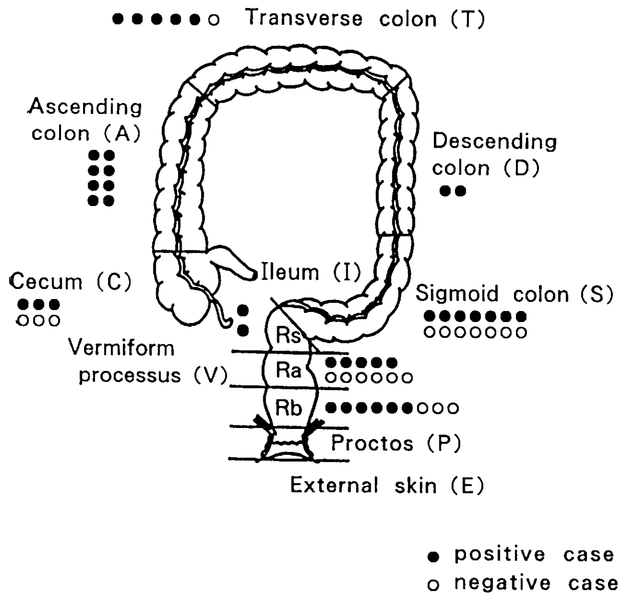
It was a tubular adenoma, and showed no accumulation on either extracorporeal scanning or scanning of specimens (Fig. 3).

Case 12. This was a 63-year-old male patient with a pedunculated polyp of the rectum 2.4×2.0 cm in size. The lesion had invaded the tunica mucosa (m), showing carcinoma in adenoma. Extracorporeal

scanning performed in the morning of operation revealed no accumulation of ^{67}Ga-citrate, but the scanning of surgical specimens revealed accumulation in the tumor site (Fig. 4).

Case 9. This was a 67-year-old male with type 1 advanced carcinoma of the sigmoid colon (polypoid tumor type). The lesion was 3.7×3.2 cm in size with infiltration to the proper muscle (pm). The histological type was moderately differentiated adenocarcinoma. Extracorporeal scanning performed in the morning of operation revealed an accumulation in the tumor site (Fig. 5).

Table 5 Relationship between accumulation of ^{67}Ga-citrate in a primary colorecal carcinoma and tumor site



DISCUSSION

In general, ^{67}Ga scintigraphy for carcinoma of the colon is clinically underevaluated, and is not popular at present, probably because of the lack of distinction due to physiological excretion of ^{67}Ga-citrate in the stools. Previous reports said that detectability was around 20–40%.[2–7]

In our early re-appraisal of the clinical usefulness of ^{67}Ga scintigraphy for carcinoma of the colon, carcinomas of the colon were visualized by ^{67}Ga scintigraphy in 15 (71.4%) of 21 patients. Detectability tended to increase with size and the degree of tumor invasion. All positive cases showed infiltration of a_2 (s) or a_i (si).[7] In order to determine the site and degree of accumulation more precisely, extracorporeal scanning images in the morning of operation and those of the surgical specimens were compared in 37 patients.

Accumulation was recognized even in Dukes' A cases, in whom preoperative extracorporeal scans failed to detect any accumulation. As mentioned in the case review, no accumulation was observed in tubular adenoma even on scanning of the surgical specimens. As seen in two cases of carcinoma associated with tubular adenoma, no accumulation was observed on scanning the surgical specimens, suggesting that ^{67}Ga-citrate accumulates in the colorectal carcinoma itself (Fig. 2).

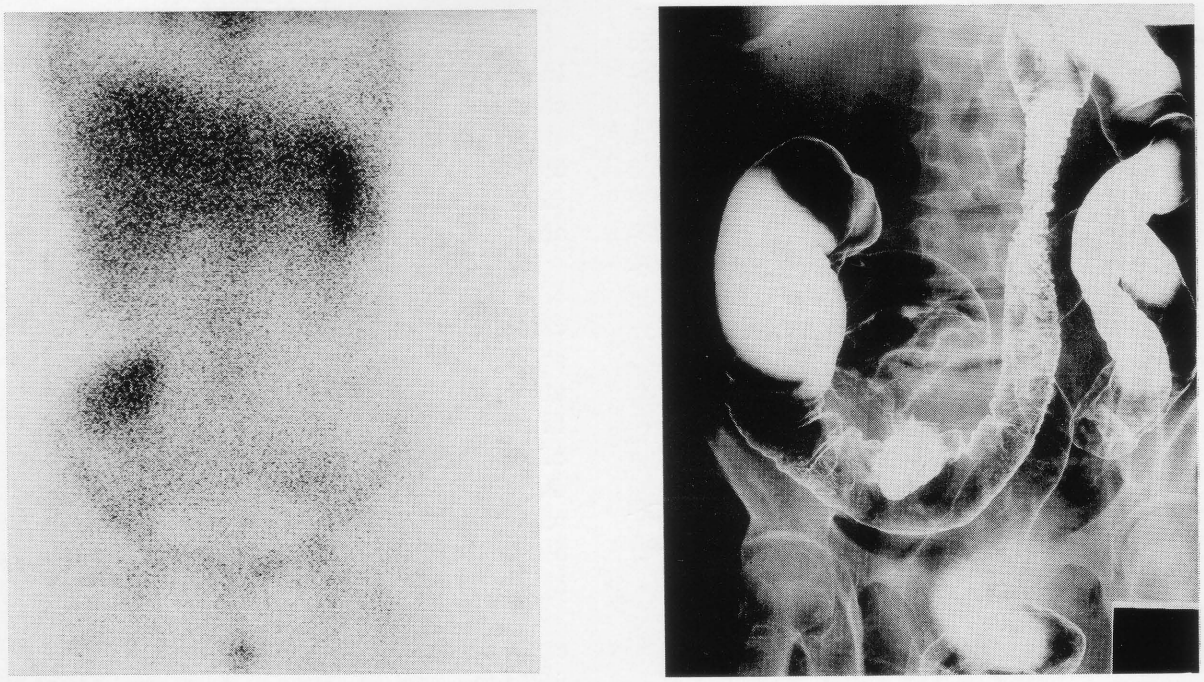
All patients in whom carcinoma was detected by extracorporeal scanning (positive cases) showed invasion beyond the a_1 (ss) level, and the accumulation of ^{67}Ga was considered to be proportional to the histological findings of invasion. Accumulation was observed in all of 14 patients in whom the tumor was more than 8 cm in greatest diameter.

The detectability of a poorly differentiated adeno-

Table 6 Relationship between accumulation of ^{67}Ga-citrate in a primary colorectal carcinoma and histological type

Well differentiated adenocarcinoma	●●●●●●●●●●●●●●●●●●●●●●●●●● ○○○○○○○○○○○○○○	26/40	65 %
Moderately differentiated adenocarcinoma	●●●●●●● ○○○	7/10	70 %
Poorly differentiated adenocarcinoma	●●●●	4/4	100 %
Others	● ○○○	1/4	25 %

● positive case
○ negative case



A B

Fig. 1 A: ^{67}Ga-citrate scintigram shows abnormal accumulation in the right lower abdomen. B: Barium enema shows type 1 advanced carcinoma of the ascending colon.

carcinoma was higher than that of a well differentiated adenocarcinoma. This indicated that ^{67}Ga-citrate accumulated well in poorly differentiated tumors. But it was still not clear whether there is a histology related difference or not in the degree of accumulation. Further investigation is necessary to find the answer.

As mentioned above, it seems to be true that ^{67}Ga-citrate accumulates in a colorectal carcinoma, although the degree varies. Clinical application of ^{67}Ga scintigraphy becomes an issue. Of course ^{67}Ga scintigraphy may not be applicable in all cases of colorectal carcinoma because of the high cost efficacy. However, ^{67}Ga scintigraphy is, at times, considered to provide useful information in cases of severe cancer-induced stenosis and elongated colon, particularly in elderly patients. All cases which were detected by extracorporeal scanning (positive cases) probably have an infiltration beyond the tunica muscularis propria. Although no information on the anatomic relationship between surrounding tissues and tumors was obtained by this procedure, the complementary use of CT is considered useful for the diagnostic evaluation of invasion to surrounding tissues. Moreover, we believe that ^{67}Ga scintigraphy is useful for the early detection of recurrent colorectal carcinoma and monitoring of radiotherapeutic effects on recurrences when CT and/or MRI fail to detect the lesions.

It seems advantageous to remove the influence of physiological excretion of ^{67}Ga in the stools to improve the extracorporeal detection of ^{67}Ga accumulation in a colorectal carcinoma. The solution of this problem may include proper measures for bowel preparation, the dosage of ^{67}Ga-citrate, and the timing of imaging. However, there are some limitations to such techniques.

Currently, there is a tendency for the number of cases of colorectal carcinoma to increase, and in this study leaves no doubt that ^{67}Ga-citrate accumulates in a colorectal carcinoma. So we believe that it is more important to manage Ba-enema examination than to concentrate on the differentiation between the physiological excretion of ^{67}Ga in the stool and the accumulation in a colorectal carcinoma.

Nowadays, ^{67}Ga scintigraphy is one of the most common radioisotope examinations for the evaluation of several diseases, and in 1989 it accounted for 15% of total radioisotope examinations in Japan. At the present time, as mentioned above, it is important for radiologists to keep in mind that ^{67}Ga-citrate sometimes accumulates in a colorectal carcinoma, and radiologists should try to use this fact as a strategic clue in the discovery of colorectal carcinoma.

CONCLUSION

The usefulness of ^{67}Ga scintigraphy was re-evaluated for carcinoma of the colon in 58 patients. Colorectal

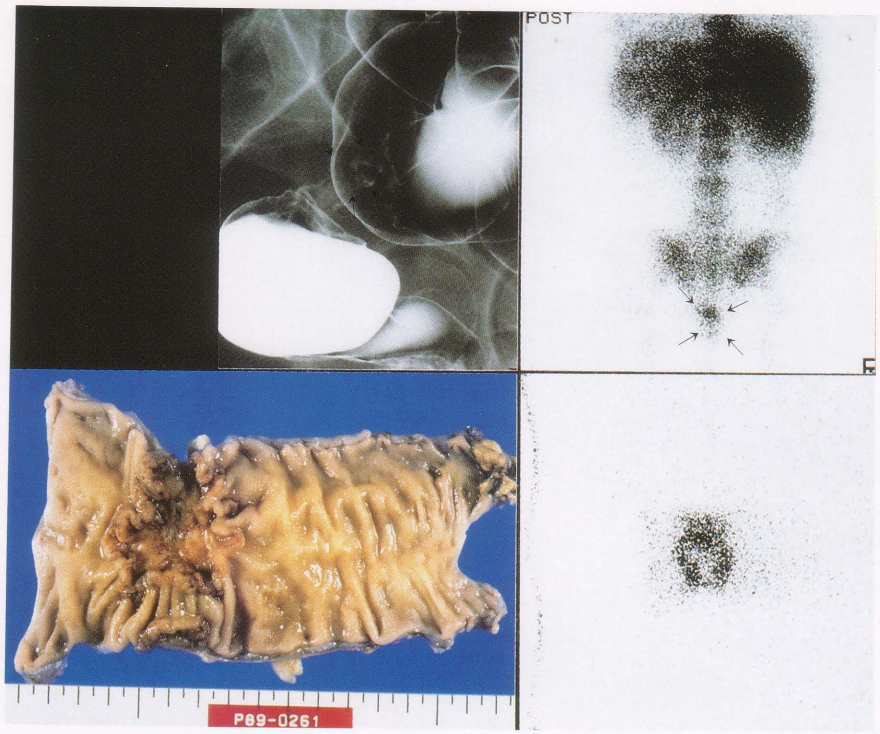


Fig. 2 A: Barium enema shows type 2 advanced carcinoma of the rectum (black arrows). B: Resected specimen. C: Extracorporeal scanning shows accumulation of ^{67}Ga-citrate (black arrows). D: Scanning of a surgical specimen also reveals accumulation in the same site.

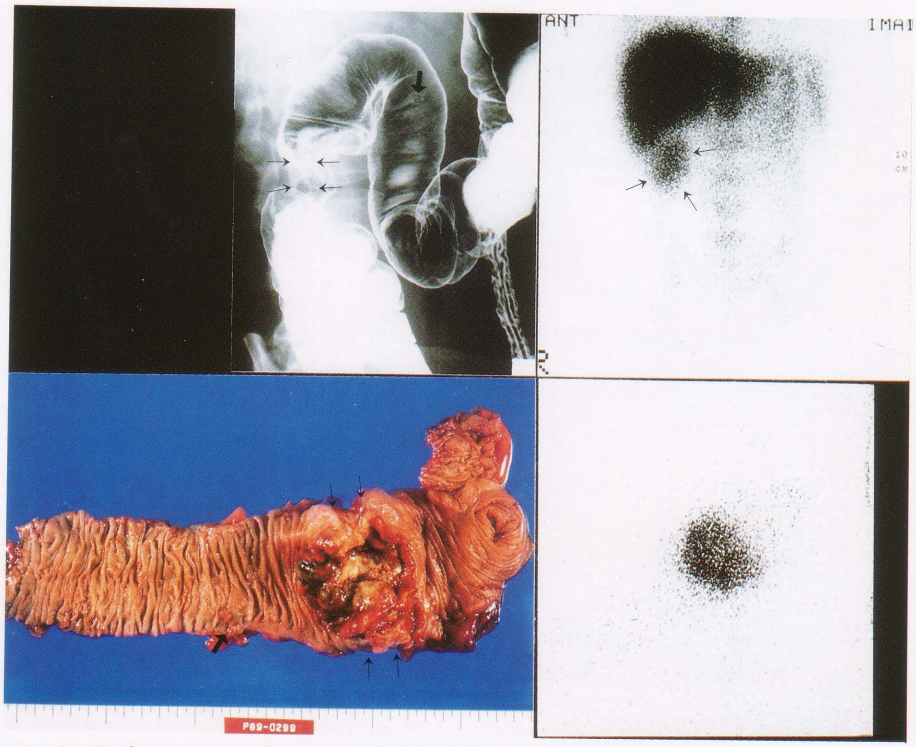


Fig. 3 A: Barium enema shows type 3 advanced carcinoma of the ascending colon (black arrows) and sessile polyp of the transverse colon (open arrows). B: Resected specimen. C: Extracorporeal scanning reveals accumulation of ^{67}Ga-citrate (black arrows). D: Scanning of a surgical specimen also shows accumulation in the main tumor. But the sessile polys shows an accumulation in either extracorporeal scanning or scanning of the surgical specimen.

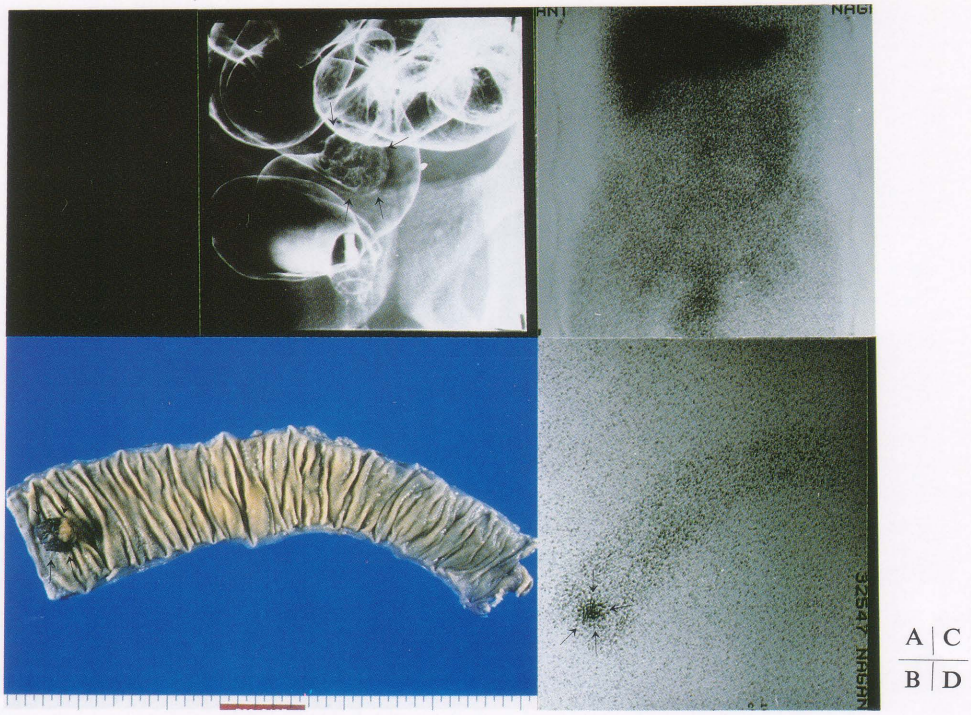


Fig. 4 A: Barium enema shows pedunculated polyp of the rectum (black arrows). B: Surgical specimen. C: Extracorporeal scanning reveals no accumulation of ^{67}Ga-citrate. D: The scanning of surgical specimen shows accumulation in the polyp (black arrows).

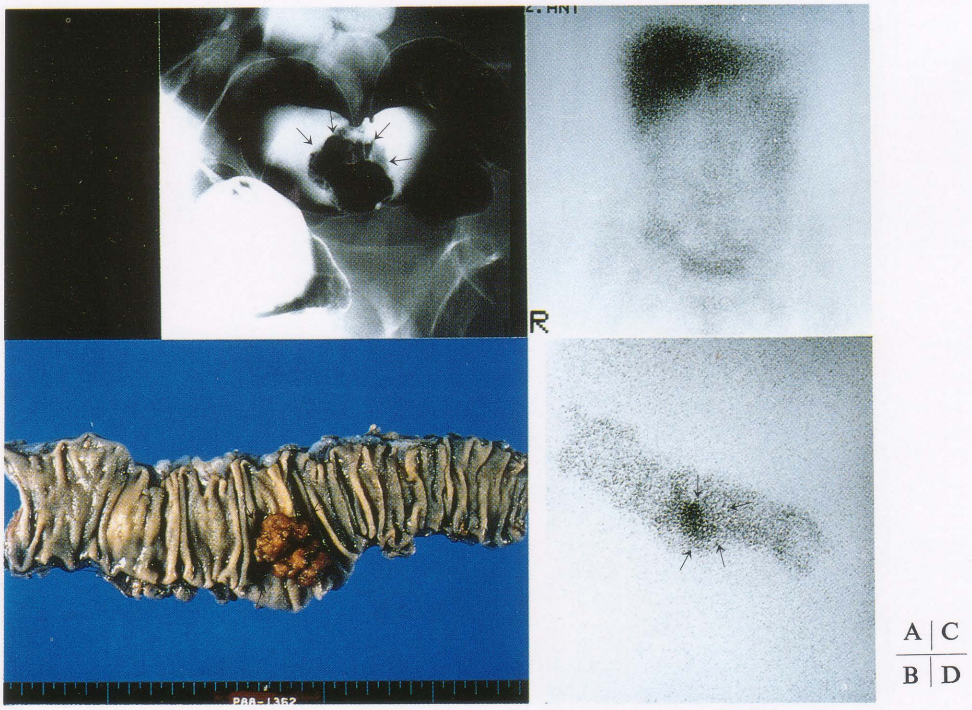


Fig. 5 A: Barium enema shows type 1 advanced carcinoma of the sigmoid colon (black arrows). B: Surgical specimen. C: Extracorporeal scanning reveals no accumulation of ^{67}Ga-citrate. D: Scanning of a surgical specimen shows accumulation in the tumor (black arrows).

carcinomas were detected in 38 patients (65.5%) by ^{67}Ga scintigraphy. Thirty-seven patients underwent preoperative scanning in the morning of operation, and postoperative scanning of the surgical specimens. The scanning of the surgical specimens revealed an accumulation of ^{67}Ga in all 37 patients. Although there remains the problem of the differentiation of the accumulation from physiological excretion in the stools, we radiologists should not devote undue attention to the differentiation between physiological excretion of ^{67}Ga in the stools and the accumulation of ^{67}Ga in the colorectal carcinoma. We believe in the active use of Ba-enema in positive cases, keeping in mind the fact that ^{67}Ga-citrate accumulates in the colorectal carcinoma, and is an important clue in discovering colorectal carcinoma.

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