Immunoscintigraphy of Recurrences of Gynecologic Carcinomas

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In a first, retrospective study, 15 patients with known ovarian carcinoma were injected with ^{131}I-OC 125 F(ab')$_2$ monoclonal antibody (MAb). The sensitivity of immunoscintigraphy based on the number of the tumor sites was 67% (12/18). In a second, prospective study, 29 patients with gynecologic carcinoma were injected with ^{131}I-OC 125 F(ab')$_2$ (24) or ^{131}I-19-9 F(ab')$_2$ (5) MAbs according to the histologic type. Based on the number of tested anatomic sites, sensitivity was 72% and specificity 86%. In two patients injected with both ^{131}I-OC-125 F(ab')$_2$ and ^{125}I-NS F(ab')$_2$ (nonspecific immunoglobulin) 1 and 4 days before tumor resection, tumor uptake of the specific antibody was 2.2 and 4.5 times greater than that of NS. Immunoscintigraphic results were complementary with those of ultrasonography and computed tomography. Finally, in one patient injected successively with ^{131}I-OC 125 F(ab')$_2$ and ^{111}In-DTPA-OC 125 F(ab')$_2$, the recurrent tumor was visualized with both radionuclides, with ^{111}In providing better abdominal tumor contrast but causing much greater liver radioactivity than ^{131}I.

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Epithelial ovarian cancers still have poor prognosis, with an overall 5-year survival rate of ~30% (*1*). A recent study concerning 770 patients reported a 5-year survival rate of <10% for stages III and IV (FIGO classification), the most common stages at the time of a first diagnosis (*2*). After initial surgery, treatment generally includes a chemotherapy regimen for advanced stages with macroscopic residue and chemotherapy and/or abdominopelvic irradiation for early stages without macroscopic residue. Following chemotherapy, second-look surgery is usually carried out to confirm possible complete remission (*3*). When complete remission is thus confirmed in patients initially with stages III and IV, a recurrence subsequently occurs in 25% of cases with poor prognosis (*4*). It would therefore be important to be able to detect such recurrences early, before the appearance of clinical signs, in the hope of improving therapeutic effectiveness.

A monoclonal antibody (MAb) designated OC 125 has been produced after immunization by a serous ovarian cystadenocarcinoma, the most common histologic type (*5*). This antibody recognizes an antigen, CA 125, associated with ovarian carcinomas particularly of the serous type, and is shed into the circulation where it can be assayed by an immunoradiometric method (*6,7*). Likewise, antibody 19-9 recognizes an antigen designated CA 19-9, associated with mucous carcinomas (*8*), that is also shed into the circulation where it can be assayed by the same method.

By serial biologic monitoring with both markers depending on histologic type, recurrences can be detected early in patients who previously reached a state of complete remission (*7*). It is then important to be able to confirm recurrences by visualization, which is the role of immunoscintigraphy (IS), in order to provide further effective surgical treatment. The aim of the present study was to specify the diagnostic value of IS both by examining patients with previously known and localized tumor sites and, especially, in a prospective view, by comparing the efficiency of the technique with that of conventional diagnostic methods.

METHODS

Antibodies

Two MAbs were used in this study—OC 125 and 19-9—with the choice depending on the type of marker that had

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significantly increased serum concentration relative to normal values. MAb OC 125 was produced and made commercially available*; its characteristics have been previously reported (5). $F(ab')_2$ fragments were obtained after pepsin digestion, and their purity was tested by SDS electrophoresis and high performance liquid chromatography (HPLC) on a TSK 3000 column. There were neither Fab' fragments nor intact antibody in the preparations. The $F(ab')_2$ fragments were labeled with iodine-131 (^{131}I), using the iodogen method, with a specific activity of 3 mCi/mg. Immunoreactivity after radioiodination was tested by affinity chromatography using a sandwich assay. CA 125 antigen was eluted through a sepharose column coupled to OC 125 MAb. The column was washed and the labeled MAb was then eluted through the column. This sandwich assay was made possible by the repetitive structure of the recognized epitope. The antigen-bound fraction of the labeled antibody was eluted with a 3*M* ammonium thiocyanate solution. The $F(ab')_2$ fragments from 19-9 MAb were labeled with ^{131}I using the same method and with the same specific activity. The labeling efficiency ranged from 80 to 90% with ^{131}I-OC 125 $F(ab')_2$ and from 90 to 95% with ^{131}I-19-9 $F(ab')_2$. The immunoreactivity of MAb 19-9 was tested in the same way as with MAb OC 125. The percentage of immunoreactivity was calculated using the ratio of radioactivity of MAb eluted with NH_4SCN to the sum of MAb radioactivity not bound to antigen plus that eluted with NH_4SCN. The percentages obtained were 47 ± 4% with ^{131}I-OC 125 $F(ab')_2$, and 80 ± 5% with ^{131}I-19-9 $F(ab')_2$. The immunoreactivity of MAb OC 125, the antibody most often used in this study, was also tested by a cell-binding assay. The cell line used (OVCAR NIH)† came from a serous ovarian adenocarcinoma and expressed the CA 125 antigen (9). Briefly, $3 \cdot 10^5$ cells were distributed in a round-bottom 96-well plate. One hundred microliters of ^{131}I-OC 125 $F(ab')_2$ were added to each well and left to incubate 3 hr at room temperature with continuous shaking. After centrifugation and three successive washes, cell radioactivity was counted. The results were expressed in percentage of total activity used for each well. In these conditions, the percentage obtained was 46%, whereas it was 1.5% with a nonspecific immunoglobulin labeled in the same conditions.

Scintigraphic Technique

An activity of 1.5-2 mCi (55.5–74 MBq) (~0.6 mg) for planar scintigraphy and 2.5-3.5 mCi (92.5–129.5 MBq) (~1 mg) for emission computed tomography (ECT) was injected into each patient after obtaining informed consent. Thyroid uptake of free ^{131}I was blocked by oral administration of Lugol's solution (100 mg/day) for 8 days beginning 2 days before injection of the radioantibody. Each radioantibody was injected intravenously over a period of ~30 min in an infusion of 100 ml of saline solution. No skin test was performed before this injection. Three and four days after injection of the radioantibody, ECT studies were performed using a rotating single-head gamma camera with a medium-energy collimator.‡ The abdomen and pelvis were evaluated in two scans 3 and 4 days after injection. Each recording first involved injection of technetium-99m (^{99m}Tc) 5 mCi (185 MBq), in different forms hydroxymethylene diphosphonate (HMDP), albumin, diethylenetriaminepentaacetic acid, or sulfur colloid) to obtain anatomic landmarks and thus facilitate interpretation of immunoscintigraphic images. This injection was followed by an initial 10-min elliptical rotation. Then, with the patient in the same position, a second 40-min rotation was performed after a 20% energy window was centered on the ^{131}I photopeak. For each recording, 6-mm-thick transverse, sagittal, and coronal sections were then reconstructed using data filtering. The same reconstruction with thicker sections (12 mm) did not change the interpretation of the images. The normal pattern of an ECT section was characterized by patchy, heterogeneous distribution with many foci more or less contrasted in relation to each other. Our interpretative criteria for considering whether a focus was pathologic required that this focus appear with the same contrast and localization features in at least three superimposed sections and two tomographic planes.

Four to seven days after injection of the radioiodinated antibody, planar scintiscans were recorded using an large field-of-view gamma camera with a medium-energy collimator, interfaced with a data processing system.§ Anterior and lateral views were recorded in order to cover the whole of the abdomen and pelvis. Before each scan, ^{99m}Tc was injected as in the ECT study.

Patients Studied

From January 1983 to March 1986, 44 patients with gynogic cancer underwent one or more immunoscintigraphic examinations. These patients can be divided into two groups on the basis of the circumstances leading to scintigraphy. For 15 patients (Group I: mean age 58 yr, range 39 to 70 yr), localization of the primary tumor or recurrence was determined by surgery, palpation of a mass, and/or ultrasonography (US) or computed tomography (CT) that showed a tumor mass prior to IS (Table 1). For the other 29 patients (Group II: mean age 61 yr, range 39 to 79 yr), IS was the first examination performed prospectively when a recurrence was suspected on the basis of significant and persistent elevation of the serum concentration of one of the two markers (CA 125 or CA 19-9) (Table 2). A total of 36 immunoscintigraphic examinations were performed in these 29 patients, with two examinations in five patients (Nos. 1, 3, 5, 7, 13) and three in Patient 4. After IS, US and/or CT was performed blindly in Group II patients without knowing the findings of IS. A total of 32 US examinations were performed with a ALOKA SSD 851 real-time equipment and 27 examinations were performed on the third generation CGR CE 10000 Scanner with a scan duration of 3.4 sec. There were fewer US and, especially, CT examinations than IS examinations since some patients considered the IS protocol too difficult and demanding and subsequently refused US and/or CT.

The localization diagnosis for recurrence (Group II) was confirmed by surgery in 14 cases, by concordant results of US and CT in six cases and by the course of the disease, with eventual appearance of a palpable mass in the location of antibody uptake, in five cases. Absence of recurrence was confirmed by surgery in three patients and suggested by the course in another patient over more than a year's time. Finally, in seven cases the diagnosis at this writing still remains undetermined. In five of these seven cases, IS was positive, suggesting recurrence, whereas US and/or CT were negative (Nos. 1b, 7b, 12, 13b, 20). In two cases (Nos. 13a, 21), all localization examinations, including IS, were negative despite elevated serum CA 125 concentrations. In all these cases the patients refused surgery, and the diagnosis remained undetermined.

Planar scintigraphy was performed in 18 cases (eight in

TABLE 1
Results of Retrospective Study Including 15 Cases of Primary or Recurrent Ovarian Carcinoma

Patient no.	Age (yr)	Serum* CA 125 U/ml	Tumor site (size, cm)	Immunoscintigraphy† PS	Immunoscintigraphy† ECT	Ultrasonography‡	Computed tomography
1	66	2,260	Abdomen 7 × 3		—	+	+
2	47	38	Pelvis >5	+		ND	+
3	56	10,000	Pelvis 6 × 6	—		+	ND
4	60	323	Abdomen >5		+	ND	ND
5	63	820	Abdomen >5		+	ND	–
6	70	ND	Pelvis >5	+		ND	ND
7	39	900	Pelvis >5	+		ND	+
8	63	152	Pelvis 4 × 3		+	+	+
9	55	157	Abdomen 6 × 3		+	+	+
10	50	1,370	Pelvis >5		+	+	ND
11	61	67	Pelvis >5	—	—	+	ND
12	63	292	Pelvis 4 × 4	+		+	+
			Abdomen 2.5 × 2.5	—		—	—
13	43	520	Diffuse carcinomatosis	—		+	—
14	50	128	Pelvis 10 × 5	+	+	—	ND
			Abdomen 3 × 3	+	+	—	ND
			Liver <1	—	—	+	ND
15	62	95	Abdomen 8 × 6		+	ND	+

* Upper limit of normal values: 40 U/ml.
† PS = Planar scintigraphy.
‡ ND = Not done.

Group I, ten in Group II) ECT in 40 cases (nine in Group I, 31 in Group II). In eight cases, patients were evaluated with both scintigraphic methods.

Three patients (Nos. 8 and 9 in Group I and No. 18 in Group II) were injected, respectively, at 4-, 6- and 8-mo intervals with an identical activity of ^{131}I-OC 125 F(ab')$_2$ and ^{111}In-DTPA-OC 125 F(ab')$_2$ to compare the scintigraphic pattern obtained with each radionuclide. Every patient who had a known recurrence of ovarian carcinoma, was evaluated by ECT in the same conditions 3 days after injection. Patient 8 had been treated after the first immunoscintigraphy with a high dose of 3,330 MBq of ^{131}I-OC 125 F(ab')$_2$.

Finally, Patients 15 and 19 were injected simultaneously with ^{131}I-OC 125 F(ab')$_2$ and ^{125}I-NS F(ab')$_2$ (a nonspecific immunoglobulin of the same class as OC 125), respectively, 1 and 4 days before second-look surgery to study distribution in the tumor and normal tissue specimens removed during the operation. The results were expressed in % of injected dose per gram of excised tissue.

RESULTS

Results of the retrospective study are given in Table 1. Among the 15 patients studied, a total of 18 tumor sites was known before IS. Twelve sites were visualized: four by planar scintigraphy, six by ECT and two by both methods. The smallest tumor was 3 cm in diameter, but most tumors visualized were >5 cm in diameter.

Figure 1 shows the case of a pelvic recurrence clearly visualized by ECT, with a transverse section image corresponding to a CT image. The tumor measured 4 × 3 cm (No. 8).

Results of the prospective study are given in Table 2. Out of 24 immunoscintigraphic examinations performed in 20 patients injected with ^{131}I-OC 125 F(ab')$_2$ whose diagnosis of recurrence was documented, 19 tumor sites were correctly visualized: six by planar scintigraphy and 13 by ECT. In one case of abdominal recurrence (No. 19), ECT was negative at Day 4, but planar scintigraphy was positive at Day 7 after a 30-min acquisition time.

Figure 2 shows a case of bilateral ovarian cancer. The two tumors were the smallest visualized in this study, measuring 2 × 2.5 and 2.5 × 3 cm (No. 1a). For the two patients simultaneously injected with the specific MAb ^{131}I-OC 125 F(ab')$_2$ and the nonspecific immunoglobulin ^{125}I-NS F(ab')$_2$, respectively, 1 and 4 days before the operation (No. 15 and 19), study of the distribution showed higher tumor uptake of the specific MAb than of the nonspecific immunoglobulin (Fig. 3). The difference in uptake was greater at Day 4 (Fig. 3B) than at Day 1 (Fig. 3A). This tumor uptake of the specific MAb was well correlated with the results of the immunohistochemical study that in both cases showed CA 125 antigen expression by over 50% of cells. In normal tissues (liver, muscle, fat, skin), radioactive concentration of the specific MAb varied little from that of the nonspecific immunoglobulin. In the two patients, tumor-to-liver, tumor-to-blood, and tumor-to-muscle ratios were, respectively, 2.45 and 2.56, 1.32 and 1.08, and 5.64 and 4.76. The specificity indices, as measured by the tumor-to-tissue ratios obtained with ^{131}I divided by the same ratios obtained with ^{125}I, ranged

TABLE 2
Results from 29 Prospectively Investigated Patients

Patient no.	Age (yr)	Primary carcinoma	Serum* CA 125 U/ml	IS‡ PS site(s)	IS‡ ECT	US*	CT	Means of diagnosis†	Tumor size (cm)
1a	69	Serous ovarian	1,070					Surgery	2 × 2.5
		carcinoma		2+ (Pelvis)		2+	1+1−		2.5 × 3
1b			18,000						
				(Pelvis)	1+	ND	—	UND	
2	79	Serous ovarian	190						
		carcinoma		(Pelvis)	1+	—	—	Surgery	4 × 5
		carcinoma		(Pelvis)	1+	1+	1+	Concordance	3 × 2.5
3b			200						
				(Pelvis)	1+	1+	ND	Evolution	
4a	58	Serous ovarian	4,000						Axillary node
		carcinoma		—		—		Surgery	3 × 3 not explored
4b			630						
				(Pelvis)	1+	—	ND	Evolution	
4c			30,000						
				(Pelvis)	1+	1+	1+	Concordance	7 × 5.5
5a	65	Serous ovarian	95						Peritoneal
		carcinoma		—		ND	ND	Surgery	seedlings
5b			670						
3a	65	Serous ovarian	1,170						
					—	ND	ND	Evolution	Pelvic mass
6	58	Serous ovarian	650						
		carcinoma		—		—	ND	Surgery	3 × 2.5
7a	72	Fallopian tube	60						
		carcinoma		(Abdomen)	1+	1+	1+	Surgery	Abdomen 4 × 4
				(Pelvis)	1−	1−	1−		Pelvis 2 × 1
7b			1,480						
				(Abdomen)	1+	—	—	UND	
8	60	Serous ovarian	450						Peritoneal
		carcinoma			—	—	ND	Surgery	seedlings
9	73	Endometrium	250						
		carcinoma		1+ (Pelvis)		—	ND	Surgery	4 × 3
10	58	Serous ovarian	900						
		carcinoma		(Pelvis)	1+	—	ND	Evolution	
11	50	Serous ovarian	2,600						
		carcinoma			1+	1+	1+	Surgery	5.5 × 6
12	57	Serous ovarian	360						
		carcinoma		(Pelvis)	1+	—	ND	UND	
13a	51	Serous ovarian	215						
		carcinoma			—	—	—	UND	
13b			260						
				(Abdomen)	1+	—	—	UND	
14	76	Serous ovarian	107						
		carcinoma		(Pelvis)	1+	—	1+	Evolution	
15	74	Serous ovarian	3,300						
		carcinoma		(Abdomen)	1+	—	1+	Surgery	>5
16	55	Serous ovarian	400			3+			
		carcinoma			—	(Abdomen)	3+	Concordance	
17	64	Serous ovarian	270						
		carcinoma		(Pelvis)	1+	—	1+	Surgery	Pelvic benign mass
18	62	Serous ovarian	220						
		carcinoma		(Abdomen)	1+	1+	1+	Concordance	4 × 4
19	47	Serous ovarian	360						
		carcinoma		1+ (Abdomen)	1−	—	—	Surgery	5 × 5
20	73	Serous ovarian	138						
		carcinoma		1+ (Pelvis)	1+	—	—	UND	
21	73	Serous ovarian	95						
		carcinoma		—	—	—	—	UND	
22	60	Serous ovarian	132						No apparent
		carcinoma		(Pelvis)	1+	—	1+	Surgery	tumor

TABLE 2 (*continued*)

Patient no.	Age (yr)	Primary carcinoma	Serum* CA 125 U/ml	IS‡ PS site(s)	IS‡ ECT	US*	CT	Means of diagnosis†	Tumor size (cm)
23	74	Serous ovarian carcinoma	1,200	1+ (Abdomen)	1+	—	—	Surgery	Peritoneal carcinosis
24	63	Serous ovarian carcinoma	1,400	2− (Abdomen) 1+ (Pelvis)	2+ 1−	—	—	Surgery	
			Serum* CA 19-9 U/ml						
25	39	Mucinous ovarian carcinoma	135	(Pelvis)	1+	—	—	Surgery	Pelvis 4 × 3
26	66	Mucinous ovarian carcinoma	75	(Pelvis) (Liver)	1+ 1−	1+ 1+	1+ 1+	Concordance	Liver 3 × 3
27	46	Mucinous ovarian carcinoma	45		—	—	—	Evolution	No recurrence
28	80	Mucinous ovarian carcinoma	>2,400	1+ (Pelvis)	1−	—	+	Concordance	
29	58	Endometrium carcinoma	35	(Pelvis)	2+	ND	—	Surgery	No apparent tumor

* See Table 1; Upper limit of normal value: 40 U/ml.
† UND = Undetermined; Concordance = Concordant results of CT and US.
‡IS = Immunoscintigraphy; PS = Planar scintigraphy.

from 1.63 to 3.37 (mean 2.50). Figure 4 shows the ECT images in the patient operated on 4 days after simultaneous injection of the specific MAb and the nonspecific immunoglobulin (Fig. 3B). This ECT study was performed 3 wk before second-look surgery. The prevertebral node recurrence is well contrasted (Fig. 4A), and its well-defined development on the coronal section corresponds with that found by the surgeon and indicated with metal clips (Fig. 4C).

In this prospective study with MAb ^{131}I-OC 125

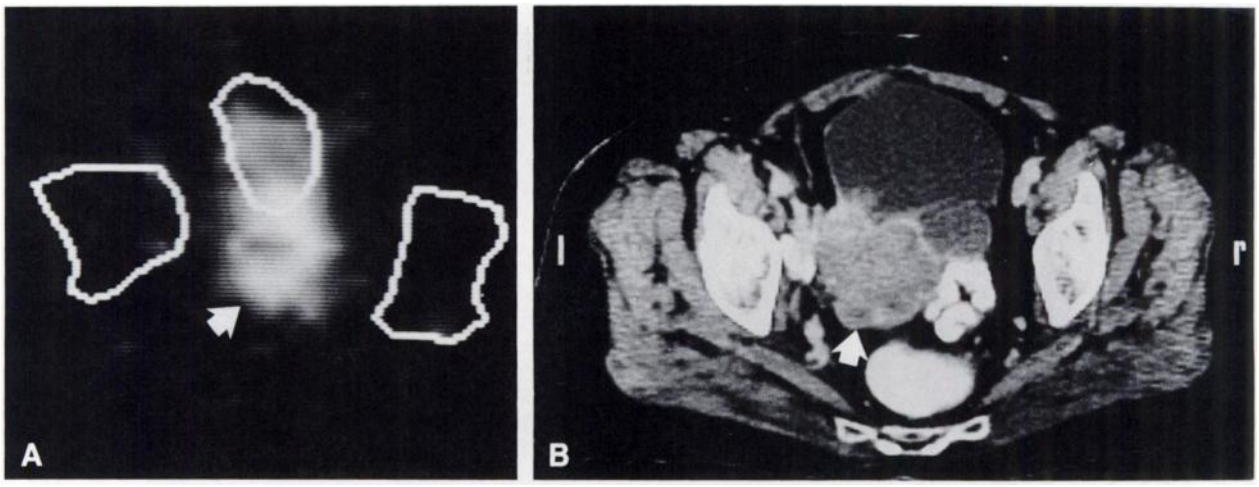


FIGURE 1
ECT image in a patient with pelvic recurrence of a serous ovarian adenocarcinoma. A: ^{131}I-OC 125 F(ab')$_2$ ECT image. A transverse section, shows an abnormal concentration of radioactivity behind the bladder (arrow). The outlines of the bladder and the pelvic bones have been sketched in from a corresponding [^{99m}Tc]HMDP section. B: A CT scan shows a mass behind the bladder (arrow) corresponding to the ECT image finding of Figure 1A. The image has been inverted to correspond to the ECT image.

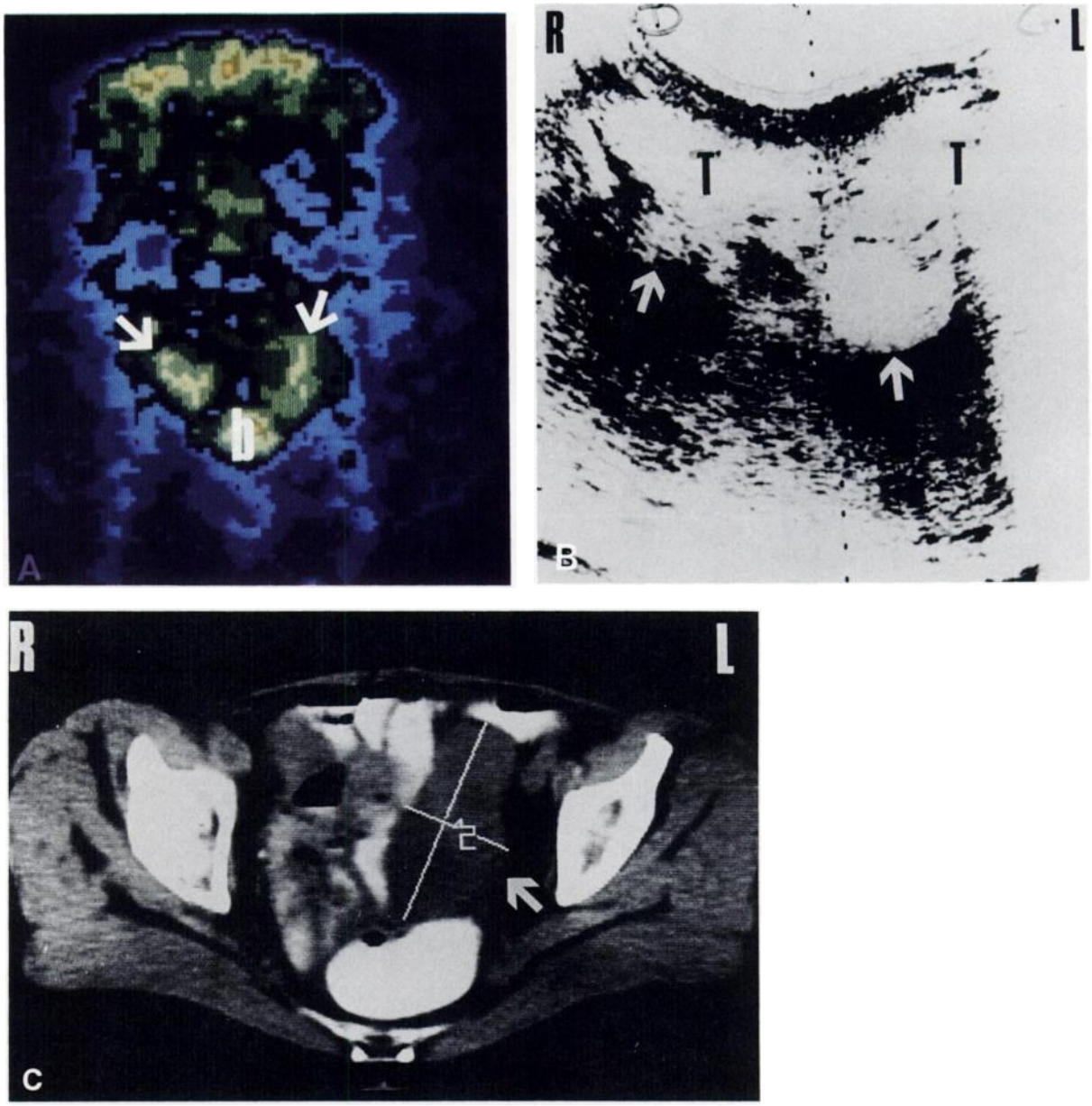


FIGURE 2
Bilateral ovarian carcinoma in a patient previously operated on for a malignant ascitis of unknown origin. A: The anterior ^{131}I-OC 125 F(ab')$_2$ scan image shows two symmetrical abnormal foci of radioactivity above the bladder (b) (arrows). B: A sonogram shows a pelvic mass (arrows) but fails to differentiate two distinct tumors. T = Tumor. C: A pelvic transverse CT scan shows a left bilobate mass (arrow) without obvious abnormality on the right side. D: The surgical view confirms the photoscan finding, showing two tumors (arrows).

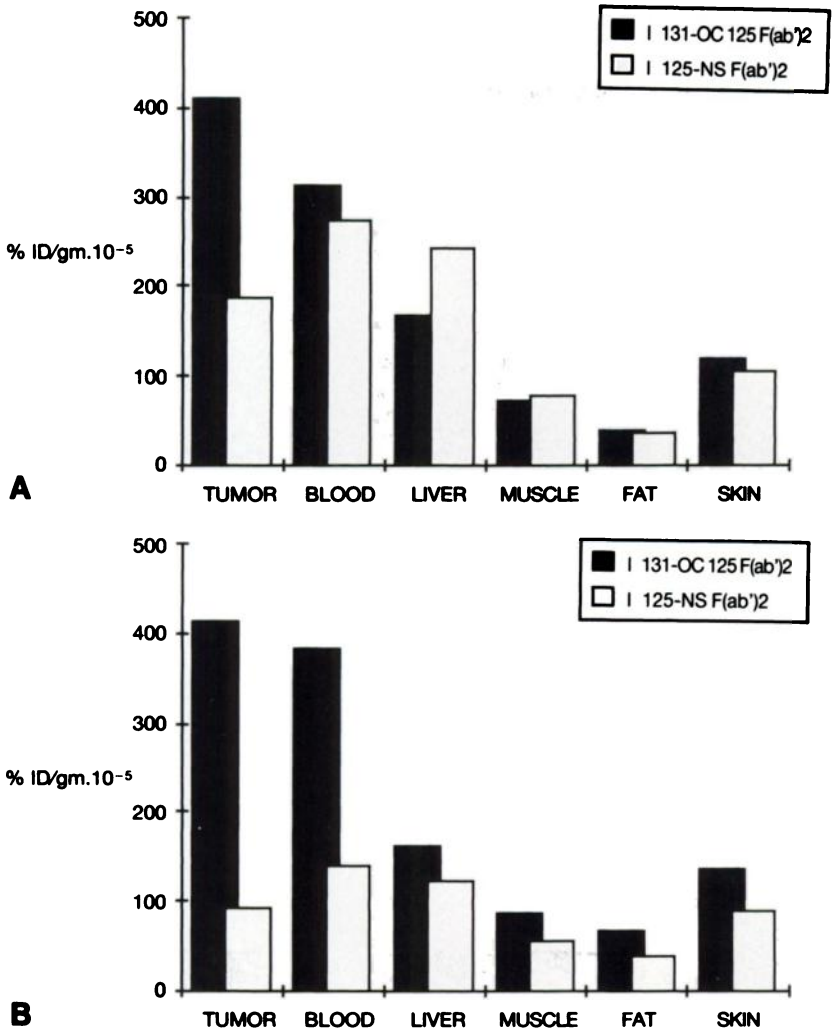


FIGURE 3
Distribution of ^{131}I-OC 125 F(ab')$_2$ and a nonspecific immunoglobulin [^{125}I-NS F(ab')$_2$] in two patients, 1 day (A) and 4 days (B) after injection. Results are expressed in mean % of injected activity per gram of tumor.

F(ab')$_2$, eight tumor sites were not visualized (false-negative results), including three abdominal recurrences in the same patient (No. 16). In two cases, the recurrence was diffuse, taking the form of peritoneal seedlings (No. 5a and 8). In one case of primary fallopian tube carcinoma, the tumor was small, 2 × 1 cm (No. 7a). In another case, a 3 × 2.5 cm pelvic recurrence was close up against the urinary bladder. The patient had only undergone planar scintigraphy at Day 4 (No. 6). Finally, in one case, recurrence was suggested by an elevated serum CA 125 concentration of 670 U/ml (No. 5b). Negative IS was not followed up by US or CT. Ten months later a pelvic recurrence was palpable. It is quite likely that this recurrence existed at the time of the immunoscintigraphic examination but was not visualized even though it was already expressed biologically.

In two cases immunoscintigraphy was considered positive, whereas the surgeon found no apparent tumor recurrence (false-positive results). For one of these patients (No. 17) there had in fact been an error in interpretation as all the ECT criteria defined were not involved. For the other patient (No. 22), a small pelvic focus had been confirmed by CT as a small retrovesical mass. The patient's course may determine whether this case was a false positive or a recurrence signaled biologically but not apparent at the time of surgery.

In five patients injected with MAb ^{131}I-19-9 F(ab')$_2$, three tumor sites were correctly identified. A single tumor site was not visualized that corresponded to a 3-cm liver metastasis (No. 26). Finally, for one patient (No. 29), two small, poorly contrasted pelvic foci that corresponded to the interpretative criteria had been considered positive but were not confirmed surgically.

Table 3 summarizes the overall diagnostic performances of IS. The results were considered to be a function of the number of anatomic sites tested and not of the number of patients. To measure specificity, two anatomic sites were considered for each patient: the pelvis and the upper abdomen, including the liver and spleen.

When results are limited to cases where diagnosis was confirmed by surgery, sensitivity was 76% (13/17) and specificity 79% (15/19).

Table 4 shows the combined results of IS, US, and

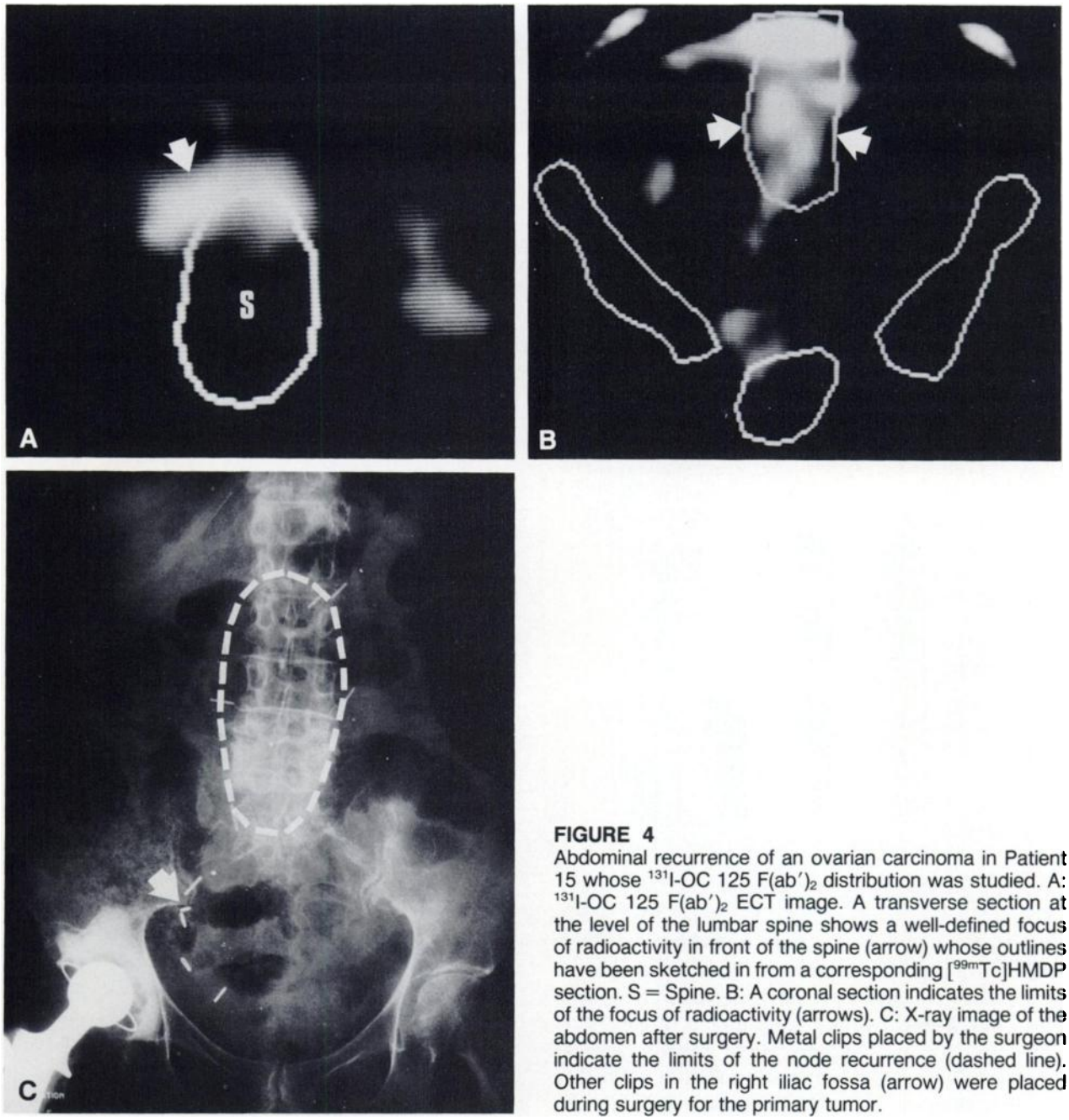


FIGURE 4
Abdominal recurrence of an ovarian carcinoma in Patient 15 whose ^{131}I-OC 125 F(ab′)$_2$ distribution was studied. A: ^{131}I-OC 125 F(ab′)$_2$ ECT image. A transverse section at the level of the lumbar spine shows a well-defined focus of radioactivity in front of the spine (arrow) whose outlines have been sketched in from a corresponding [^{99m}Tc]HMDP section. S = Spine. B: A coronal section indicates the limits of the focus of radioactivity (arrows). C: X-ray image of the abdomen after surgery. Metal clips placed by the surgeon indicate the limits of the node recurrence (dashed line). Other clips in the right iliac fossa (arrow) were placed during surgery for the primary tumor.

CT. The diagnostic sensitivity of US was 47% (14/30). For CT it was 63%(15/24). The 13 tumor sites visualized by IS and not by US corresponded to eight pelvic and five abdominal localizations. In two cases, US interpretation was hindered, once by the impossibility of keeping the patient's bladder full during examination and another time by the patient's obesity (250 lb). The eight tumor sites visualized by IS and not by CT were pelvic (four sites) and abdominal (four sites) in origin.

Figure 5 illustrates the case of Patient 2 with a moderate elevation of serum CA 125 concentration, suggesting a recurrence which was not visualized by US and CT. Positive pelvic ECT was the determining examination in the decision to perform third-look surgery. Total resection of the recurrence led to a return to normal CA 125 values that had persisted until this writing.

Finally, concerning the three patients explored successively by ^{131}I-OC 125 F(ab′)$_2$ and ^{111}In-DTPA-OC 125 F(ab′)$_2$, the recurrence in two cases was visualized with ^{131}I and not with ^{111}In. One case concerned the patient who had been treated with a high dose of ^{131}I-OC-125 F(ab′)$_2$ after the first IS. In the other case, the recurrence was a metastasis of the lower part of the right hepatic lobe. Using ^{111}In, excessive liver activity did not allow the metastasis to be clearly visualized, in

TABLE 3
Sensitivity and Specificity Based on Number of Tested Anatomic Sites

Clinical group	No of tested anatomic sites	TP*	FN†	TN‡	FP§	Sensitivity	Specificity
I	18	12	6	/	/	67% (12/18)	
II	60	23	9	24	4	72% (23/32)	86% (24/28)

*TP = True positive.
†FN = False negative.
‡TN = True negative.
§FP = False positive.

the absence of subtraction, when interpretation was made prospectively. Figure 6 illustrates the third case in which an abdominal node recurrence was visualized with both radionuclides. Although the scintigraphic contrast to the tumor compared with abdominal background is better with ^{111}In, liver radioactivity is quite high, whereas it is low with ^{131}I.

DISCUSSION

The initial retrospective part of this study showed that it was possible to visualize ~70% of primary or secondary ovarian tumors. For patients who were not examined surgically, the diagnosis of recurrence was considered highly probable on the basis of an association of a significant elevation of serum CA 125 level and a palpable and/or clearly visualized US and CT mass. Three of six false-negative results could be attributed to small tumor size (a liver metastasis <1 cm in diameter and an abdominal tumor 2.5 cm in diameter) and in one of these cases to diffuse peritoneal involvement, a condition that in the absence of focalization sometimes makes it difficult to differentiate diffuse uptake of moderate intensity from simple abdominal vascular background. In the other three false-negative cases, the tumors were large—>5 cm in diameter—that implies that the percentage of necrosis may have been high and that antibody accessibility to the tumor target was limited by lower blood flow.

The major interest of the second, prospective stage of the study was to test the value of IS when it can be truly beneficial for the patient by confirming and localizing a recurrence signaled only by an elevation in serum CA 125 or CA 19-9 concentration. This rise usually occurs early in the course of the disease, before the appearance of clinical signs, at a stage when further curative surgery is still possible. For the 29 patients in this condition, the percentage of visualized recurrences was 72% which was close to that of the retrospective study. The analysis of false-negative results was similar to that of the retrospective study: small tumors, diffuse involvement and sometimes unexplained circumstances in which the recurrence expressed CA 125 antigen, seemed well vascularized and yet was not visualized. The specificity (86%) was satisfactory and could have been improved if an error in interpretation as a result of inexperience had been avoided (No. 17), and if the pelvic focus confirmed by CT and not by surgery truly corresponded to a recurrence and is demonstrated by the patient's future course (No. 22).

Of these 29 patients in the prospective study, the diagnosis of recurrence was histologically confirmed in 14 cases. If results are limited solely to surgically confirmed cases, comprising the gold standard, sensitivity is comparable (76% versus 72%) and specificity slightly lower (79% versus 86%).

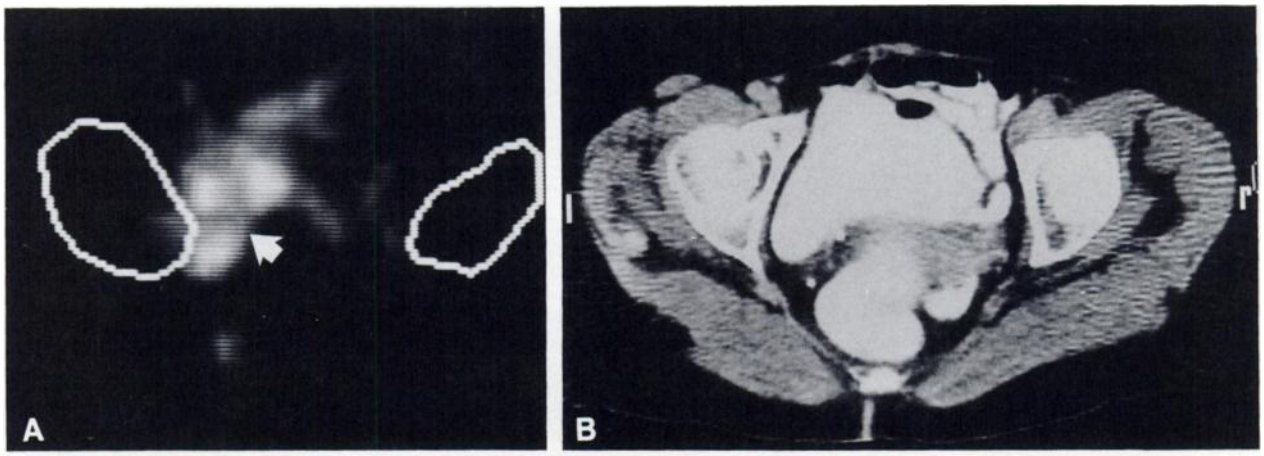
In this study, the choice of antibody injected was determined by the histologic type of the primary tumor and by the nature of the antigen for which serum concentration increased. Mainguené et al. (*8*) have shown in an immunohistochemical study that 90% (27/30) of serous ovarian carcinomas, but no mucous carcinomas, expressed CA 125 antigen. On the contrary, 93% (13/14) of mucous carcinomas, and only 13% of serous carcinomas, expressed CA 19-9 antigen. It is thus clear that OC 125 and 19-9 antibodies are complementary for ovarian carcinomas as a function of their histologic type. The theoretic limiting factors for their immunoscintigraphic application is the shedding of antigens into the circulation where they may form immunocomplexes with injected radiolabeled antibodies and thus limit the latter's accessibility to their tumor target. This limitation is, however, not confirmed in practice since tumors have been visualized at very elevated concentrations of circulating antigens (*10*), whereas a limited percentage of tumors has been visualized with antibodies such as 17-1A that recognize an antigen not shed into the circulation (*11*).

Moreover, for two patients, this study indicated that uptake in a tumor tested with paired labeling is not related to simple trapping of an immunoglobulin in the extravascular compartment of the tumor but a result of

TABLE 4
Combined Results of Immunoscintigraphy, Ultrasonography and Computed Tomography in Documented Tumor Sites

	Ultrasonography		Computed tomography	
Immunoscintigraphy*	Positive	Negative	Positive	Negative
Positive	10	13	11	8
Negative	4	3	4	1
TOTAL	14	16	15	9

*Results are to be read across.



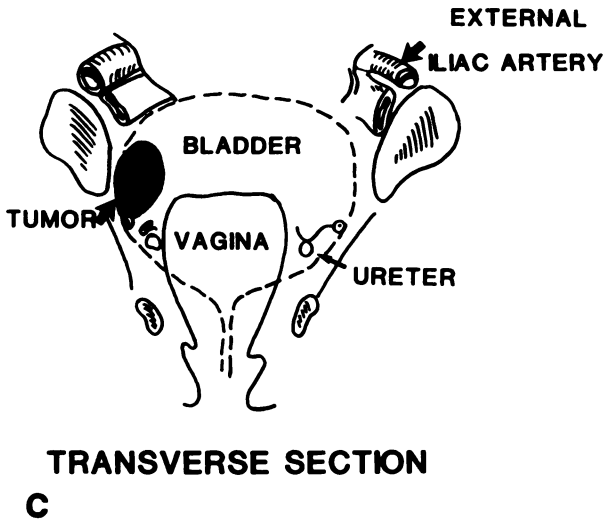


FIGURE 5
Pelvic recurrence of an ovarian adenocarcinoma in a patient with isolated elevation of serum tumor marker. A: ^{131}I-OC 125 F(ab')$_2$ ECT image. A transverse section at the level of the pelvis shows an abnormal left lateral focus of radioactivity (arrow). B: A CT scan approximately at the same level as that of ECT fails to show any abnormal mass. C: An anatomic section, drawn by the surgeon from the surgical view, shows the left-sided location of the resected recurrence, corresponding to the ECT finding of Figure 5A.

specificity of the injected antibody for its antigenic target.

F(ab')$_2$ fragments were preferred in the study since their clearance in normal tissues is faster than that of intact antibodies, whereas clearance in tumors varies little with either form (*12*).

Other MABs have been used successfully to visualize ovarian carcinomas, including antibodies directed against placental alkaline phosphatase (*13*) and an antigen of human milk fat globule membranes (*14–15*). It is not easy to compare the diagnostic results obtained with these antibodies since the selection of tested patients varied greatly from one study to another. One future possibility would be to inject antibody "cocktails" to take advantage of complementary specificities (*16*).

The choice of radionuclide is important and partly conditions IS results. Iodine-131, used in this study, has radiophysical characteristics that are not very favorable to scintigraphic detection and dosimetry but that allow exploration of the upper abdomen owing to lowliver uptake. The radionuclide providing the best compromise in associating energy, half-life, and availability is ^{111}In. Currently, its major drawback is a high level of liver uptake which hinders interpretation of the upper abdomen. However, tumor imaging of the pelvic region is markedly more contrasted than with ^{131}I (Fig. 6). It is likely that ^{111}In will be the future radionuclide of choice if liver uptake can be significantly reduced.

The mode of radionuclide detection also deserves discussion. Planar scintigraphy, with moderate doses of ^{131}I or ^{111}In 1 to 2 mCi (37 to 74 MBq), allows recording of late images 5 to 7 days after injection, the period of the best tumor-to-background contrast. However, it is difficult to interpret foci located close to normally radioactive organs such as the urinary bladder. ECT has the advantage of increasing contrast and providing three-dimensional localization of a focus (17), in which case it is easier to differentiate a pathologic focus from adjacent vesical radioactivity. However, to satisfy the count statistic, a greater dose must be injected 3 to 3.5 mCi (111 to 129 MBq) than in planar scintigraphy, and prolonged acquisition times (40 min of rotation in our study) must be used. Moreover, interpretation of the different reconstructed sections requires experience and previously defined criteria. To benefit from the respective advantages of the two detection modes, our prospective study is being followed up by another associ-

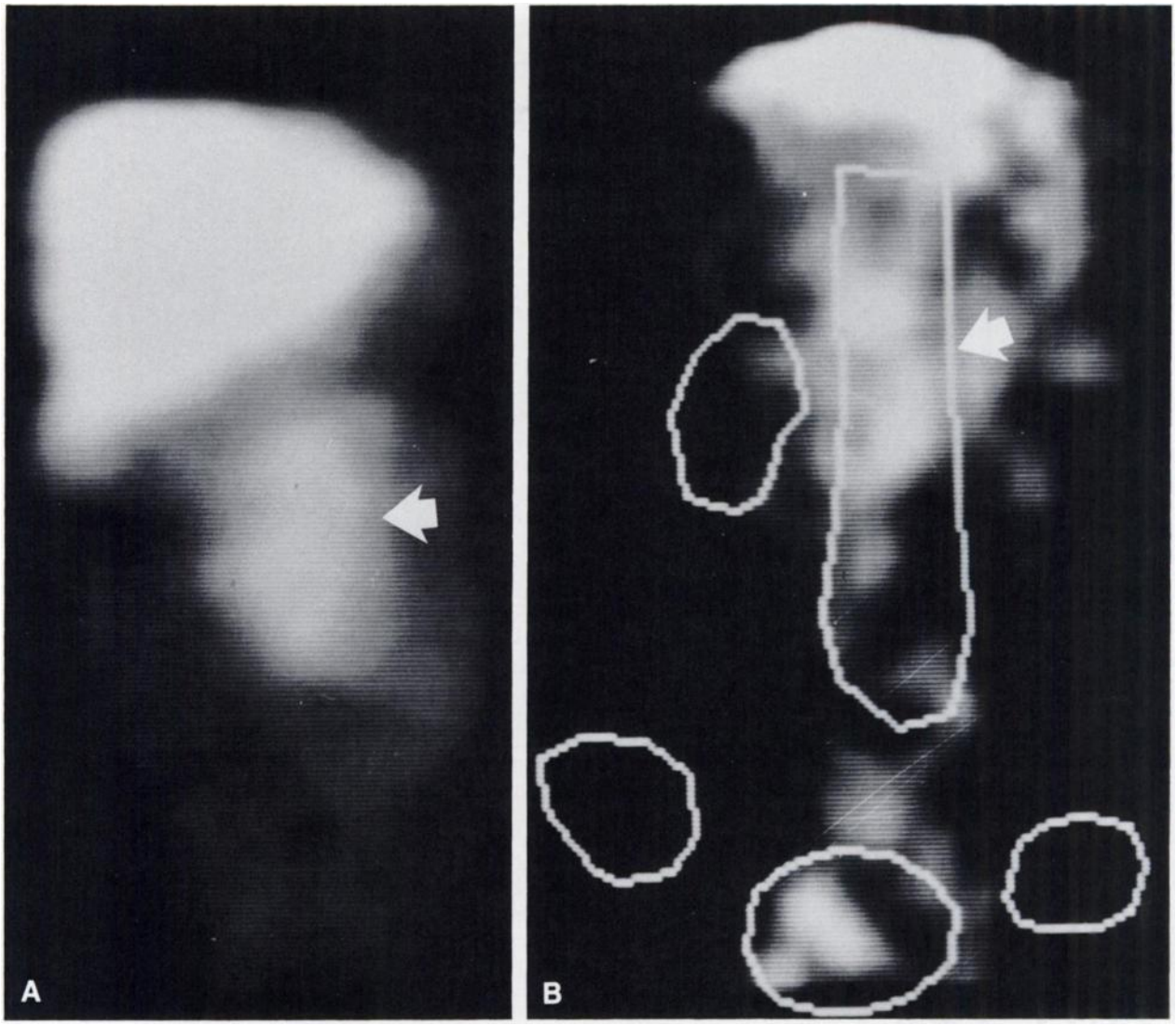


FIGURE 6
Abdominal lymph node recurrence of an ovarian adenocarcinoma. A: [^{111}In]DTPA-OC 125-F(ab′)$_2$ ECT image. On this coronal section the lumbar lymph node recurrence is clearly visualized (arrow) below and inward from an intense liver activity. B: ^{131}I-OC 125-F(ab′)$_2$ ECT image recorded 8 mo before the image of Figure 6A. The lumbar lymph node recurrence is well defined (arrow) but the contrast compared to abdominal back ground is less than with ^{111}In. However, liver radioactivity is low in comparison with that of ^{111}In.

ating both modes, in which an ECT examination is performed 3 and 4 days after injection and is followed at Day 7 by planar scintigraphy involving a global posterior abdominal view with 30 min acquisition time. For four patients (Nos. 19, 23, 24, 28) in this study tested according to this protocol, and whose diagnosis of recurrence was determined, planar scintigraphy showed three recurrence sites (two pelvic, one abdominal) not clearly visualized on the ECT sections (Nos. 19, 24, 28). However, in one case (No. 24), ECT visualized two abdominal recurrence foci which did not show up clearly in planar scintigraphy.

Finally, the clinical value of IS needs to be defined relative to the other conventional diagnostic methods. In comparison with these, which detect nonspecific morphologic alterations, IS provides in addition information about relative oncologic specificity. Numerous studies have reported the results of US in detecting primary or residual ovarian tumors after treatment (*18–21*). Although the criteria of patient selection, which vary from one study to another, make comparison of findings difficult, simple addition of results gives an overall 58% sensitivity (140/242) and 95% specificity (265/278). The most frequent causes of false negatives, other than methodologic problems involving intestinal gas and a bladder that is not full, concern small nodules < 1 cm in diameter, peritoneal studding and matted intestinal loops that are difficult to distinguish from recurrences.

Studies performed with CT are just as numerous and

offer the same variety with respect to the range of cases (*22–26*). When exercising the same caution in interpreting the overall results of these different studies, 80% sensitivity (141/176) and 95% specificity (338/355) are found. The causes of false negatives include peritoneal studding, isodense masses or masses adhering to colonic structures, masses against the pelvic side wall or paraaortic nodes. As with US, owing to a lack of oncologic specificity, fibrotic lesions may cause false positives.

There are fewer studies with magnetic resonance imaging (MRI) that have been introduced more recently. The combined results of three studies (27–29) give 85% sensitivity (23/27). As with US and CT, MRI lacks oncologic specificity and cannot distinguish inflammation or radiation changes from recurrent tumor (*27*).

In order to define diagnostic strategy with the four diagnostic methods (IS, US, CT, and MRI) in the event of biologically suspected recurrence, it is advisable to think in terms of the complementarity and not the competitiveness of these methods, as illustrated by the results of this study (Table 4). These results should admittedly be interpreted with due caution in comparing IS with US and CT since all patients did not undergo all three examinations. It is thus not possible to provide statistical comparison of the respective diagnostic sensitivities. However, for patients who underwent all three examinations, in five cases (Nos. 2, 19, 23, 24, 25), IS was the only positive examination in patients who had negative US and CT. It is also appropriate to add four of the seven cases of undetermined diagnosis which had positive IS and negative US and CT (Nos. 7b, 13b, 20). The short- and middle-term course of these patients will determine if these were also confirmed recurrences. Identical situations in which IS was determinant for localization of a recurrence have also been reported for colorectal carcinomas (*16,30*).

In fact, when an elevation in marker serum concentration suggests a recurrence, it would be desirable to employ the three methods (IS, US, and CT), thus compensating for the limitations of each and providing the surgeon with the most precise evidence relative to the different anatomic sites to guide his decision on second-look surgery.

NOTES

* Produced at the Dana Farber Cancer Institute, Boston (R. Bast, MD); Compagnie ORIS Industrie, 91190 Gif sur Yvette, France.

† National Cancer Institute, Bethesda, MD (R.F. Ozols).

‡ Gammatone 2-CGR-Sopha Medical, Les Ulis, France.

§ (Searle Siemens) Cine 200-Intertechnique, Plaisir, France.

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