Decreased intraperitoneal disease recurrence in epithelial ovarian cancer patients receiving intraperitoneal consolidation treatment with yttrium-90-labeled murine HMFG1 without improvement in overall survival

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This study analyzes the site of disease recurrence in ovarian cancer patients to assess the influence of a single intraperitoneal (IP) administration of yttrium-90-labeled murine monoclonal antibody HMFG1 (90Y-muHMFG1) on the pattern of disease recurrence. In a large phase III trial, 224 ovarian cancer patients in complete clinical remission with FIGO stage Ic-IV were randomized between standard treatment plus a single IP 90Y-muHMFG1 versus standard treatment alone after negative second-look laparoscopy. Case report forms of all patients with disease recurrence were reviewed to determine site and date of recurrent disease. In total, 447 patients were included in the study with a median follow-up of 3.5 years. Relapse was seen in 104/224 in the active and 98/223 in the control arm. Significantly fewer IP (p < 0.05) and more extraperitoneal (p < 0.05) relapses occurred in the active treatment arm. Time to IP recurrence was significantly longer (p = 0.0019) and time to extraperitoneal recurrence was significantly shorter for the active treatment arm (p < 0.001). The impact of IP radioimmunotherapy on IP relapse-free survival could only be seen in the subgroup of patients with residual disease after primary surgery (HR, 0.31; 95% CI, 0.18 to 0.53; p = 0.002). Although, there was no survival benefit for IP radioimmunotherapy as consolidation treatment for epithelial ovarian cancer, we found an improved control of IP disease, that was offset by increased extraperitoneal recurrences.

Key words: HMFG1; intraperitoneal; ovarian cancer; yttrium

The prognosis of women with advanced stage ovarian cancer remains poor despite 40 years of research into systemic therapies. Epithelial ovarian cancer is the fifth leading cause of cancer deaths and the most lethal gynecologic cancer in the United States. The introduction of platinum and subsequently taxane based chemotherapy has resulted in longer progression free (15.5–22 months) and overall (31–44 months) survivals, yet at least 50–75% of these women have persistent or recurrent disease with long-term survival (>5 years) achieved in only 25%. In the majority (82%) of the patients recurrence is seen within the peritoneal cavity, and in ~12% it occurs in the retroperitoneal lymph nodes. The rationale for intraperitoneal (IP) therapy in ovarian cancer is based on the predominately or solely peritoneal location of ovarian cancer during the early part of the natural history of the disease and the significant pharmacologic advantage of delivering antitumor agents directly into the accessible but confined space of the peritoneal cavity. Three randomized trials in ovarian cancer patients affirmed this assumption by demonstrating improved survival with IP chemotherapy as compared to similar or identical agents delivered systemically. Recently, the National Cancer Institute proposed to make IP chemotherapy part of the standard treatment in ovarian cancer.

In the recently published study of monoclonal antibody radioimmunotherapy trial, patients with advanced stage ovarian cancer in complete clinical remission were randomized to a single IP administration of yttrium-90-labeled murine monoclonal antibody HMFG1 (90Y-muHMFG1) plus standard treatment versus standard treatment alone. A total of 447 patients were included in the study of which 224 received IP 90Y-muHMFG1 plus standard treatment (active treatment group) and 223 patients only received standard treatment. During follow-up (range 1–6 years) 70 patients died and 104 patients experienced relapse in the active arm of the study compared to 61 deceased patients and 98 patients with relapse who only received standard treatment. Cox proportional hazard analysis of survival and time to relapse demonstrated no difference between the 2 treatment arms. A single IP administration of 90Y-muHMFG1 in patients with epithelial ovarian cancer who had a negative second-look laparoscopy (SLL) did not extend survival or time to relapse.

In the present study the site of disease recurrence in women participating in the international phase III trial of IP 90Y-muHMFG1 was analyzed to assess the influence of a single IP administration of 90Y-muHMFG1 on the pattern of recurrence.

Material and methods

Between February 1998 and January 2003 patients who met the eligibility criteria of the international phase III trial were enrolled in the study from 74 centers in 17 countries. Written consent was obtained from all patients. The study was approved by the appropriate scientific and ethical authorities and conducted in compliance with good clinical practice (guidelines of the European Medicines Agency) and the standards of the Declaration of Helsinki. Patients with histologically proven epithelial ovarian cancer FIGO stage Ic-IV and macroscopically negative SLL were randomized 1:1 between standard treatment plus IP 90Y-muHMFG1 and standard treatment alone. Patients in the IP arm received a single IP dose of 25 mg of the 90Y-muHMFG1 (maximum dose 1110 MBq) between 4 and 8 weeks after delivery of their final cycle of chemotherapy. Institutions were permitted to deliver other standard consolidation therapies after the study to patients in both treatment arms. Follow-up of all patients was identical with the exception that standard treatment patients attended follow-up visits only at weeks 1, 4 and 8 and patients in the active treatment arm weekly for the first 6 weeks and at week...
8. Further follow-up occurred at 3 monthly intervals for 36 months and then at 6 monthly intervals until study completion. At each visit, patients underwent clinical and laboratory examinations. Clinical disease recurrence had to be confirmed by one or more of the following independent objective assessments: radiological findings on CT scan, histological evidence of recurrence from materials obtained at surgical procedures including histological and/or cytological sampling. Date of recurrence was the date of the first CT scan, histology sample or cytology sample that confirmed disease recurrence.

Patients had a preentry CT scan with follow-up scans on a yearly basis as long as they remained in remission and on study. All preentry and follow-up CT copies were reviewed by a central reader (independent expert radiologists in the USA and Europe) at a central reading facility. The study was closed in March 2004 when 131 deaths had occurred. At the end of the study, a final CT scan was obtained for all surviving patients whose previous scan had occurred more than 3 months before the end of study date. Histologically and/or cytologically diagnosed recurrence of disease was also reviewed by the central histopathology facility.

The case report forms of all patients with disease recurrence were reviewed after disclosure of the international phase III trial. Operation reports, CT-scans, MRI scans, chest X-rays, histopathology and cytopathology reports and physical examination documents were analyzed to determine site and date of disease recurrence.

Time to disease recurrence was measured as the number of days between SLL and the date of documented disease recurrence up to the end of study date. Patients who had not developed recurrent disease at study closure were censored as of that date.

Recurrence categories

Patients with disease recurrence were categorized into 4 main groups: IP recurrence, extraperitoneal recurrence, combination of intra- and extraperitoneal recurrence and unknown site of recurrence. Patients assigned to the IP relapse group demonstrated peritoneal and/or diaphragm involvement as the only site of recurrence. The metastases in this group are the result of direct IP tumor spread. Patients with evidence of recurrent disease confined to extraperitoneal sites were subdivided into those with nodal and distant patterns of recurrence. Nodal involvement included disease recurrence in pelvic, paraaortic, inguinal, axillary and/or mediastinal lymph nodes. Patients categorized as having distant metastases included all women with extraperitoneal relapse sites, which were not located in lymph nodes, e.g. liver (intraparenchymal), lung, brain and abdominal wall. When both IP and extraperitoneal sites of disease were documented at time of initial recurrence, patients were assigned to the combination relapse group. Patients with recurrent disease but no documented site or unknown site of disease recurrence were assigned to the unknown site group.

Statistical analysis

All statistical calculations were performed using SPSS 12.0.1 software packet (SPSS, Chicago). Differences between characteristics were compared using the Wilcoxon rank sum test. All statistical tests were performed at the 0.05 level of significance and were two-sided. The recurrence-free survival rates were calculated by the Kaplan-Meier method and the difference was determined by log rank test. Patients who developed recurrent disease at a different site than analyzed in the Kaplan Meier method were censored in that analysis. The Cox proportional hazards regression model was used to identify prognostic factors. Step-backward regression was used to build a valid statistical model for the association of prognostic factors with relapse-specific time to relapse among patients.

Results

In total 447 patients were included in the study with a median follow-up of 3.5 years. Patient characteristics are summarized in Table I. The active and passive treatment arms consisted of 224 patients with a median age of 54.4 years and 223 patients with a median age of 53.7 years, respectively. Differences in age, FIGO stage and histologic tumor subtype were not statistically significant.

Recurrent disease was documented in 104/224 patients assigned to active therapy and in 98/223 patients in the control arm. Of the 104 patients with disease recurrence in the active treatment arm, 7 patients had incomplete records, leaving 97 patients eligible for evaluation. In the standard treatment arm, 4 patients of the 98 patients with recurrent disease had missing data and 94 patients were eligible for evaluation.

The distribution of initial disease recurrence sites is summarized in Table II. Solely IP relapses were diagnosed significantly more frequent in the standard treatment arm (69/94) than in the active treatment arm (40/97, p < 0.05). Pure extraperitoneal recurrence occurred in 47 of the 97 (48.5%) patients in the active treatment arm compared to 13 of the 94 (14%) patients assigned to the standard treatment arm (p < 0.05). Most of the extraperitoneal relapses in the active treatment arm were lymphatic, 36 of the 47 (77%), with the majority in the paraaortic region, (22 of the 36). In the standard treatment arm only 10 of the extraperitoneal recurrences occurred in the lymph nodes. In total 30 of the 97 (32%) patients assigned to the active treatment arm had either IP (40
patients) or simultaneous IP and extraperitoneal recurrence (10 patients) as compared to 81 of the 94 (89%) patients assigned to the control arm (69 IP and 12 a combination of IP and extraperitoneal disease recurrence).

Kaplan-Meier plots of time to IP and extraperitoneal disease recurrence are shown in Figures 1 and 2, respectively. The mean interval from SLL to the diagnosis of IP recurrence was 53.4 months (SEM = 2 months) for the active and 46.4 months (SEM = 1.16 months) for the standard treatment group. For the extraperitoneal recurrences mean interval time from SLL to extraperitoneal recurrence was 51 months (SEM = 2 months) for the active and 63.6 months (SEM = 1.6 months) for the standard treatment group. Time to IP recurrence was significantly longer for the active treatment arm (logrank test, $p = 0.0019$) and time to extraperitoneal recurrence was significantly shorter for the active treatment arm (logrank test, $p < 0.001$). The mean time from SLL to diagnosis of a combination of IP and extraperitoneal disease recurrence in the active treatment group was 63 months (SEM = 1 month) and 64 months (SEM = 1.5 months) for the standard treatment group. The mean time from SLL to unknown recurrence in the active and standard treatment group were 64 months (SEM = 1 month) and 67 months (SEM = 1 month), respectively.

Multivariate regression analysis evaluating factors that could influence site of disease recurrence demonstrated that for both recurrence sites (IP and extraperitoneal) patients with FIGO stage III or greater were at significantly higher risk for recurrence than patients with FIGO stage II or less (Table III). Patients with residual disease after primary surgery were at significantly increased risk of IP disease recurrence compared to patients without residual disease. For an overview see Table III. The impact of IP radiomunotherapy on IP relapse-free survival could only be seen in the subgroup of patients with residual disease after primary surgery, as relapse-free survival in patients with residual disease was significantly better in the active treatment arm (HR, 0.31; 95% CI, 0.18–0.53; $p = 0.002$). For patients without residual disease after primary surgery, consolidation treatment with $^{90}$Y-muHMFG1 did not influence IP relapse-free survival. Kaplan-Meier plots of time to IP disease recurrence in patients with and without residual disease are shown in Figure 3.

**Discussion**

In this retrospective analysis there is a significant difference in pattern of disease recurrence between patients who received a single IP treatment with $^{90}$Y-muHMFG1 and those in the control arm. Patients in the active treatment arm had significantly fewer IP recurrences compared to the standard arm and time to IP recurrence of disease was significantly longer for the active treatment group. Conversely, in the active treatment group, extraperitoneal recurrences were more frequent and presented earlier.

This study provides useful natural history data regarding patterns of disease recurrence in a large group of ovarian cancer patients who achieved a complete clinical remission after primary cytoreduction and platinum-based chemotherapy confirmed by negative SLL. In our study 44% of the patients in the standard treatment arm had experienced a relapse by the end of study date. Gaducci et al. and Bolis et al. found similar relapse rates while studies with slightly longer follow-up have reported higher recurrence rates, 52% and 64%. In our control group, 89% of the women demonstrated IP disease at time of first recurrence, which is similar albeit modestly higher than IP recurrence rates reported elsewhere. On the other hand, the incidence of recurrent disease localized in the retroperitoneal lymph nodes was lower in this study than reported elsewhere. The discrepancy is likely due to inclusion of women with lower stage disease in our study since the risk of lymph node involvement rises with advanced stage disease to more than 50%. The study population of the international phase III trial comprised patients with FIGO stage Ic-IV while studies performed by Gaducci et al. and Rubin et al. were limited to patients with FIGO stage III and IV.

Significantly, fewer IP recurrences were seen in the active treatment arm. An explanation for this observation could be that exposing the peritoneal cavity to a single dose of $^{90}$Y-muHMFG1 successfully eradicated residual microscopic tumor deposits. Another option could be that IP β-radiation may negatively influence peritoneal vascularity and causes fibrosis, which again may negatively affect peritoneal tumor implants. Furthermore, by using a murine monoclonal antibody specifically directed against an antigen expressed on ovarian tumor cells, an induced immunologic
response against the tumor might also contribute to the destruction of microscopic IP tumor deposits.

The increased incidence of extraperitoneal relapse in the active treatment arm as compared to the standard treatment arm is both striking and difficult to explain. This is not what one would expect after IP therapy with ⁹⁰Y-muHMFG1 if treatment resulted in eradication of tumor at the predominant site of persistent disease. By administering ⁹⁰Y-muHMFG1 straight into the peritoneal cavity, a positive regional effect seems to occur, while simultaneously the ⁹⁰Yttrium causes reversible myelosuppression, as described in the previous publication on the international phase III trial. This myelosuppressant effect may explain the apparent high number of extraperitoneal recurrences in the active treatment arm. The possibility that such therapy may induce detrimental systemic effects should be considered and explored further. More likely, our findings may indicate that extraperitoneal dissemination of ovarian cancer occurs more often than previously assumed; development of IP disease recurrence may mask the presence of systemic and/or nodal metastasis since the majority of patients treated with standard therapeutic strategies experience predominantly IP failure and disease progression.

We found a difference in pattern of disease recurrence in ovarian cancer patients in complete clinical remission treated with a single IP ⁹⁰Y-muHMFG1 administration compared to the standard treatment group, even though the international phase III study did not find any overall difference in progression free survival. IP radioimmunotherapy with ⁹⁰Y-muHMFG1 improved tumor control in the IP cavity, but at the same time was associated with more extraperitoneal recurrences. This shift in recurrence ultimately resulted in comparable mean progression free survival times in both arms of the international phase III trial.

Findings from this study should be evaluated in the appropriate context. Specifically, the analysis of pattern of disease recurrence was not specifically noted as a primary or secondary endpoint of the study and hence these data were not collected prospectively or independently audited. In addition, the protocol did not specifically indicate that comprehensive staging was required at the time.

TABLE III – COX REGRESSION ANALYSIS OF TIME TO INTRAPERITONEAL AND EXTRAPERITONEAL RELAPSE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intraperitoneal relapse</th>
<th>Extraperitoneal relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% CI</td>
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<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Active</td>
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<td>0.48–1.63</td>
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<td>FIGO stage</td>
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<td></td>
</tr>
<tr>
<td>≤IIc</td>
<td>1.00</td>
<td>Reference</td>
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<tr>
<td>≥III</td>
<td>2.78</td>
<td>1.50–5.17</td>
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<tr>
<td>Residual disease</td>
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<td></td>
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<tr>
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<tr>
<td>Yes</td>
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<tr>
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<tr>
<td>Active</td>
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<td>0.15–0.79</td>
</tr>
</tbody>
</table>

FIGO, International Federation of Gynecology and Obstetrics; NS, not significant; NC, not calculated.

![Figure 3](image.png)  
**Figure 3** – Kaplan-Meier curves of intraperitoneal relapse-free survival in (a) patients without residual disease and (b) all patients with residual disease after primary surgery.
of disease recurrence and hence the search for extraperitoneal disease was of variable intensity across this international study. Nevertheless data were evaluable for over 90% of the cases. Furthermore, the confirmation of extraperitoneal disease including extraperitoneal lymphadenopathy in patients with cancer is not an exact science and most women did not have surgical or pathological confirmation of disease recurrence in extraperitoneal or IP sites. Finally, the detection method of disease recurrence is similar to the one used during follow-up of patients in daily practice with the same limitations. The CT-scan modality has a poor sensitivity for detection of small tumor implants, especially on the small intestine or mesentery, but improvement of the CT modality has allowed detection of 28–50% of the peritoneal implants as small as 5 mm in diameter.16

In conclusion, this retrospective analysis of a large prospective and randomized trial identifies a difference in pattern of disease recurrence in patients with ovarian cancer assigned to receive a single IP administration of 90Y-muHMFG1 with no significant effect on total overall and progression-free survival because of the higher incidence of extraperitoneal disease recurrence.

References