Radioimmunoscintigraphy in Patients with Ovarian Cancer

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The targeting potential of three different monoclonal antibodies (MAbs) was assessed in patients with ovarian cancer. HMFG1, OC-125 and H17E2 labelled with ^{111}In or ^{123}I were evaluated prospectively for their ability to localize ovarian tumour. Forty two patients with ovarian cancer, aged 40–78 years (median = 58 years) were studied using OC-125 (n = 9), HMFG1 (n = 11) and H17E2 (n = 22). Imaging data were compared with the CT and the surgical findings. Presence of tumour was confirmed in 35/42 (83%) patients (8/9 OC-125, 10/11 HMFG1 and 17/22 H17E2) and correlated well with the conventional radiology diagnostic methods. One patient with a negative H17E2 scan and a large abdominal mass detected at laparotomy revealed a PLAP-negative tumour on immunohistochemistry. Scintigraphy revealed the presence of active disease, confirmed by laparotomy/laparoscopy in 6/8 patients considered to be in clinical remission. The sensitivity of the method was high enough and the diagnostic contribution of this approach should be further evaluated.

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Ovarian cancer is the most lethal of gynaecological cancers and accounts for 4% of all cancer diagnoses and 5% of all cancer deaths (1). At diagnosis, 60–70% of patients present with disease that has progressed outside the pelvis (stages III and IV). Patients who have disease that persists after primary platinum-based chemotherapy are generally not curable and have a median survival duration of 1 to 2 years (2, 3). After Taxol's success in second-line and upfront treatment of ovarian cancer, incorporation of new drugs, such as topotecan, etoposide, gemcitibine, etc, in second-line therapy at clinical relapse has provided the means of obtaining useful responses in terms of palliation but questionable effect in prolonging survival. Patients with pathologically documented complete remissions after initial chemotherapy have a 40–50% probability of remaining disease free at 5 years. Patients with minimal residual disease, namely ≤ 1 cm tumour deposits or positive cytology of peritoneal washings, after front-line therapy may benefit from intraperitoneal platinum-based chemotherapy (4). Invasive procedures, such as second-look laparotomy with multiple biopsies, are required to identify patients most likely to benefit from second-line treatment. Conventional radiology with CT and MRI scanning are methods that cannot reliably estimate small volume peritoneal deposits or differentiate between active and necrotic tumour nodules. Proportional decline of disease-associated markers, such as CA-125, after one or two cycles of carboplatinum has been proposed as an indirect measure of tumour response to induction chemotherapy, but at present its validity remains controversial (5). New techniques must be developed that will allow determination of the actual disease status in patients with primary or persistent ovarian cancer.

Radiolabelled anti-tumour MAbs hold promise in improving in vivo tumour diagnosis and therapy, as they have shown their ability successfully to localize on microscopic tumour deposits (6). Radioimmunoscintigraphy (RIS) of ovarian cancer lesions in patients has been performed mostly with radiolabelled MAbs HMFG1, HMFG2 (7), OC-125 (8), B72.3 B72 (9, 10) and OVTL3 (11). Monoclonal antibody-guided targeting of epithelial ovarian cancer plays an important role in the modern management of this disease (12). However, it is not known at present which type of MAb is the most efficient for RIS in ovarian cancer patients.

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In the present prospective study, we compared three different MAbs, HMFG1, OC-125 and H17E2, for radioimmunoscintigraphy in order prospectively to evaluate their diagnostic accuracy in imaging the disease in patients with ovarian cancer. Furthermore, we compared the differences between the targeting efficiency of two different radiolabels, ^{111}In and ^{123}I.

MATERIAL AND METHODS

Patient characteristics

Forty two patients with ovarian carcinoma, aged between 40 and 78 years (mean: 58 years) were studied prospectively with HMFG1 (11 patients), OC-125 (9 patients) and H17E2 (22 patients). All patients had overt disease as assessed clinically or after chest x-rays and abdominal CT. Nine out of 22 patients studied with H17E2 were in clinical and radiological complete response after initial debulking surgery, followed by cisplatin- or carboplatin-based chemotherapy, but second-look laparotomy or laparoscopy revealed the presence of minimal residual disease (usually $\leq$ 1cm $\pm$ positive peritoneal washings). The above study was approved by the Institutional Review Board and informed consent was obtained from every patient before entering the study.

Monoclonal antibodies

HMFG1. This is a murine IgG1 MAb raised against human milk fat globule membranes (MFG) and which recognizes an epitope of polymorphic epithelial mucin (PEM), a large mucin molecule (Mr $>$ 400 kDa) expressed in secretory epithelium of the breast during lactation (13) and by a wide range of carcinomas, including those of the ovary, lung (non-small cell lung cancer) and colon.

OC—125. This is a murine IgG1 MAb which reacts with the cell-surface glycoprotein CA 125 present in $>$ 80% of the non-mucinous ovarian cancer subtypes (14).

H17E2. This is a murine IgG1 MAb raised against purified placental membranes of normal-term placenta. It precipitates PLAP activity at a single band of 67 kDa consistent with the Mr of PLAP (15). This enzyme is expressed as a surface membrane antigen on many neoplasms, including 60–85% of ovarian carcinomas, as well as testicular germ-cell tumours (16).

Radiolabelling

Labelling of MAbs with ^{123}I (AERE, Harwell, UK) was performed using the iodogen method (17). Radiolabelling with ^{123}I resulted in a labelling efficiency of approximately 70–90% and a specific activity of 2–4 mCi/mg of MAb. Labelling with ^{111}In (Amersham International, UK) involved conjugation with diethylenetriamine pentaacetic acid (DTPA) by means of the cyclic anhydride (Sigma Chemical Co., UK) (18). Free ^{123}I or ^{111}In were separated by gel filtration using a sephadex G-50 column. In vitro and in vivo stability was evaluated before and after radiolabelling procedures. MAb samples as well as serum samples after antibody administration were analysed by polyacrylamide gel electrophoresis (PAGE) and autoradiography. Most of the radioactivity was found to be associated with monomeric MAbs. There was no significant aggregate formation.

All reagents produced were tested for sterility and pyrogenicity before administration to patients by an independent pharmacy laboratory and were found to be sterile and apyrogenic.

Immunoperoxidase staining

Fresh frozen tumour sections were stained by an indirect two-stage immunoperoxidase procedure (19). The concentration of the antibody was 10 μg/ml. Sections were tested against the MAbs, as well as negative controls. Positive tissues were scored when 50% or more tumour cells, seen under light microscopy, stained positive.

Imaging studies

Imaging studies were carried out using a 40-cm useful-field-of-view (UFV) gamma camera (General Electric, Maxi camera 400T and Siemens, ZLC 370S) fitted with a medium- or low-energy collimator for ^{111}In or ^{123}I, respectively. Anterior and posterior whole body scans as well as planar images were obtained. A baseline blood pool image was acquired at 5 min following the initial injection of MAbs. The sequential scans were then carried out for up to 5 days with ^{111}In and 3 days with ^{123}I-labelled MAb. Amounts of administered MAbs ranged between 250 and 800 μg. The uptake of the radiolabelled antibody by the liver was quantified using regions of interest in the whole-body scans (20).

Kinetics of radiolabelled MAbs

Blood samples were obtained at t = 0, 1 h and during the times of subsequent scans.

Immune response

HAMA response was determined by an ELISA method that has been previously described (21).

Statistical analysis

Statistical analysis of the data was carried out using the Student's t-test to compare the mean and standard deviation of each group. The threshold of significance was taken as $p < 0.05$.

RESULTS

Patients

Forty two patients with ovarian cancer were studied with HMFG1, OC-125 and H17E2. RIS results of patients investigated as well as their correlation with conventional

investigations (abdominal CT scans, ultrasound scans, laparoscopy and laparotomy) are shown in Tables 1 and 2.

Imaging studies

HMFG1 labelled with ^{123}I. Results for the 11 patients with ovarian carcinoma imaged with ^{123}I-HMFG1 MAb are presented in Table 1. Positive scans were obtained in 10 patients and there was no uptake of the antibody in sites not involved with the disease. The sensitivity of imaging with HMFG1 was 90.9%. Specificity could not be calculated since there were no true negative or false-positive cases. Tumours became visible within the first 18 h after injection of the MAb.

OC—125 labelled with ^{111}In. Results for the 9 patients studied with ^{111}In-OC-125 MAb are presented in Table 1. Positive scans were obtained in 8 patients and there was no uptake of the antibody in disease-free sites (Figs. 1 and 2). The sensitivity and specificity of imaging with OC-125 was 89%. Specificity could not be calculated since there were no true negative and false-positive cases. Best images were obtained at 48 h. In all patients studied with ^{111}In-OC-125 there was observable uptake of the radiolabelled MAb by the liver and spleen. Furthermore, some kidney uptake was usually seen at 4 h but markedly diminished later on.

H17E2 labelled with ^{111}In and ^{123} I. RIS was performed in 22 women with ovarian carcinoma, 12 with ^{123}I and 10 with ^{111}In-labelled H17E2. Positive scans were obtained in 17 patients (9 with ^{123}I and 8 with ^{111}In), compared with negative scans seen in 5 patients (Table 1). The latter included: failure to localize a large abdominal mass and a neoplastic left pleural effusion which were found to be negative for H17E2 expression by immunoperoxidase staining performed on frozen tissue specimens, no uptake of MAb by liver metastases measuring 1–2 cm on CT scan, failure to localize CT-negative residual disease (< 1 cm in diameter) detected at second-look laparotomy in two cases and technically unsatisfactory procedure due to aggregate formation of the MAb. The case with antigen-negative ovarian cancer is thus considered as a true negative, since uptake of the MAb by this tumour would have been non-specific. Therefore in 17 out of 21 cases (80%) with PLAP-positive ovarian cancer, the H17E2 MAb scan was able accurately to localize tumour deposits. In 8 out of 22 patients, conventional radiological studies (abdominal CT) were negative (sensitivity = 63%) and the H17E2 antibody scan revealed the presence of intra-abdominal disease in 6 patients, which was subsequently confirmed by laparotomy or laparoscopy. Therefore, the sensitivity and specificity of RIS by H17E2 are 81% and 100%, respectively.

The images obtained with all MAbs were of good quality without the need of computer-based image enhancement techniques. Best images were seen at 48 h after ^{111}In-labelled MAbs and 24 h after ^{123}I-labelled MAbs. In all patients studied with ^{111}In-OC-125 and ^{111}In-H17E2 there was observable uptake of the radiolabel by the liver and spleen. Uptake of the radiolabel by the liver was quantified and found to be approximately 30% of the administered dose 48 h after antibody administration. This technique is therefore unsuitable for imaging hepatic metastases. Patients studied with ^{123}I-labelled MAbs had observable uptake of the isotope by the thyroid gland and the stomach.

Kinetics

Kinetic studies were performed with HMFG1 (7 patients) and H17E2 (18 patients). Blood clearance was biphasic and $T_{\frac{1}{2}}\alpha$ ($\pm$ SD) in hours was 24.0 ± 2.8, 20.0 ± 5.0 and 26.0 ± 3.5 and $T_{\frac{1}{2}}\beta$ 58.0 ± 3.8, 30.6 ± 6.0 and 36.0 ± 4.8 for ^{123}I-HMFG1, ^{123}I-H17E2 and ^{111}In-H17E2, respectively.

Humoral immune response

None of the patients with ovarian carcinoma studied with MAbs developed HAMA within six months of continuous monitoring for that response, other than pre-existing low affinity antiglobulin reactivity.

DISCUSSION

The management of ovarian cancer still poses a challenging medical problem. The current study demonstrates that the presence of active disease in patients with ovarian cancer can be localized successfully with a high degree of accuracy using three different MAbs, HMFG1, OC-125 and H17E2.

The presence of active disease was consistently detected and correlated well with conventional diagnostic methods, particularly CT, in detecting intra-abdominal disease spread in ovarian cancer. The observed successful localization of ovarian tumours using all three different MAbs can be explained by the ability of these antibodies to bind avidly and specifically to tumours, thus resulting in a high sensitivity of the method. The observation that not all patients with active disease had positive immunolocalization studies can be explained by the heterogeneity of tumour-associated antigen expression between patients with ovarian cancer and different tumour sites in the same patient, the latter reflecting the discordance generally observed in antigen expression between primary tumour and metastatic sites.

The ultimate goal of using RIS in ovarian cancer would be to detect residual disease after chemotherapy and thus direct decisions about second-line therapy, which is still at experimental stage. Given that new drugs, such as taxanes and camptothecins, exhibit high activity in relapsed disease and possible prolongation of survival (1), it would be ideal to define by non-invasive means, after a standard induction course, those patients with small volume residual disease who would be most likely to benefit from treatment, before overt clinical relapse becomes evident. How-

Table 1

Clinical and histopathological characteristics, results of conventional radiological investigations and findings of RIS using ^{123}I or ^{111}In-labelled H17E2, HMFG1 and OC-125 monoclonal antibodies

Patient	Histology stage	Mabs	Conventional investigations surgery	RIS	Correlation of findings
1.	Cystadenoca-IIIa	^{123}I-H17E2	Ascites, pelvic mass, doubtful mass in liver	Diffuse and focal uptake in left lower abdomen, no uptake in liver	+
2.	Cystadenoca-IIc	^{111}In-H17E2	Left ovarian cyctic mass 5 cm	Uptake in left pelvis	+
3.	Adenoca-IIIa	^{111}In-H17E2	CT−,+washings at laparoscopy	Uptake in small (0.5 cm) abdominal nodule	+
4.	Cystadenoca-IIb	^{111}In-H17E2	Large pelvic mass	Intense uptake in pelvis	+
5.	Adenoca-IIIb(PLAP-)	^{111}In-H17E2	Large abdominal mass, left pleural effusion	Abdomen and chest −	−
6.	Cystadenoca-IIIb	^{111}In-H17E2	Tumour deposits 1–2 cm found diffusely in abdomen	Aggregate formation, bad procedure	−
7.	Adenoca-IIIc	^{111}In-H17E2	Diffuse disease in abdomen	Diffuse uptake in abdomen	+
8.	Adenoca-IIb	^{111}In-H17E2	Mass in right iliac fossa	Mass in right iliac fossa	+
9.	Cystadenoca-IIIb	^{111}In-H17E2	No radiological abnormality, small tumour nodules (<2 cm) at 2nd LL	Diffuse uptake in pelvis up to the right peritoneal reflection/aortic bifurcation	+
10.	Adenoca-IIIa	^{111}In-H17E2	Pelvic mass ≤2 cm, CT+	Uptake in pelvic mass	+
11.	Cystadenoca-IIIc	^{111}In-H17E2	Ascites, pelvic mass, CT+	Uptake in pelvic mass	+
12.	Adenoca-IIb	^{123}I-H17E2	Pelvic mass 2 cm, CT−	Uptake in pelvic mass	+
13.	Adenoca-IIIb	^{123}I-H17E2	CT−, RD<1 cm at 2nd LL	Uptake in nodules, pelvis	+
14.	Adenoca-IIIc	^{123}I-H17E2	CT−, RD<1 cm at 2nd LL	Uptake in nodules	−
15.	Cystadenoca-IIb	^{123}I-H17E2	Mass in pelvis	Uptake in pelvis, abdomen	+
16.	Adenoca-IIIa	^{123}I-H17E2	CT−, RD<1 cm at 2nd LL	No uptake	−
17.	Adenoca-IIIa	^{123}I-H17E2	Washings+, nodule <1 cm at 2nd LL, CT−	Uptake in nodule	−
18.	Cystadenoca-IIIc	^{123}I-H17E2	RD at 2nd LL (<1 cm), CT–	–	+
19.	Adenoca-IV	^{123}I-H17E2	Hepatic metastases (1–2 cm)	No uptake	+
20.	Cystadenoca-IIIa	^{123}I-H17E2	Left ovary, uterus, omentum, right external lymph nodes	Diffuse uptake in abdomen, focal in pelvis	+
21.	Adeno-IIIa	^{123}I-H17E2	Pelvic mass ≤2 cm, CT+	Uptake in pelvic mass	−
22.	Adenoca-IIIb	^{123}I-H17E2	Mass in left sacroiliac region	Focal uptake in left pelvis	+
23.	Adenoca-IV	HMFG1	Abdominal and lung metastases	Abdomen and lung +	+
24.	Adenoca-IV	HMFG1	Abdominal and lung metastases	Abdomen −, Lung +	+
25.	Adenoca-IIb	HMFG1	Pelvic disease	Pelvis +	+
26.	Adenoca-IIb	HMFG1	Pelvic disease	Pelvis +	
27.	Adenoca-IIIa	HMFG1	Abdominal and pelvic deposits	Abdomen and pelvis +	+
28.	Adenoca-IIIa	HMFG1	Widespread tumour in the abdomen	Abdomen +	+
29.	Adenoca-IIIb	HMFG1	Widespread tumour in the abdomen	Abdomen +	+
30.	Adenoca-IV	HMFG1	Abdomen and pleural effusion	Pleura and abdomen +	+
31.	Adenoca-IV	HMFG1	Abdominal and lung metastases	Lung and abdomen +	+
32.	Adenoca-IV	HMFG1	Lumbar spine and lung metastases	Lung and abdomen +	+
33.	Adenoca-IIIb	HMFG1	Intra-abdominal mass	Intra-abdominal mass	+
34.	Adenoca-IIIb	^{111}In-OC125	Pelvic mass	Uptake in pelvic mass	+
35.	Cystadenoca-IIIc	^{111}In-OC125	Pelvic mass	Uptake in pelvic mass	+
36.	Cystadenoca-IIIc	^{111}In-OC125	Pelvic mass	Uptake in pelvic mass	+
37.	Adenoca-IV	^{111}In-OC125	Left supraclavicular mass, skull+, CT+	Uptake	+
38.	Adenoca-IIb	^{111}In-OC125	Pelvis mass <2 cm, CT+	Uptake in pelvic mass	+
39.	Adenoca-IIIb	^{111}In-OC125	Pelvis cystic mass, CT+	Uptake in pelvic mass	+
40.	Cystadenoca-IIIc	^{111}In-OC125	Diffuse disease in abdomen	Diffuse uptake in abdomen	+
41.	Adenoca-Iib	^{111}In-OC125	Pelvis mass <2 cm	No uptake	−
42.	Adenoca-IIIb	^{111}In-OC125	Pelvis mass, CT+	Uptake in pelvis	+

Adenoca = adenocarcinoma; Cystadenoca = cystadenocarcinoma; 2nd LL = second-look laparotomy; RD = residual disease.

Table 2

RIS result analysis

	OC-125 (n = 9)	HMFG1 (n = 11)	H17E2 (n = 22)
True (+)	8	10	17
False (+)	0	0	0
True (–)	0	0	1
False (–)	1	1	4
Sensitivity (%)	88.9	90.0	80.9

ever, as is apparent from the present study, this may not always be feasible, because of the possibility of missing small volume (< 1 cm) disease and disease detected by peritoneal washing cytology. Therefore a solution to that problem would be to perform RIS, and to subject those patients who are negative by RIS to laparoscopy and peritoneal washing procedure. Another aspect of using RIS would be in the context of interval debulking surgery. The latter procedure has gained momentum after showing improved outcome for patients undergoing surgical cytoreduction after three courses of chemotherapy (22).

In this study, RIS was proved to be more sensitive than conventional diagnostic imaging methods. Abdominal CT scan is not a sensitive method for evaluating tumour extension across peritoneal surfaces, a pattern of spread that is seen in the majority of ovarian cancer cases. It is also standard practice not to rely on abdominal CT scan as a guide to decisions concerning second-line treatment. However, even with RIS a proportion of patients with active disease (17%) were not successfully detected even though HMFG1 and OC-125 showed greater sensitivity than H17E2 in a non-randomized prospective comparison within the present study. This apparent difference could be explained

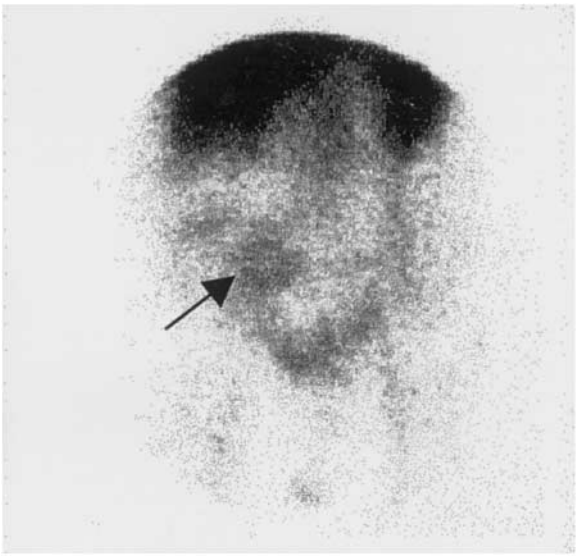

Fig. 1. ^{111}In-labelled OC-125 MAb scan 48 h after injection shows uptake in a pelvic mass caused by ovarian carcinoma.

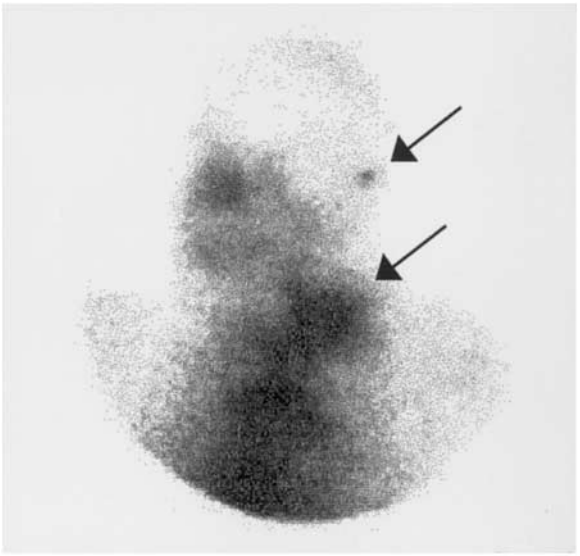

Fig. 2. ^{111}In-labelled OC-125 MAb scan at 48 h post-injection showing a high uptake of the radiopharmaceutical in a large superclavicular mass as well as a focal site in the skull, secondary to ovarian carcinoma.

by the fact that patients studied with HMFG1 and OC-125 carried a higher tumour burden as evidenced by the high detection rate after applying clinical or conventional radiological investigations. RIS using H17E2 was addressed in a group of patients bearing a smaller tumour burden as 11 of the 22 patients had only surgically detectable disease. In addition, one of these patients, being negative by RIS, had a non-PLAP expressing tumour. Therefore, the specificity with H17E2 RIS would be higher if that case was excluded. Furthermore, one case with hepatic metastases detected by CT showed negative results with MAb targeting. Abdominal CT scan is well acknowledged for its high specificity in detecting liver metastases. A limitation of RIS is the intense non-specific liver uptake when using ^{111}In-labelled MAbs, thus carrying the potential to complicate interpretation in the presence of liver metastases and therefore an alternative approach would be to use ^{123}I-labelled MAbs instead. This finding is in agreement with our previous experience where ^{111}In-labelled MAbs were used for the diagnosis of germ-cell tumours (23). In fact, very few patients with ovarian cancer present or develop intrahepatic metastases, with direct expansion to the serosal peritoneal surface of the liver being the usual pattern of metastatic spread.

The issue of non-specific MAb uptake by the tumour, raised in previous studies of our group (20, 24) was not adequately addressed in the present study. However, indirect evidence that non-specific MAb uptake was not a problem was indicated by the absence of H17E2 MAb uptake in one patient with PLAP-negative ovarian tumour.

MAb scans can also be used as an adjuvant to other conventional methods in patients where there is uncertainty about disease status, such as in patients with elevated tumour marker levels but no evidence of disease on

imaging studies, and to determine whether an ovarian cyst, detected by non-invasive imaging and/or pelvic examination is likely to be malignant or benign. In addition, MAb scans can also serve to reduce the unacceptably high false-positive rates reported in the ovarian cancer screening literature (25, 26). Furthermore, RIS can contribute to preparing patients for surgery and in determining the surgical technique to be used (i.e. laparoscopy or laparotomy). However, further improvement in the sensitivity of the radioimmunoconjugates is needed before they can replace surgical techniques for the detection of recurrent disease. Antibody fragments $F(ab')_2$, Fab or single chain Fv domains may show better accessibility profiles and provide improved tumour to normal tissue ratios, thus allowing for improved RIS results.

In conclusion, MAb-guided imaging using three different MAbs has demonstrated improved targeting of ovarian cancer resulting in a highly sensitive and specific method. Since these tumours represent a potentially curable disease, MAb scanning could contribute mainly to accurate staging and localization of active disease after chemotherapy and to monitoring for the presence of recurrent disease. However, the diagnostic contribution of this approach should be further evaluated by performing a prospective study in a large number of patients. Future studies should also include more patients without evidence of disease, in order to provide more meaningful estimates of specificity.

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