

---

# Radioimmunotherapy with Intravenously Administered $^{131}\text{I}$ -Labeled Chimeric Monoclonal Antibody MOv18 in Patients with Ovarian Cancer

Iwona van Zanten-Przybysz, Carla F. Molthoff, Jan C. Roos, Marian A. Plaizier, Gerard W. Visser, Rik Pijpers, Peter Kenemans, and René H. Verheijen

*Departments of Obstetrics and Gynecology, Nuclear Medicine/PET Center, and Radio Nuclide Center, University Hospital Vrije Universiteit, Amsterdam, The Netherlands*

---

We investigated the safety and pharmacokinetics of  $^{131}\text{I}$ -labeled chimeric monoclonal antibody MOv18 ( $^{131}\text{I}$ -c-MOv18 IgG) in patients with ovarian cancer and the estimated radiation dose to cancer-free organs and tumor. **Methods:** Three patients were injected intravenously with 3 GBq  $^{131}\text{I}$ -c-MOv18. Toxicity was evaluated according to the World Health Organization toxicity scales. Blood sampling was performed for 12 wk after injection. Whole-body and SPECT imaging was performed frequently. Dose rates were obtained with a portable dose-rate measure. Quantitative activity analysis of several organs was performed with the region-of-interest technique. Absorbed doses were calculated using MIRDOSE3. **Results:** Transient changes in hematologic profiles were seen in 2 patients. Pancytopenia developed in 1 patient; on analysis, she entered the study probably with exhausted bone marrow reserves. Nonhematologic toxicity was mild. No human antichimeric antibody responses were observed. Mean isolation time was 12 d. The plasma elimination half-life increased almost 3-fold compared with that after tracer doses of c-MOv18. Dosimetry showed mean absorbed doses of 163, 380, 276, 338, 781, and 216 cGy, for whole-body, liver, kidney, spleen, lung, and red marrow, respectively. Tumor-absorbed doses ranged from 600 to 3800 cGy. All patients achieved a stable disease state, as confirmed by CT and carcinoma-associated antigen CA 125, lasting from 2 to >6 mo. **Conclusion:**  $^{131}\text{I}$ -labeled c-MOv18 can safely be given to patients with noncompromised bone marrow reserves and may have therapeutic potential particularly in patients with minimal residual disease.

**Key Words:** radioimmunotherapy; chimeric monoclonal antibody MOv18; ovarian cancer; dosimetry

**J Nucl Med 2000; 41:1168–1176**

---

**O**varian cancer is the major cause of death caused by gynecologic malignancies. A combination of extensive cytoreductive surgery and platinum-based chemotherapy has resulted in an overall response rate of 60%–80% and an overall 5-y survival below 40% (1). The disease is generally

symptom free, and 70% of patients present with advanced disease and a 5-y survival of only 5%–20% (2). Drug resistance may occur, and responses after salvage therapies, including the use of taxanes, are of short duration (3). Radiation therapy has been used to treat early-stage ovarian cancer and has cured selected patients with small-volume disease (4). Using a suitable carrier system, such as monoclonal antibodies (MAbs) carrying a  $\beta$  emitter, higher doses of radiation can potentially be delivered specifically at the tumor site. Radioimmunotherapy (RIT) has been used to treat ovarian cancer, with promising results in patients with minimal residual or microscopic disease (5–8). We have extensively studied the MOv18 MAb binding to the membrane folate receptor, a 38-kDa glycoprotein that is highly expressed on ovarian carcinoma cells (9–12). Murine and chimeric MOv18 have been studied preclinically and in patients with ovarian cancer (7,13,14).

In this study, we investigated the safety, pharmacokinetics, and logistics of a therapeutic dose of intravenously administered  $^{131}\text{I}$ -labeled c-MOv18 IgG in patients with ovarian cancer. In addition, we evaluated methods to predict the length of hospital stay and estimated the absorbed doses to normal organs and tumor tissue.

## MATERIALS AND METHODS

Patients who appeared to have progressive cancer, as suggested by diagnostic imaging techniques or CA 125 serum profile after receiving conventional treatment, were entered in the study after they signed an informed consent form. The study was approved by the institutional review board of the University Hospital Vrije Universiteit, Amsterdam, The Netherlands. Patients had a life expectancy of at least 3 mo and a World Health Organization (WHO) performance status of 0–3. Patients were excluded if they had an unstable medical condition that could interfere with the assessment of possible toxic effects of the study agent.

Before administration of  $^{131}\text{I}$ -c-MOv18, the medical history, vital signs, and performance status were obtained and a physical examination, electrocardiography, and chest radiography were performed. Biochemical and hematologic blood profiles were recorded frequently, and carcinoma-associated antigen CA 125 was determined in serum.

Patients received  $^{131}\text{I}$ -c-MOv18 in a total volume of 21 mL,

---

Received Apr. 21, 1999; revision accepted Nov. 1, 1999.

For correspondence or reprints contact: Carla F. Molthoff, PhD, Department of Nuclear Medicine/PET Center, University Hospital Vrije Universiteit, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands.

0.9% sodium chloride, over a period of 5 min, followed by a 5-mL, 0.9% sodium chloride flush. During and after the infusion, vital signs were frequently recorded. All concomitant medication was recorded. Blood samples were obtained at 0, 1, 6, and every 24 h after injection until patients were discharged and, if possible, weekly thereafter. Imaging was performed within 1 h after injection and frequently thereafter until discharge. Patients remained in the hospital on a special ward that has been adapted for treatment and care of patients who are treated with high-dose  $^{131}\text{I}$ . Patients received orally 130 mg/d of Lugol's solution starting 2 d before injection and until 3–4 wk after injection. The dose rate ( $\mu\text{Sv/h}$ ) was measured twice daily at 1- and 2-m distance from the patient using a portable dose-rate measure (FAG Kugelfischer, Werkerlangen, Germany). According to Dutch government regulations, patients were discharged from the hospital when the dose rate at 1 m from the patient was less than  $20 \mu\text{Sv/h}$  (400 MBq). To minimize any radiation risk to the environment, patients were asked to follow safety directives after discharge. Toxicity was evaluated according to the WHO toxicity scales.

### Immunogenicity

Human antichimeric antibody (HACA) response was determined in serum samples taken before infusion and weekly up to a maximum of 12 wk after injection, as described previously (15,16).

### Antibody Characteristics

Chimeric MOv18 was constructed by fusion of the variable regions of murine MOv18 IgG with the constant regions of human IgG1 (17). Affinity and immunoreactivity of the c-MOv18 IgG have been shown to be identical to their murine counterpart (13). No reactivity with peripheral blood cells, bone marrow, or spleen cells was demonstrated (12). The c-MOv18 was provided by Centocor B.V. (Leiden, The Netherlands) as a sterile, pyrogen-free, highly purified MAb and approved for human use.

### Radiolabeling Procedure and Quality Control

Labeling of c-MOv18 with  $^{131}\text{I}$  was performed automatically with 35  $\mu\text{g}$  Iodogen (Pierce, Oud Beijerland, The Netherlands) in a labeling hood with microprocessor-controlled devices under aseptic conditions and under strict safety regulations. Starting doses were 3350–3500 MBq  $^{131}\text{I}$ , with labeling yields of 85%–89%.  $^{131}\text{I}$ -c-MOv18 was purified by gel filtration on a SepharoseG25 PD10 column (Pharmacia, Roosendaal, The Netherlands) and analyzed for radiochemical purity, degradation products, and immunoreactivity. Radiochemical purity of the conjugate (defined as percentage of  $^{131}\text{I}$  bound to the MAb) was analyzed by thin-layer chromatography (TLC) on glass fiber sheets with 0.1 mol/L sodium citrate as eluent. Aggregation and degradation products were analyzed by high-pressure liquid chromatography (HPLC) using a Superdex200HR 10/30 column (Pharmacia/LKB, Roosendaal, The Netherlands) eluted with a mixture of 0.05 mol/L sodium phosphate, 0.15 mol/L sodium chloride, and 0.05% sodium azide, with a pH of 6.8, a flow rate of 0.5 mL/min, and simultaneous radioactivity detection (Ortec406A single-channel analyzer, Drew3040 data collector, and Merck-HitachiD2000 integrator; Merck, Darmstadt, Germany). Quantitative recovery of the radioactivity of >98% was found in all cases. Gel electrophoresis was performed on 7.5% sodium dodecyl sulfate-poly acrylamide gel electrophoresis (SDS-PAGE) gels under nonreducing conditions followed by the analysis and quantification of the radioactivity of the bands using Phosphor-Imager screens (PhosphorImager; Molecular Dynamics, Zoetermeer, The Netherlands). Immunoreactivity was determined in a

cell-binding assay as described previously (13,18). The radiolabeling procedure was validated with respect to the final quality of the conjugate, sterility, and endotoxin levels.

### Pharmacokinetics

Serial blood samples were drawn before, during, and after completion of the infusion. The amount of radioactivity in blood and plasma was measured in a  $\gamma$  well counter (Compugamma; Wallac, Turku, Finland) and expressed as the percentage injected dose per liter (%ID/L). A set of standards was prepared from the injectate. Corrections were performed for background and radioactive decay. HPLC analysis of the serum samples revealed that the radioactivity was confined to the antibody. The plasma clearance of c-MOv18 was analyzed by a model-dependent, 2-compartment, nonlinear estimation program (MW Pharm; MediWare, Groningen, The Netherlands).

### Imaging and Dosimetry

Imaging was performed with a dual-headed gamma camera (Genesys; ADAC Laboratories, Milpitas, CA) containing a high-energy collimator up to 28 d after injection. A standard of 10 MBq  $^{131}\text{I}$  was placed in the field of view. Quantitative activity analysis of several organs of interest, a background region, and tumor was estimated with the region-of-interest (ROI) technique. Except for the whole body, liver, and lung, tissue counts were corrected for the background (for kidneys and spleen, 75% and 50% of background activity were subtracted, respectively), as described by Buijs et al. (19). In patient 1, background correction for tumor in front of the lumbar vertebrae (just above the aortic bifurcation) was based on the ROI of lumbar vertebrae. From the anterior and posterior ROI counts, the geometric mean was calculated. The radioactivity in the various organs at subsequent postinjection time points was calculated as percentage of whole-body dose, and for absorbed dose calculations, the MIRDOSE3 program (Oak Ridge Associated Universities, Oak Ridge, TN) was used (20). For red-marrow dose calculations, an activity ratio between red marrow and blood of 0.3 was used (21). The accumulated activity in the tumor was estimated from a ROI around the tumor using the partial background correction method described by Buijs et al. (19) and Weber et al. (22). The tumor dose was calculated using the S value ( $r_b \rightarrow r_b$ ) for the contribution of the photons in the remaining body to the tumor-dose and equilibrium-dose constants of MIRD for the contribution of the nonpenetrating radiation in the tumor to the tumor dose assuming an absorbed fraction of 1. The contribution of the photon emission in the tumor to the tumor dose was neglected. We preferred this approach over the application of the S values for nodules of MIRDOSE3 because these values are estimated for a limited number of tumor masses and neglect the kinetics of the activity in the remaining body. Tumor volumes were obtained from volumetric analysis of CT scans.

### Patient Isolation

After injection, patients were housed on a special ward designed for patients injected with high doses of  $^{131}\text{I}$ . For the daily imaging procedure, patients were temporarily transported to the Department of Nuclear Medicine at the University Hospital Vrije Universiteit, Amsterdam, The Netherlands. Only a limited number of personnel were involved in patient care. Visitors, who were placed behind a mobile lead wall, were allowed for restricted periods of time.

## RESULTS

Three patients who were 46, 47, and 50 y old and had recurrent or residual ovarian cancer entered the study (Table 1). Patients received 10 mg c-MOv18 labeled with 275.6, 301.5, and 292.3 MBq <sup>131</sup>I/mg MAb, respectively. There were no effects of <sup>131</sup>I-c-MOv18 administration on patients. Mean isolation time was 12 d. Isolation was well tolerated. Patients were actively involved in clinical procedures and sufficient diversion (i.e., physical exercise, amusement) was provided.

### Toxicity

All patients showed changes in hematologic profiles (Fig. 1A). Grade 1 thrombopenia and leukopenia developed in patient 1, with nadirs 5 and 6 wk after injection, respectively, returning to normal by week 7 (Figs. 2A and B). She also experienced grade 1 myalgia and arthralgia (Fig. 1B). Prolonged grade 4 thrombopenia developed in patient 2, with a nadir 7 wk after injection, and a slow increase in platelet count from week 9 after injection. Grade 4 leukopenia also developed in patient 2, with a nadir 4 wk after injection, and the first signs of recovery were seen 10 wk after injection. An antimicrobial and antifungal prophylaxis was given up to 14 wk after injection. There were no occurrences of infection or bleeding. Patient 2 also experienced grade 3 anemia, with a nadir 7 wk after injection, that lasted more than 14 wk after injection. Nonhematologic side effects consisted of grade 1 diarrhea, myalgia, and arthralgia; grade 2 malaise; and grade 1 chills. All side effects resolved spontaneously. Transient grade 3 leukopenia and grade 2 thrombopenia developed in patient 3 (Figs. 2A and

B), with nadirs 5 and 4 wk after injection, respectively. Grade 2 nausea resolved spontaneously.

### Immunogenicity

Pre- and postinjection serum samples of all 3 patients were analyzed for the occurrence of anti-c-MOv18 antibodies. No HACA responses could be found at any time after injection.

### Radiolabeling

Radiochemical purity of the conjugate, analyzed by TLC, measured  $98.2\% \pm 0.9\%$  (range, 97.2%–99.0%). Aggregation and degradation products analyzed by HPLC and SDS-PAGE were <2% in all cases ( $99.0\% \pm 0.8\%$ ; range, 98.3%–99.9%). Immunoreactivity measured  $70\% \pm 2\%$  (range, 68.0%–72.0%) specific binding.

### Pharmacokinetics

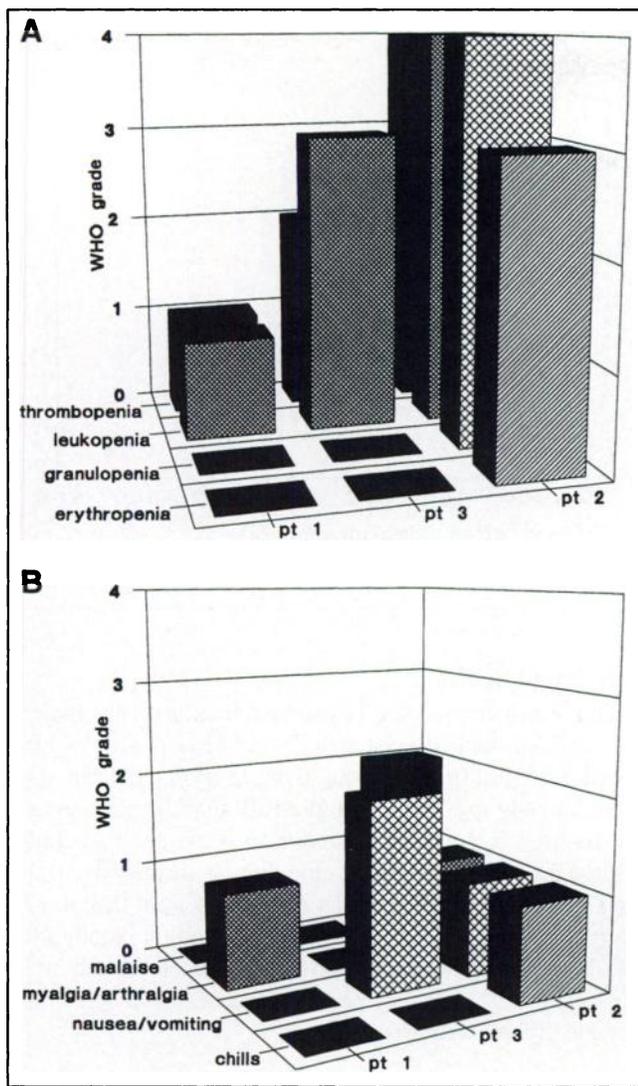
The disappearance of <sup>131</sup>I-c-MOv18 from the circulation was best described by a 2-compartment model with a  $t_{1/2\alpha}$  and  $t_{1/2\beta}$  of 31 and 229 h, 54 and 326 h, and 45 and 313 h for patients 1, 2, and 3, respectively (Fig. 3).

Whole-body clearance best fit a 1-compartment model (Table 2). Effective half-lives that were based on the disappearance from the scans were 100 h, 92 h, and 98 h, for patients 1, 2, and 3, respectively (Table 2, Fig. 4). Effective half-lives that were based on the dose-rate results using the portable dose-rate measure at 1 m were 102, 123, and 112 h, and at 2 m were 111, 129, and 131 h, for patients 1, 2, and 3, respectively (Table 2, Fig. 5). The observed differences in mean effective half-lives for the 2 methods did not result in differences in the day of discharge from the hospital.

**TABLE 1**  
Patient Characteristics at Study Entry

Patient no.	Age (y)	Histology and grade	FIGO stage	Previous treatments(s)	Sites of lesions	Baseline CA 125 (U/mL)
1	50	Serous, poorly differentiated	IIIC	Cytoreductive surgery 6× cisplatin/paclitaxel/etoposide Second-look operation 5× intraperitoneal cisplatin/etoposide 6× paclitaxel	Left obturator node Tumor in mesentery 3 small tumor deposits in supracolic omentum	11
2	46	Serous, poorly differentiated	IIIC	Cytoreductive surgery 6× cisplatin/cyclophosphamide 6× carboplatin/paclitaxel 6× cisplatin/paclitaxel/etoposide Secondary debulking 4× intraperitoneal cisplatin/etoposide 5× cisplatin/gemcitabine 3× gemcitabine Tamoxifen	Tumor above aortal bifurcation Tumor on ascending colon Tumor on cecum	1881
3	47	Serous, moderately differentiated	IIIC	Cytoreductive surgery 6× cisplatin/paclitaxel/etoposide Second-look operation 3× carboplatin/cyclophosphamide	Right obturator node Tumor next to sigmoid Tumor in liver	237

FIGO = Fédération Internationale de Gynaecologie et Obstetrique.



**FIGURE 1.** Incidence and degree of side effects in patients injected with  $^{131}\text{I}$ -labeled c-MOv18 IgG. (A) Hematologic toxicity. (B) Nonhematologic toxicity. Pt = patient; abscissa = various side effects in individual patients; ordinate = grade of toxicity according to WHO toxicity scale.

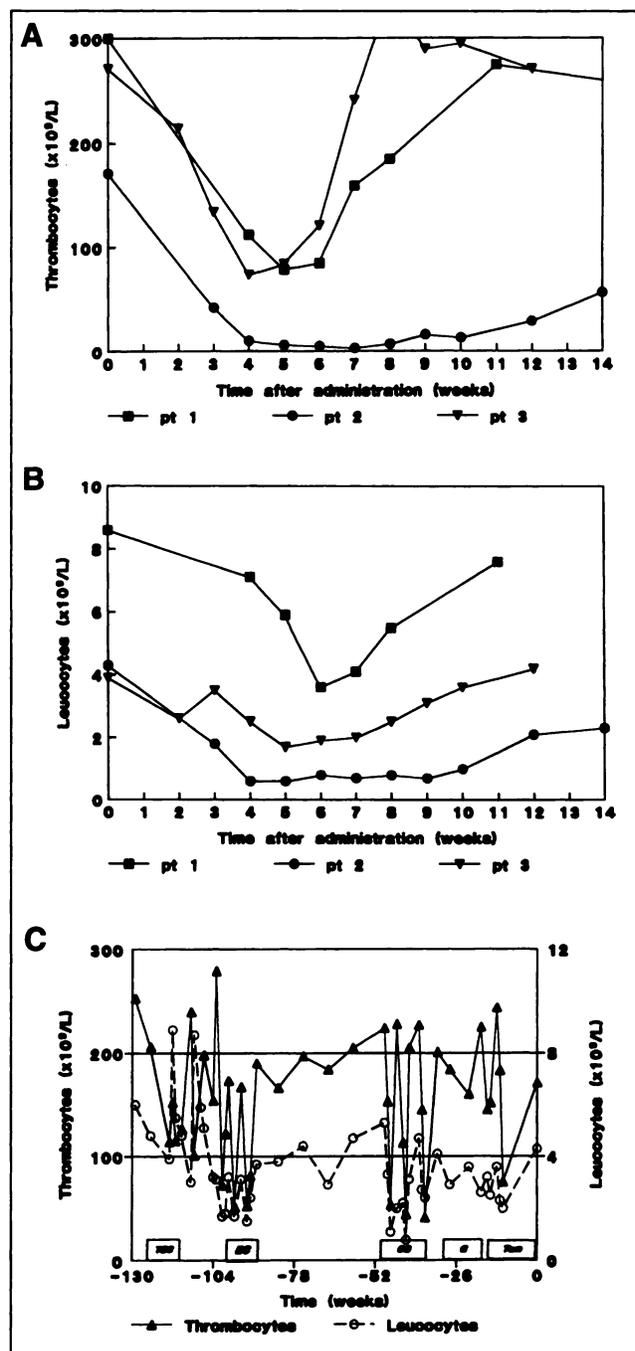
### Imaging

Patients were imaged for at least 21 d. On the early planar images of patient 1, activity was seen in the liver, spleen, and kidneys. On days 2, 7, and 10, an irregular distribution of the tracer was seen in the abdominal region, probably because of fecal excretion, which partly obscured the visualization of a tumor lesion in front of the lumbar spine. Clear tumor uptake was present in 1 of 3 tumors in patient 1, as determined by CT (localized in the left side of the abdomen), and was also confirmed by SPECT imaging.

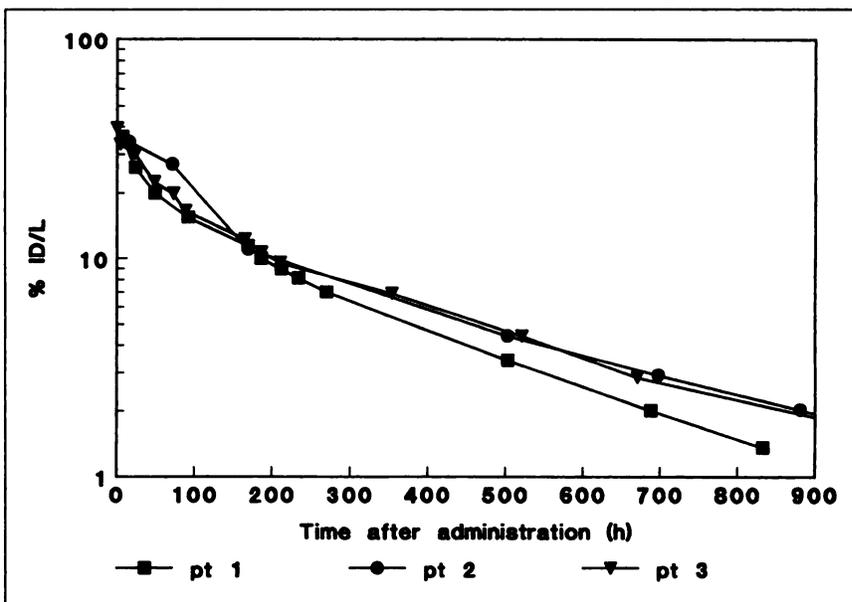
Planar images of patient 2 were obtained up to 21 d after injection. In the abdominal region, 2 of 3 tumors were present, as determined by conventional imaging techniques. Hot spots in the right abdomen and just above the aortic bifurcation, corresponding with lesions on the CT scan obtained before the treatment (Fig. 6A), could be seen on all

planar images (Fig. 6B) and were confirmed by SPECT (Fig. 6C). Blood-pool activity was seen clearly up to day 21, indicating a slower disappearance of the antibody from the body.

On the planar images of patient 3, activity was seen in the midline of the pelvic region on days 4, 7, and 10. However,



**FIGURE 2.** Hematologic toxicity profile after intravenously injected  $^{131}\text{I}$ -labeled c-MOv18 IgG: thrombocytes (A) and leucocytes (B). (C) Hematologic toxicity profile of patient 2 over 2.5 y before RIT revealed possible indication for cumulative bone-marrow suppression. T = Taxol (paclitaxel; Bristol-Myers Squibb Co., Princeton, NJ); E = etoposide; C = cisplatin; G = gemcitabine; Tam = tamoxifen.



**FIGURE 3.** Plasma disappearance curves of intravenously injected  $^{131}\text{I}$ -labeled c-MOv18 IgG in patients 1, 2, and 3. Pt = patient.

those spots were not confirmed by SPECT and did not correspond with lesions seen on the CT scan of the abdomen. Intense activity was also observed in front of the left kidney, extending to the midline. In patients 1 and 3, activity in the heart region and the lungs was seen up to 3 and 4 wk, respectively, which could be explained by persistent blood-pool activity. In addition, in patients 2 and 3, some activity in breast tissue was seen.

#### Dosimetry

Table 3 lists the estimated absorbed dose for the whole body, liver, kidney, spleen, right lung, red marrow, and tumor. Similar absorbed doses were calculated for the normal tissues of the 3 patients, and relatively high absorbed doses were estimated for lung tissue. The red-marrow dose in patient 2 was higher compared with that in the other 2 patients.

In patient 1, tumor absorbed dose estimates could be obtained from 1 tumor (left obturator node) with a volume of 2 cm<sup>3</sup> and measured 3800 cGy. In patient 2, tumor dose estimates could be calculated for 2 tumor lesions (on the ascending colon and above the aortic bifurcation) with volumes of 41 and 25 cm<sup>3</sup> and measured 600 and 1900 cGy, respectively. Unfortunately, no tumor dose estimates could be obtained for patient 3.

**TABLE 2**

Effective Half-Lives of  $^{131}\text{I}$ -c-MOv18 from Serial Whole-Body Images and from Results of Portable Dose-Rate Measure

Patient no.	Whole-body scan (h)	Dose rate at 1 m (h)	Dose rate at 2 m (h)
1	100	102	111
2	92	123	129
3	98	112	131
Mean $\pm$ SD	97 $\pm$ 4	112 $\pm$ 10	124 $\pm$ 11

#### Antitumor Effects

Tumor responses could be assessed in all patients. Patient 1 achieved a stable disease state, as confirmed by CT, which lasted for 5 mo. In this patient, CA 125 level had been <35 U/mL already for over 1 y before RIT and, therefore, could not be used for response monitoring. Patient 2 had stable disease for 2 mo. Thereafter, tumor burden increased and she died of cancer 6 mo after injection. In patient 2, CA 125 decreased from 1881 to 1519 U/mL in the first month after RIT but rose rapidly as the cancer progressed. In patient 3, subsequent CT scans obtained after the treatment confirmed a stable disease lasting for >6 mo.

#### DISCUSSION

The safety, kinetics, tissue dosimetry, and logistics after RIT with  $^{131}\text{I}$ -labeled c-MOv18 IgG were studied in 3 patients with ovarian cancer. Mild hematologic toxicity was observed in 2 patients but was found to be severe and long lasting in 1 patient. Nonhematologic toxicity was mild and without any clinical significance. Antitumor effects were seen in all patients.

Major toxicity in this study was caused by bone-marrow suppression. Patients 1 and 3 developed mild, transient bone-marrow toxicity. In patient 2, however, severe and long-lasting pancytopenia developed, which resolved without consequence. In this patient, there was no indication for any myeloproliferative disorder and no exogenous agents had been used that could have negatively affected her condition. Compared with the other patients, patient 2 was more heavily pretreated and possibly entered the study with impaired bone-marrow reserves, most probably because of prior excessive chemotherapy (Fig. 2C). Most patients with ovarian cancer who are eligible for RIT trials are heavily pretreated with chemotherapy. Studies evaluating the contribution of the dose and type of prior chemotherapy to

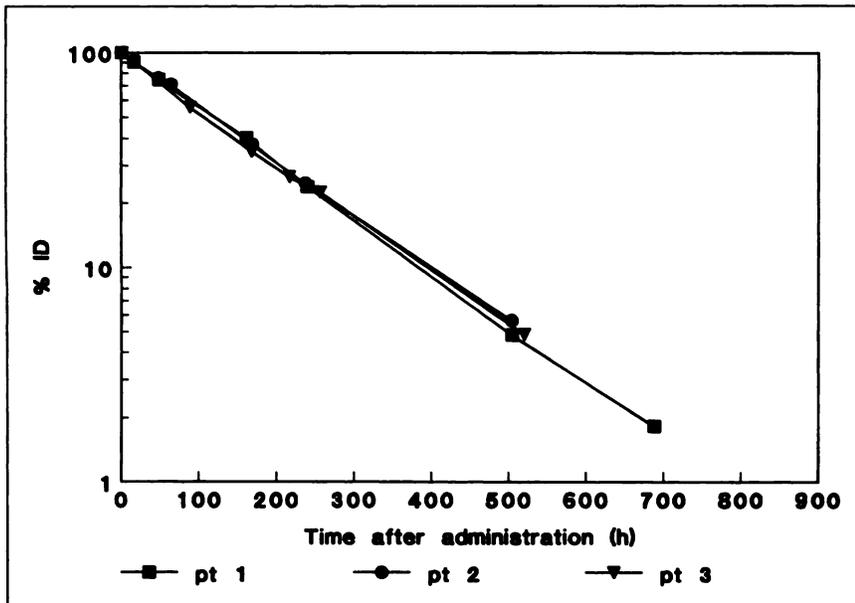


FIGURE 4. Whole-body disappearance curves of intravenously injected  $^{131}\text{I}$ -labeled c-MOv18 IgG in patients 1, 2, and 3, as calculated from whole-body images. Pt = patient.

myelotoxicity induced by RIT have indicated that the maximum tolerated dose (MTD) is lower in patients compromised by previous myelosuppressive therapy (23,24), but it varies among patients and even within the same patient during multiple RIT courses (25). The severity of hematologic toxicity in patient 2 could also be attributed to the slightly prolonged antibody retention, as seen in Figure 6B, which resulted in a higher absorbed dose to the red bone marrow of 243 cGy. However, this dose should be well tolerated in patients with normal bone-marrow function (26). Hence, patients with impaired bone-marrow reserves, in whom more severe bone-marrow toxicity is likely to develop, should be identified beforehand.

Nonhematologic toxicity was mild and of no clinical significance. Observed symptoms were considered to be

constitutional in nature and, therefore, could not be distinguished from symptoms related to disease, prolonged administration of oral iodine, or prolonged myelosuppression. To date, no HACA responses have been seen at any time point after injection in over 50 patients injected with c-MOv18, which confirms its low immunogenicity (15,16).

The ability of  $^{131}\text{I}$ -c-MOv18 to visualize metastatic tumor was moderate. Because of the limitations of the gamma camera, lesions <1 cm without clear focal uptake are difficult to visualize. Furthermore, tumor visualization, especially in the abdominal cavity, is hampered by large, well-vascularized organs such as the liver, spleen, and kidneys and by the major blood vessels. In patient 1, 1 lesion measuring 1.5 cm could be visualized, whereas the other 2 lesions <1 cm could not. In patient 2, 2 of 3 well-defined

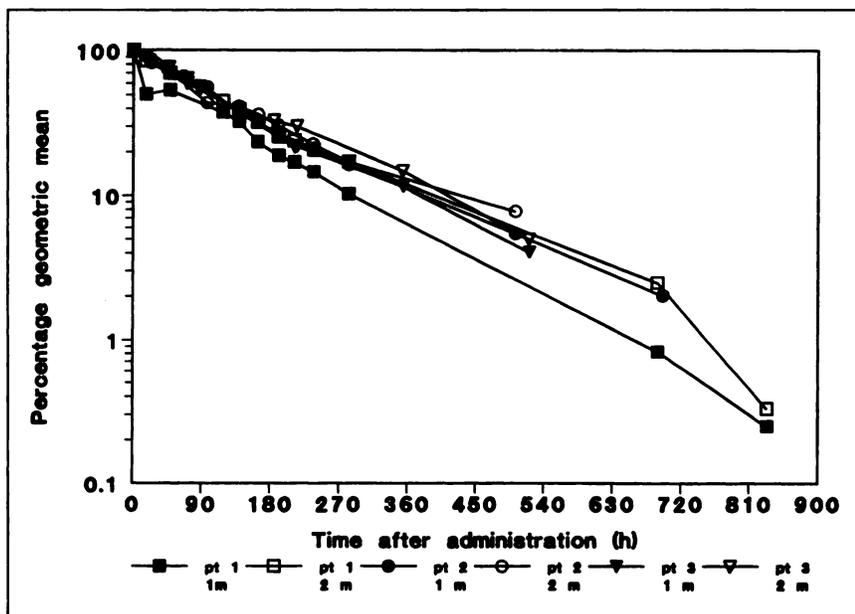
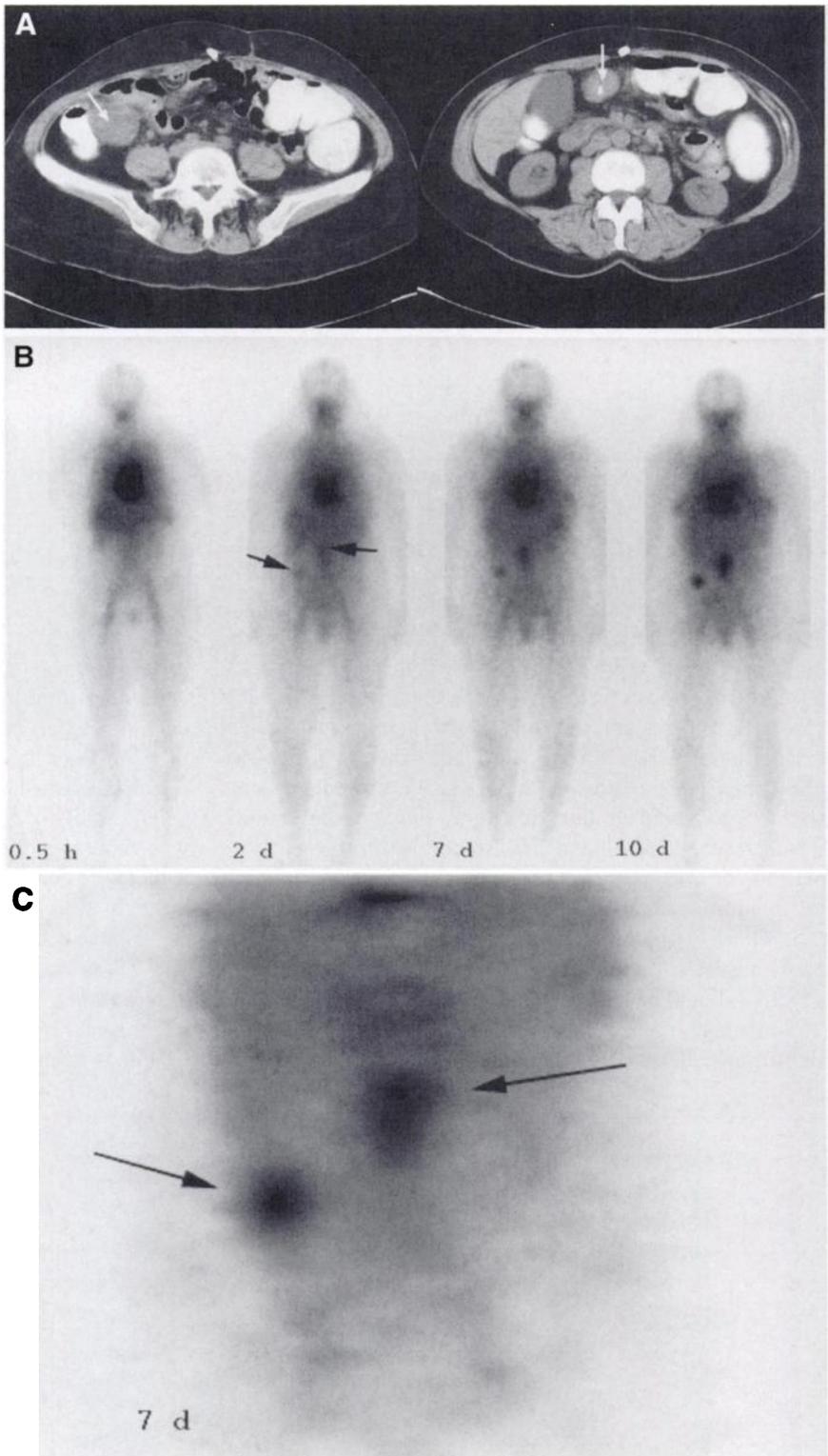


FIGURE 5. Whole-body disappearance curves of intravenously injected  $^{131}\text{I}$ -labeled c-MOv18 IgG in patients 1 (A), 2 (B), and 3 (C), using portable dose-rate measure at 1 and 2 m. Pt = patient.



**FIGURE 6.** CT scans of pelvis (left) and abdomen (right) (A) before injection and whole-body anterior images (B) of patient 2, 0.5 h after injection with  $^{131}\text{I}$ -c-MOV18 IgG and 2, 7, and 10 d after injection. Arrows indicate metastases in right abdomen and above aortic bifurcation. (C) SPECT image of abdomen 7 d after injection.

tumor localizations could be visualized. In patient 3, none of the 3 tumor lesions, which were all 1.5 cm, could be visualized.

The disappearance of  $^{131}\text{I}$ -c-MOV18 from the blood observed in this study differed from our previous reports on c-MOV18 (14,16). The elimination half-life after infusion of

1 mg c-MOV18 IgG in 22 patients with ovarian cancer was 70 h (range, 30–124 h) (14). The terminal half-life of 0.5 mg murine MOV18 reported by Crippa et al. (27) was also 70 h (range, 31.5–165 h). The elimination half-life in this study (10 mg c-MOV18) increased almost 3-fold. Prolonged blood clearance at higher protein doses has been observed in other

**TABLE 3**  
 Dosimetric Analysis of Patients Injected with <sup>131</sup>I-labeled  
 c-MOV18 IgG

Site	Absorbed dose (cGy)		
	Patient 1	Patient 2	Patient 3
Whole body	151	169	170
Liver	340	408	399
Kidney	264	276	289
Spleen	321	424	268
Lung	729	880	735
Red marrow	187	243	218
Tumor	3800*	600†, 1900‡	—

\*Left obturator node.  
 †Tumor on ascending colon.  
 ‡Tumor above aortal bifurcation.

studies as well: the chimeric G250 IgG cleared twice as fast when 2 mg was administered compared with 5-mg doses (28). The observed increase in terminal half-life for chimeric antibodies compared with its murine counterpart, as reported by several investigators (29), has not been found for chimeric MOV18; therefore, the chimerization process was probably not the cause of the prolonged half-life in this study.

Whole-body clearance determines the isolation time for the patient. Whole-body clearance can be accurately estimated from the images. If one is using higher therapeutic doses of <sup>131</sup>I-c-MOV18, however, frequent imaging may not be desirable because of radiation safety restrictions. In this study, we showed the efficacy and simplicity of the use of a portable dose-rate measure to predict the day of discharge from the hospital. Results obtained with this method were comparable with calculations from the images.

We observed an increased radioactivity in lung tissue on all images of patients 1 and 3 in this study and in 1 of 2 patients injected with a dose of 740 MBq <sup>131</sup>I-c-MOV18 in a previous pilot study (data not given). This lung activity contributed very little to the total lung dose, and, therefore, the absorbed dose for the 3 patients in this study was similar and no lung toxicity was expected. Researchers have shown that c-MOV18 binds to the ciliated epithelium in the bronchi and to pneumocytes (12,30). Neither intravenous injections with tracer doses of iodinated c-MOV18 nor intraperitoneal administration of a therapeutic dose of <sup>131</sup>I-m-MOV18 showed an accumulation of activity in the lung (7,14,31). Research that addresses the pulmonary toxicity from RIT is scarce and describes only a few cases in which myeloablative doses were applied. Juweid et al. (32) reported a 280-cGy mean absorbed dose to the lung after intravenous administration of <sup>131</sup>I-MN-14. Although the absorbed radiation dose to the lung in our patients was 2.7-fold higher, it still remained within safety limits (33). One study reported that nonspecific uptake of <sup>131</sup>I in the lungs is related to pre-existing chronic inflammatory lung condition in patients

receiving this radionuclide for treating thyroid cancer (34). Patients 1 and 3, and the patient injected with 740 MBq <sup>131</sup>I-c-MOV18 mentioned above, were heavy smokers. Whether there is any relationship with the heavy-smoking habits in these 3 patients as opposed to the other patients is unclear. None of the patients had any history of pulmonary disease. To date, patients 1 and 3 have not experienced any acute or long-term side effects. The radiation dose estimates to the liver, kidneys, and red marrow did not vary significantly among patients and agreed with other studies (32,35).

In RIT, only patients with minimal residual or microscopic disease are very likely to achieve an optimal therapeutic effect. Applying RIT in such patients is even more attractive because it has been shown in several studies that small tumor lesions have a higher uptake of radiolabeled antibodies (36,37). Thirty percent to 45% of patients with ovarian cancer will have a negative second-look laparotomy after cytoreductive surgery and subsequent chemotherapy (1), but most patients will have a recurrence of disease. Because the disease predominantly spreads to the abdominal cavity, the intraperitoneal route of MAb administration could be preferable. Locoregional delivery, however, is not always desirable. Pre-existing adhesions and peritoneal carcinomatosis might impair locoregional delivery or make this approach hazardous. Furthermore, we found no essential differences in tumor uptake in a study comparing intraperitoneal and intravenous delivery of radiolabeled c-MOV18 in the same patient (38). After considering these factors, we chose the intravenous route for administration.

In regards to tumor dosimetry, we estimated the tumor absorbed doses, which were reported by Buijs et al. (31) for tracer doses of intravenously delivered <sup>131</sup>I-c-MOV18, for a dose of 3 GBq and calculated 510–660 cGy. In contrast, in our study, the accumulated activity in the tumor ranged from 600 to 3800 cGy. The fact that all patients showed a clinical response is an important finding in these patients because they had advanced-stage ovarian carcinoma and also because ovarian cancer is known to be relatively radio-resistant. The short-lasting response in patient 2 was predictable, given the substantial tumor burden. In the other 2 patients with small tumors (2 cm), responses lasted for several months. Crippa et al. (7), who treated 16 patients with ovarian cancer and minimal residual disease intraperitoneally with <sup>131</sup>I-m-MOV18, achieved an overall response rate of 69%. Human antimouse antibodies (HAMA) responses were observed in 94% of these patients. Because of the lack of HACA responses using c-MOV18, dose fractionation should be possible, which could increase the therapeutic efficacy of <sup>131</sup>I-labeled c-MOV18 and help patients more appropriately cope with marrow toxicity (39,40).

## CONCLUSION

Although the number of patients was small, results from this study show that <sup>131</sup>I-labeled c-MOV18 can safely be given to patients who have noncompromised bone-marrow reserves and may have a therapeutic potential in the

treatment of ovarian cancer patients with minimal residual disease.

## ACKNOWLEDGMENTS

The authors thank Curt W. Burger and Klaas Hoekman for clinical assistance, Wim den Hollander and Bram C. Wilhelm for assisting with the antibody infusion, Jacqueline W. Klein Gebbinck and Rob Klok for technical assistance, Greet van Zanten and Marian Ouwens for outstanding patient care, and Sven O. Warnaar for his continuous support. This study was supported by the Dutch Cancer Society and the Dutch Medical and Health Research Organization NWO.

## REFERENCES

1. Disaia PJ, Creasman WT. Epithelial ovarian cancer. In: Disaia PJ, Creasman WT, eds. *Clinical Gynecologic Oncology*. St. Louis, MO: Mosby Year Book; 1993:333-425.
2. Venesmaa P. Epithelial ovarian cancer: impact of surgery and chemotherapy on survival during 1977-1990. *Obstet Gynecol*. 1994;84:8-11.
3. Trimble EL, Adams JD, Vena D, et al. Paclitaxel for platinum-refractory ovarian cancer: results from the first 1,000 patients registered to National Cancer Institute Treatment Referral Center 9103. *J Clin Oncol*. 1993;11:2405-2410.
4. Lanciano RM, Reddy S, Randall M. Update on the role of radiotherapy in ovarian cancer. *Semin Oncol*. 1998;25:361-371.
5. Stewart JSW, Hird V, Snook D, et al. Intraperitoneal yttrium-90-labeled monoclonal antibody in ovarian cancer. *J Clin Oncol*. 1990;8:1941-1950.
6. Muto MG, Finkler NJ, Kassiss AI, et al. Intraperitoneal radioimmunotherapy of refractory ovarian carcinoma utilizing iodine-131-labeled monoclonal antibody OC125. *Gynecol Oncol*. 1992;45:265-272.
7. Crippa F, Bolis G, Seregni E, et al. Single-dose intraperitoneal radioimmunotherapy with the murine monoclonal antibody I-131 MOv18: clinical results in patients with minimal residual disease of ovarian cancer. *Eur J Cancer*. 1995;31A:686-690.
8. Alvarez RD, Partridge EE, Khazaeli MB, et al. Intraperitoneal radioimmunotherapy of ovarian cancer with <sup>177</sup>Lu-CC49: a phase I/II study. *Gynecol Oncol*. 1997;65:94-101.
9. Miotti S, Canevari S, Menard S, et al. Characterization of human ovarian carcinoma associated antigens defined by novel monoclonal antibodies with tumor restricted specificity. *Int J Cancer*. 1987;39:297-303.
10. Campbell IG, Jones TA, Foulkes WD, Trowsdale J. Folate-binding protein is a marker for ovarian cancer. *Cancer Res*. 1991;51:5329-5338.
11. Coney LR, Tomassetti A, Carayannopoulos L, et al. Cloning of a tumor-associated antigen: MOv18 and MOv19 antibodies recognize a folate-binding protein. *Cancer Res*. 1991;51:6125-6135.
12. Buist MR, Molthoff CFM, Kenemans P, Meijer CJLM. Distribution of OV-TL 3 and MOv18 in normal and malignant ovarian tissue. *J Clin Pathol*. 1995;48:631-636.
13. Molthoff CFM, Buist MR, Kenemans P, Pinedo HM, Boven E. Experimental and clinical analysis of the characteristics of a chimeric monoclonal antibody, MOv18, reactive with an ovarian cancer-associated antigen. *J Nucl Med*. 1992;33:2000-2005.
14. Buist MR, Kenemans P, den Hollander W, et al. Kinetics and tissue distribution of the radiolabeled chimeric monoclonal antibody MOv18 and F(ab')<sub>2</sub> fragments in ovarian carcinoma patients. *Cancer Res*. 1993;53:5413-5418.
15. Buist MR, Kenemans P, van Kamp GJ, Haisma HJ. Minor human antibody response to a mouse and chimeric monoclonal antibody after a single i.v. infusion in ovarian carcinoma patients: a comparison of five assays. *Cancer Immunol Immunother*. 1995;40:24-30.
16. Molthoff CF, Prinssen HM, Kenemans P, vanHof AC, den Hollander W, Verheijen RHM. Escalating protein doses of chimeric monoclonal antibody MOv18 immunoglobulin G in ovarian carcinoma patients: a phase I study. *Cancer*. 1997;80:2712-2720.
17. Coney LR, Mezzanzanica D, Sanborn D, Casalini P, Colnaghi MI, Zurawski VR. Chimeric murine human antibodies directed against folate binding receptor are efficient mediators of ovarian carcinoma cell killing. *Cancer Res*. 1994;54:2448-2455.
18. Lindmo T, Boven E, Cuttitta F, Fedorko J, Bunn PA. Determination of the immunoreactive fraction of radiolabeled monoclonal antibody by linear extrapolation to binding at infinite antigen excess. *J Immunol Methods*. 1984;72:77-89.
19. Buijs WC, Siegel JA, Boerman OC, Corstens FH. Absolute organ activity estimated by five different methods of background correction. *J Nucl Med*. 1998;39:2167-2172.
20. Stabin MG. MIRDOSE: personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med*. 1996;37:538-546.
21. Plaizier MABD, Roos JC, Teule GJJ, et al. Comparison of non-invasive approaches to red marrow dosimetry for radiolabelled monoclonal antibodies. *Eur J Nucl Med*. 1994; 21:216-222.
22. Weber DA, Eckerman KF, Dillman LT, Ryman JC, eds. *MIRD: Radionuclide Data and Decay Schemes*. New York, NY: Society of Nuclear Medicine; 1989.
23. Lane DM, Eagle KF, Begent RHJ, et al. Radioimmunotherapy of metastatic colorectal tumours with iodine-131-labelled antibody to carcinoembryonic antigen: phase I/II study with comparative biodistribution of intact and F(ab')<sub>2</sub> antibodies. *Br J Cancer*. 1994;70:521-525.
24. Syrigos KN, Epenetos AA. Radioimmunotherapy of ovarian cancer. *Hybridoma*. 1995;14:121-124.
25. DeNardo GL, DeNardo SJ, Macey DJ, Shen S, Kroger LA. Overview of radiation myelotoxicity secondary to radioimmunotherapy using I-131-Lym-1 as a model. *Cancer*. 1994;73:1038-1048.
26. Larson SM, Carrasquillo JA, Colcher DC, et al. Estimates of radiation absorbed dose for intraperitoneally administered iodine-131 radiolabeled B72.3 monoclonal antibody in patients with peritoneal carcinomatosis. *J Nucl Med*. 1991;32:1661-1667.
27. Crippa F, Buraggi GL, Di Re E, et al. Radioimmunoscinigraphy of ovarian cancer with the MOv18 monoclonal antibody. *Eur J Cancer*. 1991;27:724-729.
28. Steffens MG, Boerman OC, Oosterwijk-Wakka JC, Oosterhof GO, Wijtes JA. Targeting of renal cell carcinoma with iodine-131-labeled chimeric monoclonal antibody G250. *J Clin Oncol*. 1997;15:1529-1537.
29. Biletta R, Lobuglio AF. Chimeric antibodies. *Intern Rev Immunol*. 1993;10:165-176.
30. Stein R, Goldenberg DM, Mattes MJ. Normal tissue reactivity of four anti-tumor monoclonal antibodies of clinical interest. *Int J Cancer*. 1991;47:163-169.
31. Buijs WCAM, Tibben JG, Boerman OC, et al. Dosimetric analysis of chimeric monoclonal antibody cMOv18 IgG in ovarian carcinoma patients after intraperitoneal and intravenous administration. *Eur J Nucl Med*. 1998;25:1552-1561.
32. Juweid ME, Swayne LC, Sharkey RM, et al. Prospects of radioimmunotherapy in epithelial ovarian cancer: results with iodine-131-labeled murine and humanized MN-14 anti-carcinoembryonic antigen monoclonal antibodies. *Gynecol Oncol*. 1997;67:259-271.
33. Emani B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. 1991;21:109-122.
34. Höschl R, Choy DHL, Gandevia B. Iodine-131 uptake in inflammatory lung disease: a potential pitfall in treatment of thyroid carcinoma. *J Nucl Med*. 1988;29:701-706.
35. Siegel JA, Pawley DA, Lee RE, et al. Tumor, red, marrow, and organ dosimetry for <sup>131</sup>I-labeled anti-carcinoembryonic antigen monoclonal antibody. *Cancer Res*. 1990;50(suppl):1039S-1042S.
36. van Hof AC, Molthoff CFM, Davies Q, et al. Biodistribution of indium-111 labeled engineered human antibody CTM01 in ovarian cancer patients: influence of protein dose. *Cancer Res*. 1996;56:5179-5185.
37. Blumenthal RD, Fand I, Sharkey RM, Boerman OC, Kashi R, Goldenberg DM. The effect of antibody protein dose on the uniformity of tumor distribution of radioantibodies: an autoradiographic study. *Cancer Immunol Immunother*. 1991; 33:351-358.
38. Molthoff C, van Hof AC, Buist M, van Zanten-Przybyls I, Verheijen R, Kenemans P. Comparison of the intravenous versus the intraperitoneal route of administration of chimeric monoclonal antibody MOv18 for targeting ovarian cancer [abstract]. *Cancer Biother Radiopharm*. 1998;13:312.
39. Schlom J, Molinolo A, Simpson JF, et al. Advantage of dose fractionation in monoclonal antibody-targeted radioimmunotherapy. *J Natl Cancer Inst*. 1990;82: 763-771.
40. Molthoff CFM, Pinedo HM, Schluper HMM, Boven E. Influence of dose and schedule on the therapeutic efficacy of I-131 labelled monoclonal antibody 139H2 in a human ovarian cancer xenograft model. *Int J Cancer*. 1992;50:474-480.