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# The Use of Monoclonal Antibody B72.3 in the Management of Gynecologic Malignancies

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Monoclonal antibodies are currently used in the diagnosis of gynecologic malignancies by way of immunohistochemical assays, serum assays, and in situ radiolocalization of carcinoma lesions. Among them is MAb B72.3, generated against a human tumor-associated antigen (TAG-72). Using immunohistochemical techniques, MAb B72.3 has shown reactivity with 100 percent of common epithelial ovarian carcinomas and endometrial carcinomas and non-reactivity with normal adult tissues, with the exception of normal secretory endometrium. B72.3 appears to be a valuable immunocytologic adjunct, with greater than 90 percent of effusions and fine-needle aspiration biopsies from gynecologic carcinomas showing reactivity. Using a serum assay developed to detect the presence of the TAG-72 antigen, 48 percent of patients with ovarian carcinoma demonstrated TAG-72–positive sera versus 1 percent of control sera. $^{131}$I-labeled MAb B72.3 IgG and gamma scanning have been used for the in situ detection of metastatic carcinoma. Twelve of 15 patients with ovarian carcinoma showed positive gamma scans, and approximately 80 percent of the lesions demonstrated specific localization of the antibody. These studies indicate the potential utility of MAb B72.3 in the diagnosis of gynecologic carcinoma.

## INTRODUCTION

Endometrial and ovarian carcinoma together are responsible for 19 percent of all malignancies in women, with 39,000 and 18,000 new cases diagnosed each year, respectively. Ovarian carcinoma is the fourth most frequent cause of cancer death in women, and the leading cause of gynecologic cancer death in the U.S. [1], despite recent advances in therapy [2]. Prognosis is critically dependent on the clinical and surgical stages of the disease. Initial detection is often delayed because of the asymptomatic nature of the disease; tumors have metastasized either regionally or intraperitoneally in two-thirds of all cases at the time of initial diagnosis [2].

The use of immunoglobulins in the diagnosis of gynecologic carcinoma may be divided into three main areas: *(a)* immunohistochemical and immunocytochemical assays, *(b)* serum assays, and *(c)* the use of radiolabeled monoclonal antibody (MAb) to detect carcinoma lesions in situ. Several MAbs reactive with various tumor-associated antigens (TAA) have demonstrated reactivity with gynecologic cancers, including ovarian, endometrial, and cervical neoplasms [3–8]. Some of the more extensively characterized monoclonal antibodies that show reactivity to ovarian carcinoma are shown in Table 1. Some of these antibodies react preferentially with tumors of non-mucinous epithelial origin and others react preferentially with mucinous ovarian



*Abbreviations:* ABC: avidin-biotin complex cpm: counts per minute FNAB: fine-needle aspiration biopsy MAb: monoclonal antibody RI: radiolocalization index TAA: tumor-associated antigen TAG: tumor-associated glycoprotein

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TABLE 1
Monoclonal Antibodies Reactive with Human Ovarian Carcinoma

| Monoclonal Antibody | Reactive Antigen (molecular weight) | Reference |
|---|---|---|
| OC125 | >200 K | [6,8,23] |
| CA19-9 | GICA[a] | [11] |
| $ID_3$,$ID_5$ | Unk | [9] |
| OC133 | 80 K | [8] |
| B72.3 | >$10^6$K TAG-72 | [3,19] |
| HMFG1<br>HMFG2 | HMW gp<br>80–400 K | [15] |
| OVB3 | Unk | [10] |
| HB21 | Human TFR$\alpha$[b] | [18] |
| 454A12 | Human TFR | [17] |
| 454C11<br>260F9<br>280D11<br>245E7 | Unk | [16] |
| MOv1<br>MOv2 | Unk | [12] |
| MOv16<br>MOv18<br>MOv19 | 48–50 K<br>38–40 K<br>38–40 K | [14] |

[a]Glycoprotidic antigen
[b]Transferrin receptor
Unk: Unknown

carcinomas. Of the former, OC125 reacts with virtually all ovarian carcinoma cell lines tested, more than 80 percent of non-mucinous epithelial ovarian carcinomas, and one of 12 non-ovarian neoplastic cell lines [6]. OC125 appears to demonstrate cell surface binding to an antigen that exhibits better than 90 percent correlation with disease regression or progression.

MAb OC133 detects a separate antigen and binds predominately to serous ovarian neoplasms [9]. It is reactive with endometrium and endocervix but not with normal ovary or fallopian tube. Antibodies $ID_3$ and $ID_5$ are representative of the group of antibodies reacting with mucinous ovarian carcinoma; these two antibodies bind to extracts of undifferentiated mucinous ovarian carcinoma but not to those extracts tested of normal ovary, human serum, benign mucinous tumors, non-epithelial ovarian carcinomas, or other malignant neoplasms [10]. MAb OVB3 raised against OVCAR-3 cells shows reactivity with both mucinous and serous cystadenocarcinoma (but not normal ovary) and reacts with 4/4 human ovarian cancer cell lines [11]. MAb anti-carbohydrate 19-9 (anti-CA 19-9) also reacts with both mucinous and serous ovarian carcinomas [12]. Two MAbs (MOv1 and MOv2) were generated, using a membrane preparation of a mucinous ovarian cystadenocarcinoma [13]. MOv2 reacts with the vast majority of mucinous, serous, and endometrioid carcinomas, as well as benign serous and mucinous cystadenomas and some normal epithelia [14]. Using a

TABLE 2
MAb B72.3 Reactivity with Formalin-Fixed Specimens of Human Neoplasia[a]

| Organ | Histologic Tumor Type | No. Reactive/ No. Tested (%) | >20% Reactive Malignant Cells (%)[b] |
|---|---|---|---|
| Ovary | Serous cystadenocarcinoma | 32/32 (100) | 16/32 (50) |
| | Mucinous cystadenocarcinoma | 14/14 (100) | 10/14 (71) |
| Uterus | Endometrial carcinoma | 32/32 (100) | 26/32 (81) |
| Lung | Squamous cell carcinoma | 3/3 (100) | 1/3 |
| | Adenocarcinoma | 28/29 (97) | 20/29 (69) |
| | Large cell carcinoma | 1/1 | 0/1 |
| Colon | Adenocarcinoma | 51/54 (94) | 23/54 (43) |
| Breast | Invasive ductal carcinoma | 37/44 (84) | 12/44 (27) |

[a]Adapted from [22]
[b]Numbers in parentheses show percentage.

poorly differentiated ovarian carcinoma as immunogen, MAbs MOv16, MOv18, and MOv19 were generated [15]; the latter two show restricted specificity for ovarian carcinomas and cystadenomas.

Several MAbs originally directed against human breast cancer have shown cross-reactivity with human ovarian neoplasms. For example, HMFG1 and HMFG2, directed against a component of human milk fat globule membranes, react strongly with adenocarcinoma of the ovary [16]. Four MAbs originally obtained against human breast cancer cells, 260F9, 454C11, 280D11, and 245E7, also cross-react with ovarian carcinoma cell lines[17]. MAb 454A12 [18] and MAb HB21 [19], directed against human transferrin receptor, have been conjugated to toxins and show anti-ovarian tumor activity *in vitro* [19], using OVCAR cell lines and in a nude mouse model [18].

Monoclonal antibody B72.3 [20] was developed by the immunization of mice with membrane-enriched fraction of a metastatic breast carcinoma. It has demonstrated reactivity with a mucin-like molecule of high molecular weight [21], termed tumor-associated glycoprotein (TAG-72). MAb B72.3 has been reacted with a variety of human adult and fetal tissues, using avidin-biotin-complex (ABC) immunohistochemical techniques to evaluate the expression of the reactive TAG-72 antigen [22]. Using formalin-fixed, paraffin-embedded tissues or frozen sections, MAb B72.3 has demonstrated reactivity with several types of carcinoma (Table 2), including most common epithelial ovarian carcinomas, endometrial carcinomas, colorectal adenocarcinomas, carcinomas of the breast, and non-small cell lung carcinomas, as well as the majority of pancreatic and gastric carcinomas [22,23]. CA-125, an antigen first identified in an ovarian carcinoma cell line [6], can be detected using MAb OC125 with frozen sections in the majority of non-mucinous ovarian carcinomas [24]. Using frozen tissue sections and modified ABC-immunoperoxidase techniques, Thor et al. demonstrated that MAb B72.3 and MAb OC125 recognize distinct antigenic determinants and are non-coordinately expressed [3]. MAb B72.3 is minimally or non-reactive with benign lesions of the colon, breast, and ovary or with a variety of normal adult tissues [22]. An exception is the reaction of MAb B72.3 with normal secretory endometrium (detailed below, [23]). The pancarcinoma distribution of TAG-72 and lack of significant

TABLE 3
MAb B72.3 Reactivity with Malignant Ovarian Tumors[a]

| Histologic Tumor Type | No. Reactive/ No. Tested (%) | >25% Reactive Malignant Cells (%)[b] |
|---|---|---|
| Serous cystadenocarcinoma | | |
| Primary tumors | 32/32 (100) | 16/32 (50) |
| Metastatic tumors | 16/30 (53) | 13/30 (43) |
| Mucinous cystadenocarcinoma | | |
| Primary tumors | 14/14 (100) | 10/14 (71) |
| Metastatic tumors | 7/7 (100) | 6/7 (86) |
| Undifferentiated carcinomas | | |
| Primary tumors | 8/8 (100) | 3/8 (38) |
| Metastatic tumors | 5/6 (83) | 2/6 (33) |
| Endometrioid carcinoma | | |
| Primary tumor | 1/1 | 0/1 |
| Metastatic tumor | 1/1 | 1/1 |
| Clear cell carcinoma, primary | 1/1 | 0/1 |
| Malignant Brenner tumor, primary | 1/1 | 0/1 |

[a]Adapted from [3]
[b]Numbers in parentheses show percentage.

reactivity of MAb B72.3 with normal adult tissues suggest its potential diagnostic and therapeutic use in the management of gynecologic carcinomas.

## REACTIVITY OF MAb B72.3 WITH OVARIAN NEOPLASMS

The immunoreactivity of MAb B72.3 with epithelial ovarian neoplasms (accounting for 80–90 percent of all ovarian neoplasms) has been well characterized [3]. Various histologic types of malignant ovarian tumors were reacted with purified immunoglobulin preparations of MAb B72.3, using the ABC immunohistochemical technique [25]. All 57 primary and 41 of 44 metastatic common epithelial tumors contained tumor cells that were immunoreactive with MAb B72.3. The percentages of cellular reactivity for epithelial tumors ranged from 1 to 100 percent for primary tumors and from 0 to 95 percent for metastatic lesions (Table 3). Of the epithelial tumors examined, 80 percent of primary and 75 percent of metastatic tumors demonstrated 5 percent or more reactive cells, whereas strong reactivity ($\geq$25 percent of malignant cells reactive) was present in approximately half of primary and metastatic carcinomas (Table 3). Mucinous cystadenocarcinomas demonstrated the most cellular expression of TAG-72, with 71 percent of primary and 86 percent of metastatic tumors showing strong cellular reactivity. Serous cystadenocarcinomas were less reactive, with 50 percent of primary and 43 percent of metastatic tumors demonstrating strong cellular reactivity. Less frequent common epithelial tumor types, including undifferentiated, endometrioid, and clear cell carcinomas were the least reactive, although 100 percent of primary and 86 percent (six of seven) of metastatic tumors demonstrated cellular expression of TAG-72.

Some heterogeneity of TAG-72 expression was noted between primary and metastatic masses, among various metastases, and within single tumor masses. There was no strict correlation between the percentage of cellular reactivity with MAb B72.3 and

TABLE 4
Monoclonal Antibody B72.3 Reactivity with Endometrial Adenocarcinoma[a]

| Clinicopathologic Parameter[b] | No. Reactive/ No. Tested | >75% Reactive Malignant Cells |
|---|---|---|
| Endometrial carcinoma ($n$ = 32) | 32/32 | 19/32 |
| Depth of invasion | | |
| endometrium | 3/3 | 2/3 |
| 1/3 myometrium | 8/8 | 6/8 |
| >1/2 myometrium | 4/4 | 3/4 |
| to serosa | 2/2 | 1/2 |
| Histologic tumor grade | | |
| I | 8/8 | 3/8 |
| I–II | 4/4 | 2/4 |
| II | 9/9 | 7/9 |
| II–III | 2/2 | 2/2 |
| III | 4/4 | 1/4 |
| Patient Age | | |
| <50 | 4/4 | 0/4 |
| 51–59 | 7/7 | 4/7 |
| 60–69 | 7/7 | 4/7 |
| 70–79 | 7/7 | 5/7 |
| >80 | 2/2 | 2/2 |

[a]Adapted from [23]
[b]Where available

the degree of histologic differentiation for either serous or mucinous cystadenocarcinomas. There was a trend, however, for those tumors that were least differentiated (assigned to the undifferentiated tumor category) to show the lowest cellular reactivity with MAb B72.3 in both primary and metastatic sites [3]. Synchronous metastases from 19 of 20 cases showed similar levels of TAG-72 as in the primary epithelial neoplasm [26].

## REACTIVITY OF MAb B72.3 vs. ENDOMETRIAL NEOPLASMS

The expression of TAG-72 in endometrial carcinomas [23] was studied using MAb B72.3 and a modification of ABC immunoperoxidase methods [25]. Thirty-two of 32 cases of endometrial adenocarcinoma were reactive, although heterogeneity in the expression of TAG-72 by malignant epithelial cells was observed. These cases could be separated into two groups, based on percentage of cellular reactivity: nineteen cases showed >75 percent cellular reactivity, and 13 cases showed reactivities between 1 and 50 percent. There was no striking correlation between percentage of cellular reactivity with MAb B72.3 and depth of tumor invasion, histologic tumor grade, or patient age (Table 4).

Secretory endometrium has also been shown to react with MAb B72.3, whereas proliferative phase specimens were negative [22]. This observation prompted a more detailed study of normal endometrial reactivity to help define which physiologic conditions might regulate TAG-72 expression [23]. As shown in Table 5, all 38 post-ovulatory (secretory) specimens showed cellular reactivity with MAb B72.3 with an average percentage of reactivity of 40.8 ± 28.6 percent. The average percentage

TABLE 5
MAb B72.3 Reactivity with Normal Endometrium[a]

| Endometrial Phase | No. Reactive/ No. Tested | >25% Reactive Cells |
|---|---|---|
| Proliferative endometrium ($n$ = 7) | | |
| (day 7–13) | 0/7 | 0/7 |
| Secretory endometrium ($n$ = 38) | | |
| (day 16–20) | 6/6 | 3/6 |
| (day 21–24) | 22/22 | 13/22 |
| (day 25–28) | 10/10 | 8/10 |
| Resting endometria from post-menopausal patients ($n$ = 10) | 0/10 | 0/10 |

[a]Adapted from [23]

of cellular reactivity was not statistically different in the early, middle, or late post-ovulatory samples. Middle to late proliferative phase endometria ($n$ = 7) failed to demonstrate reactivity with MAb B72.3. Ten resting endometria from post-menopausal women failed to react with MAb B72.3.

## THE USE OF MAb B72.3 AS AN ADJUNCT IN THE IMMUNOCYTOLOGIC DIAGNOSIS OF GYNECOLOGIC CARCINOMA

The vast majority of immunocytochemical studies in clinical cytology have been applied to specimens of serous effusions and fine-needle aspiration biopsies (FNAB). These types of specimens are likely to contain cancer cells in a significant proportion of cases [27–29]. When compared to other types of cytologic specimens, effusions and FNABs are notorious for the pitfalls that may be encountered in their interpretation. Effusions may contain reactive but benign mesothelial cells, which may mimic cancer cells. If malignant cells are present, recognition of their origin may be impossible by conventional morphological analysis alone. FNABs may also present significant limitations and diagnostic problems in spite of their current effectiveness and accuracy when interpreted in experienced laboratories. The type of specimen obtained from an FNAB has features of both a tissue section from an open biopsy and purely exfoliated cells. Thus the diagnostic problems posed by an undifferentiated malignant neoplasm in a histologic section may become even more difficult in a fine-needle aspirate.

MAb B72.3 has demonstrated utility as an immunocytologic adjunct to diagnosis of carcinoma in cell block and cytocentrifuge preparations of human serous effusions, with selective reactivity for tumor cells (particularly adenocarcinoma) over reactive mesothelium [30,31]. Using the ABC-immunoperoxidase method on formalin-fixed, paraffin-embedded cell blocks, MAb B72.3 detected tumor cells in 97 percent of effusions from patients with ovarian serous cystadenocarcinoma (Table 6). Ninety-three percent of carcinomas of the uterus and cervix reacted with B72.3, including all 38 endometrial carcinomas (Table 6). In addition, MAb B72.3 detected tumor cells in effusions from the majority of patients with adenocarcinoma, including those from lung (non-small cell), breast, and gastrointestinal tract. In contrast, 821 benign effusions showed no reactivity with MAb B72.3 (Table 6).

MAb B72.3 has also been used with FNABs and corresponding surgically excised tumors to determine cellular reactivity [29,31]. Positive staining with MAb B72.3 was observed in 91 percent (10 of 11) of FNABs from ovarian serous cystadenocarcinomas;

TABLE 6
Summary of Immunoreactivity of Effusions and FNABs with MAb B72.3[a]

| Lesion | Reactivity of Effusion: No. Reactive/ No. Tested (%) | Reactivity of FNAB: No. Reactive/ No. Tested (%) |
|---|---|---|
| Ovary | | |
| Adenocarcinoma | 110/113 (97) | 10/11 (91) |
| Uterus and cervix | 40/43 (93) | 32/35 (91) |
| Lung | | |
| Benign lesions | | 0/99 (0) |
| Non-small cell carcinoma | 36/40 (90) | 145/157 (92) |
| Breast | | |
| Benign lesions[b] | | 0/10 (0) |
| Adenocarcinoma | 43/46 (93) | 40/44 (91) |
| Gastrointestinal tract | 14/17 (82) | 36/41 (88) |
| Miscellaneous benign aspirates | | 0/326 |
| Benign effusions | 0/821 | |

[a]Adapted from [31]
[b]Excluding apocrine metaplasia

32 of 35 (91 percent) carcinomas of the uterus and cervix, including all 30 endometrial adenocarcinomas, demonstrated reactivity with MAb B72.3. In addition, positive staining with MAb B72.3 was observed in FNABs from the majority of carcinomas from the lung (non-small cell), breast, and gastrointestinal tract, whereas most benign lesions showed no staining (Table 6). In many cases, tumor-bearing tissue had also been resected and was available for comparative examination with MAb B72.3. In more than 90 percent of these cases, the staining pattern of tumor cells in the FNABs was predictive of antibody reactivity in the comparable surgically resected tumors. From these studies, we concluded that MAb B72.3 may be used as an adjunct for the diagnosis of neoplasms in effusions and FNABs.

## THE USE OF AN MAb TO DISTINGUISH OVARIAN CARCINOMA FROM COLORECTAL CARCINOMA

The distinction between primary ovarian carcinomas and metastatic carcinoma to the ovary from another site may be difficult using clinical, surgical, and pathologic criteria. Cancers which commonly metastasize to the ovary include carcinoma of the breast, gastrointestinal tract, and genital tract [32]. MAb COL-4, reactive with carcinoembryonic antigen, has been shown to react preferentially with adenocarcinomas of the colon versus a variety of normal tissues [33]. Using ABC-immunoperoxidase techniques, Thor et al. [34] demonstrated differential reactivity of MAb COL-4 with colon carcinoma versus ovarian carcinoma (Table 7). COL-4 reacted with the vast majority of primary ($n = 50$) and metastastic ($n = 62$) colonic carcinomas. In contrast, MAb COL-4 demonstrated little or no reactivity with primary ($n = 53$) and metastatic ($n = 23$) carcinomas of the ovary using $\geq 10$ percent reactive cells as an arbitrary criterion (Table 7). Hence MAb COL-4 can be used as an immunohistochemical adjunct for the differentiation of ovarian from gastrointestinal adenocarcinomas.

TABLE 7
Reactivity of Human Colon and Ovarian Carcinoma with MAb COL-4[a]

| Lesion | No. Reactive/ No. Tested (%)[b] | >10% Reactive Malignant Cells (%) |
|---|---|---|
| Colon Carcinoma | | |
| Primary | 49/50 (98) | 35/50 (70) |
| Regional metastases | 40/42 (95) | 27/42 (64) |
| Distant metastases | 19/20 (95) | 11/20 (55) |
| Ovarian Carcinoma | | |
| Primary | 9/53 (17) | 1/53 (2) |
| Metastatic | 6/23 (26) | 1/23 (4) |

[a]Adapted from [34]
[b]Numbers in parentheses show percentage.

## DETECTION OF TAG-72 IN SERA OF CARCINOMA PATIENTS

Serum assays employing specific MAbs may be useful in detecting occult carcinoma, monitoring the efficacy of standard therapy, and identifying potential patients for therapy with a specific MAb. A rigorous effort is under way to identify TAAs that can lead to the detection of early ovarian carcinoma, because most patients currently are diagnosed when they already have advanced disease. Several serum assays for ovarian TAA are currently in use, including CEA, CA125, CA15-3 [1,35], and human placental alkaline phosphatase [36].

Serum assays for the detection of CA125 have been shown to be a sensitive marker for the presence of non-mucinous ovarian tumors [35]. Using a value of >65 U/ml, Soper et al. [37] have shown a sensitivity of 90 percent; however, 7 of 47 (15 percent) patients with benign pelvic masses had elevated (>65 U/ml) CA125 in their serum (see below).

An immunoradiometric assay has been developed using MAb B72.3 to quantitate TAG-72 in human serum [38]. In a simultaneous immunoradiometric assay, the mean TAG-72 concentration in 1,099 serum samples from healthy blood donors was 1.83 ± 2.03 U/ml. An upper limit of normal of 10 U/ml included 99 percent of healthy blood donors. There was no significant ($p < 0.06$) effect of sex upon TAG-72 levels in the blood donor group in which age and sex were known ($n = 675$). This is important in light of the strong expression of TAG-72 by secretory endometrium. Nine of 19 (47 percent) patients with ovarian carcinoma demonstrated TAG-72 positive serum samples; the average TAG-72 level in ovarian carcinoma patients was 65.42 U/ml. Only four of 101 (4 percent) serum samples from patients with benign gastrointestinal disease were elevated, whereas 15 of 26 (58 percent) and 14 of 25 (56 percent) sera from patients with rectal and colon carcinoma, respectively, were positive. The ability of this assay to discriminate between malignant and benign disease suggests its further evaluation for monitoring patients with known or suspected carcinoma [38], either alone or in combination with preexisting assays.

Soper et al. [37] used the combination of CA125 and TAG-72 serum levels to detect non-mucinous ovarian tumors; 46 percent (18 of 39) of patients with malignant disease had positive levels (>10 U/ml) of TAG-72 and only 2 percent of patients with benign pelvic disease had positive serum levels of TAG-72. When TAG-72 was used in combination with CA125, the specificity was increased to 98 percent.

A prospective study [39] using the combination of TAG-72 and CA125 is currently being conducted on 5,000 apparently healthy women to determine whether use of a combination of markers might permit cost-effective screening for occult malignancy in an apparently healthy population.

## USE OF RADIOLABELED MAb B72.3 FOR THE LOCALIZATION OF METASTATIC CARCINOMA

Studies have demonstrated that radiolabled MAbs to TAAs can detect carcinoma lesions using gamma scanning. These studies were conducted using MAbs to carcinoembryonic antigen. MAbs 1083-17-1A and 19-9, and MAbs to human milk fat globule membranes [40–51].

The administration of $^{131}$I-labeled B72.3 in patients with colorectal carcinoma and the quantitative evaluation of its reactivity with tumor versus a wide range of normal tissues has been recently reported [52]. Gamma scanning followed by a comprehensive direct examination of tumor and a variety of normal tissues was achieved. Specimens were weighed and placed in a gamma counter to determine counts per minute (cpm) per gram values. Fixed biopsy specimens were analyzed for *(a)* percentage of tumor cells present and *(b)* TAG-72 antigen-positive cells using MAb B72.3 and ABC-immunoperoxidase techniques. Positive gamma scans (confirmed at surgery) were observed in 14 of 27 patients and in 10 of 20 patients in whom direct examination of tissues was available. This result is rather promising considering that $^{131}$I was used, since this isotope is not optimal for gamma scanning. Gamma scans accurately identified tumor lesions in the liver, bone, orbit, rectum, colon, cecum, pelvis, and diffusely in the peritoneal cavity. No anaphylaxis, serum sickness, bone marrow suppression, or other toxicity was observed [52].

The radiolocalization index (RI) value is defined as the ratio of the uptake of $^{131}$I-labeled MAb per gram of tumor to that of histologically confirmed normal tissue; average values (cpm per gram) from biopsy of normal liver and/or normal intestinal tissue of each patient were normalized to 1.0. RI values $\geq 3$ were arbitrarily considered as "positive" for these studies. At least one tumor lesion in 17 of 20 of the colorectal cancer patients studied had an RI $\geq 3$. In eight of these patients, all 50 tumor lesions biopsied had RI $\geq 3$. In total, 99 of 142 (70 percent) carcinoma lesions biopsied showed RI values $\geq 3$. Of 210 histologically confirmed normal tissues biopsied, 198 had negative ($\leq 3$) RI values [52].

Martin et al. have used a hand-held, gamma-detecting probe intraoperatively to detect carcinoma lesions following an intravenous administration of $^{125}$I-labeled B72.3 [53]. Positive probe counts were detected in 47 of 66 patients (71 percent) with various carcinomas, including ovarian carcinoma.

Salvatore et al. [54] performed radioimmunoscintigraphy following intravenous injection of either $^{131}$I- or $^{111}$In-labeled B72.3 on a variety of patients with primary or metastatic carcinoma. Twelve of 15 patients with ovarian carcinoma showed positive gamma scans, with 27 of 33 carcinoma lesions detected (82 percent).

## INTRAPERITONEAL ADMINISTRATION OF RADIOLABELED MAb B72.3 AND TARGETING OF CARCINOMA IMPLANTS

Recent studies were conducted to *(a)* determine the feasibility of intraperitoneal administration of radiolabeled B72.3 for peritoneal tumor localization, *(b)* compare tumor localization of intravenously versus intraperitoneally administered MAb by the

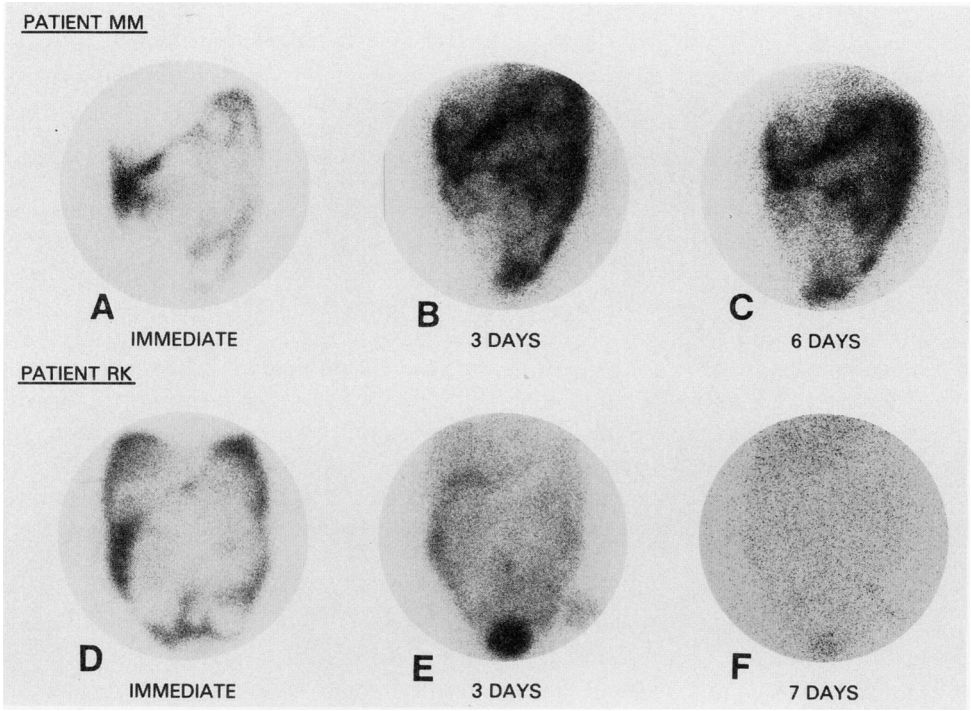


FIG. 1. Radioimmunoscintigraphy in patients with metastatic colorectal cancer after intraperitoneal administration of $^{131}$I-B72.3 IgG [55]. Two patients were scanned immediately after antibody administration and at various times. A positive scan is seen in patient MM, where $^{131}$I-B72.3 localizes peritoneal implants. In patient RK, no peritoneal tumor is present and there is no MAb localization observed. Both patients show accumulation of radiolabeled MAb in the peritoneal gutters immediately after intraperitoneal MAb administration and in the bladder at three days after intraperitoneal administration.

stimultaneous administration of $^{125}$I-labeled B72.3 intravenously, and $^{131}$I-labeled B72.3 intraperitoneally, and *(c)* define the pharmacokinetics of plasma clearance of both intraperitoneally and intravenously administered radiolabeled MAb B72.3.

All patients were part of a pre-existing NCI Surgery Branch protocol for the surgical resection of suspected or confirmed peritoneal metastatic colorectal carcinoma followed by intraperitoneal administration of therapeutic agents. Four to seven days before surgery, all patients were administered $^{131}$I-labeled B72.3 intraperitoneally via a catheter. All patients received between 0.76 and 1.2 mg of IgG and between 5.0 and 10.0 mCi $^{131}$I, with specific activities of $^{131}$I-B72.3 IgG ranging from 6.6 to 11.0 mCi/mg [55,56].

On the day of or prior to surgery, patients were scanned with a gamma camera; all scan results were interpreted before surgery. Gamma scans of seven of ten patients showed clearly discernable concentrations of radiolabeled MAb in various distinct regions of the peritoneum. In all such cases, these lesions were identified at surgery as tumor and later confirmed as carcinoma via light microscopic examination. A representative positive gamma scan is shown in Figs. 1A–1C (patient MM). Note the accumulation of radiolabeled MAb in the peritoneal gutters immediately after intraperitoneal MAb administration (Fig. 1A) and at three days after MAb administration (Fig. 1B). The gamma scan at six days post-MAb administration, however,

TABLE 8
RI Values of Patients Injected Intraperitoneally with $^{131}$I-Labeled B72.3[a]

| | RI | | | | | |
|---|---|---|---|---|---|---|
| | Tumor | | | Normal | | |
| Name | <3 | 3–10 | >10 | <3 | 3–10 | >10 |
| NM | 0 | 1 | 17 | 12 | 0 | 0 |
| MH | 2 | 4 | 0 | 10 | 0 | 0 |
| RK | 5 | 3 | 0 | 8 | 0 | 0 |
| MM | 4 | 5 | 18 | 11 | 0 | 0 |
| MG | 11 | 0 | 0 | 7 | 0 | 0 |
| WJ | 2 | 7 | 3 | 25 | 0 | 0 |
| EP | 0 | 7 | 2 | 1 | 0 | 0 |
| SM | 5 | 6 | 1 | 6 | 0 | 0 |
| JB | 0 | 0 | 6 | 12 | 1 | 0 |
| JK | 0 | 0 | 3 | 3 | 0 | 0 |
| Total Lesions | 29 | 33 | 50 | 95 | 1 | 0 |
| Percentage | 26 | 29 | 45 | 99 | 1 | 0 |

[a]Adapted from [56]

shows MAb concentration in distinct areas of the peritoneum (confirmed as carcinoma at surgery and by light microscopic examination). These findings can be contrasted with the negative gamma scans of patient RK (Figs. 1D–1F); who had no intraperitoneal disease [56].

Three of the ten patients studied were positive for MAb localization via gamma scanning (confirmed at surgery) but were negative for tumor via CT scan and X-ray studies. Lesions as small as approximately 1.5 cm in diameter were clearly defined by gamma scans. All specimens removed at surgery were analyzed for cpm per g of tissue. Specimens were then fixed, embedded, and analyzed for percentage of carcinoma cells present.

Table 8 shows the RI values (based on % ID MAb uptake per kg of tumor versus % ID MAb uptake per kg of normal tissue) of the biopsy specimens of tumor and normal tissues from the ten patients receiving intraperitoneally administered MAb B72.3. An RI of $\geq 3$ was arbitrarily chosen as a positive radiolabeled uptake; 83 of 112 (74 percent) of carcinoma lesions showed RI values $\geq 3$. In some patients with a large tumor burden, as much as 40 percent of the injected dose was bound to carcinoma. Note that of the 29 lesions negative for MAb uptake, 11 were from patient MG, the only patient in whom all tumor lesions were negative for TAG-72 antigen expression. Of the 95 histologically confirmed normal tissues biopsied, all but one demonstrated RI values <3 (Table 8). The one exception had an RI of 3.5 and was a histologically normal spleen from patient JB. Interestingly, this patient had the highest level of circulating antigen $^{131}$I-B72.3 IgG immune complex as determined by HPLC and RIA. The other 94 normal tissue biopsies with RI values <3 were from numerous sites, including colon, ileum, duodenum, pancreas, liver, spleen, lymph node, kidney, ovary, and fallopian tube; the vast majority of RI values ranged from 0.5 to 1.5 [56].

Studies were next conducted to determine the relative efficacies of intraperitoneally versus intravenously administered MAb to localize tumor lesions [56]. Patients were concomitantly administered $^{131}$I-labeled B72.3 intraperitoneally and $^{125}$I-labeled B72.3

TABLE 9
Concomitant Administration of $^{131}$I-B72.3 Intraperitoneally and $^{125}$I-B72.3 Intravenously (Patient NJ): Advantage of Intraperitoneal Route[a]

| Tissue Description | % ID/kg | | % ID/kg Ratios | RI[b] | | % Tumor |
|---|---|---|---|---|---|---|
| | Intraperitoneal $^{131}$I | Intravenous $^{125}$I | $^{131}$I/$^{125}$I | Intraperitoneal $^{131}$I | Intravenous $^{125}$I | |
| Carcinoma | | | | | | |
| Omentum | 44.51 | 5.85 | 7.61 | 32.6 | 12.2 | 80 |
| Mesentery, sigmoid colon | 40.04 | 5.42 | 7.39 | 29.3 | 11.3 | 80 |
| Peritoneum, liver capsule ($n$ = 4) | 39.62 | 9.19 | 5.64 | 29.0 | 19.1 | 66 |
| Peritoneum, gastro-esophageal junction | 39.27 | 8.45 | 4.65 | 28.8 | 17.6 | 80 |
| Omentum, greater | 11.41 | 2.75 | 4.16 | 8.4 | 5.7 | 40 |
| Peripancreatic | 45.27 | 11.30 | 4.01 | 33.2 | 23.5 | 85 |
| Omentum, lesser ($n$ = 2) | 27.08 | 7.54 | 3.68 | 19.8 | 15.7 | 63 |
| Diaphragm ($n$ = 3) | 27.23 | 7.76 | 3.48 | 19.9 | 16.2 | 68 |
| Splenic capsule ($n$ = 4) | 29.30 | 10.72 | 2.77 | 21.5 | 22.3 | 69 |
| Normal | | | | | | |
| Adipose tissue | 0.07 | 0.05 | 1.31 | 0.1 | 0.1 | 0 |
| Mesentery, transverse colon | 0.52 | 0.49 | 1.07 | 0.4 | 1.0 | 0 |
| Peritoneum | 0.84 | 0.66 | 1.26 | 0.6 | 1.4 | 0 |
| Peritoneal adhesions ($n$ = 3) | 1.21 | 0.78 | 1.56 | 0.9 | 1.6 | 0 |
| Abdominal scar | 0.99 | 0.47 | 2.09 | 0.7 | 1.0 | 0 |
| Falciform ligament | 1.04 | 0.37 | 2.82 | 0.8 | 0.8 | 0 |
| Spleen ($n$ = 3) | 2.70 | 3.45 | 0.78 | 2.0 | 7.2 | 0 |

[a]Adapted from [56]
[b]RI was determined by dividing the % ID/kg of the tumors by the averaged % ID/kg of all normal biopsies.

intravenously. Both the intraperitoneally and intravenously administered MAb preparations in each of four patients were identical in milligram dose and radiolabeling conditions. In 35 of 55 carcinoma lesions biopsied, the intraperitoneally administered B72.3 localized at least two times better in terms of % ID/kg than the intravenously administered MAb. In seven lesions, MAb localization was comparable via either route, and in 13 lesions, the intravenously administered MAb B72.3 localized at least two times better than the intraperitoneally administered MAb. For example, as noted for patient NJ (Table 9), the % ID/kg taken up by carcinoma lesions ranged from 11.4 to 45.3 for intraperitoneally administered B72.3 ($^{131}$I cpm/kg) versus values of only 2.8 to 11.3 percent ID/kg for the intravenously administered B72.3 ($^{125}$I cpm/kg). The ratios of uptake of the intraperitoneally administered MAb were from 2.8 to 7.6 times greater for individual lesions than the intravenously administered MAb. The levels of uptake in the normal tissues were similar [56].

In an attempt to determine the reason(s) for the difference in uptake of intraperito-

neally and intravenously administered MAb among different carcinoma lesions, three pathologists independently examined these lesions (two did so without knowing the reason for the exercise) and characterized them as to various properties. The most striking correlation with differential MAb uptake was the type of metastasis, i.e., either peritoneal implant (in which intraperitoneal route was superior) or "non-implant" (in which intravenous route was superior).

Plasma samples from eight different patient studies were obtained before MAb administration and at various time points after MAb administration [56]. The plasma clearance of the intravenously administered $^{125}$I-labeled B72.3 IgG and the $^{125}$I-BL-3 control IgG were similar, with approximately 50 percent of the injected dose in plasma at day 7 post-MAb administration. In contrast, no more than 30 percent of the injected dose of intraperitoneally administered B72.3 IgG or BL-3 appeared in the plasma at any point in time, with peak values obtained at days 2 to 3.

There are several diagnostic implications from these studies. Radiolabeled B72.3 may now be considered for use in the localization of suspected colorectal or ovarian carcinoma lesions. Carcinoma can be detected by intraperitoneally administered $^{131}$I-labeled B72.3 when in some cases, other radiologic procedures, including CT scan, may not detect lesions [56]. Ovarian carcinoma, because its metastases are often limited as implants in the peritoneum, is an ideal type of tumor for immunodiagnosis and immunotherapy using intraperitoneally administered MAb. Based on intraperitoneal administration of radiolabeled B72.3 in colorectal patients and early reports in ovarian carcinoma patients [53,54], B72.3 may be a useful diagnostic and therapeutic modality for ovarian carcinoma patients, using MAb B72.3 either coupled to drugs, effector cells, or radionuclides. Preliminary reports from several institutions have shown localization of radiolabeled B72.3 to biopsy-proven ovarian carcinoma lesions, including subdiaphragmatic and peritoneal implants. Direct analysis of biopsy and plasma specimens have permitted dosimetry calculations [57] that indicate, in selected patients, higher doses of $^{131}$I-B72.3 IgG may be delivered to tumor masses for cell killing with minimal toxicity to normal tissues. Efficiency of killing will increase, moreover, when more efficient cytotoxic radionuclides, such as $^{90}$Y, are coupled to MAbs; studies to develop such reagents are currently in progress. It has been shown that only a fraction of the intraperitoneally administered radiolabeled MAb IgG is found in the plasma at any time, potentially an important point to consider if one wishes to minimize plasma-borne radiolabeled MAb as a possible source of marrow toxicity. Thus, these studies have demonstrated the necessity of considering either sole use of intracavitary administered MAb or the concomitant use of intracavitary and intravenously administered MAb in protocols aimed at MAb-guided diagnosis or perhaps therapy of gynecologic carcinomas.

In summary, monoclonal antibodies may make significant contributions to the management of gynecologic malignancies. Because of the asymptomatic nature of ovarian carcinoma, early diagnosis is essential to prognosis. Through the use of serum assays, MAbs may identify asymptomatic patients. Radioimaging with $^{131}$I-labeled MAb has detected carcinoma lesions that otherwise escaped the usual radiologic detection methods. Due to the suboptimal imaging characteristics of $^{131}$I, the use of low-energy gamma emitters such as $^{111}$In, $^{99m}$Tc, or $^{123}$I, which have favorable scanning properties, will result in better diagnostic gamma scans. Immunohistochemical assays and serum assays may be important in the selection of appropriate patients whose tumors demonstrate high levels of a given tumor antigen.

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