

# Circulating CA125 in Patients with Peritoneal Mesothelioma Treated with Cytoreductive Surgery and Intraperitoneal Hyperthermic Perfusion

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**Background:** Recent phase I/II trials report encouraging results in selected patients with peritoneal mesothelioma (PM) treated with cytoreductive surgery (CRS) and intraperitoneal hyperthermic perfusion (IPHP). Circulating tumor markers have never been extensively investigated in the management of PM. We assessed the clinical role of markers in a large series of patients with PM undergoing CRS and IPHP.

**Methods:** Clinical data on 60 patients with PM operated with the intention to perform adequate CRS (residual tumor nodules  $\leq 2.5$ mm) and IPHP were prospectively collected. Marker levels were determined pre-operatively, post-operatively, and routinely during long-term follow-up. Baseline diagnostic sensitivity, accuracy in monitoring response to treatment or tumor progression and prognostic significance were determined.

**Results:** Baseline diagnostic sensitivity was 53.3% for CA125, 0 for CEA, 3.8% for CA19.9 and 48.5% for CA15.3. Forty-six patients underwent adequate cytoreduction and IPHP; gross residual tumor was left after the operation in fourteen. Postoperatively, CA125 became negative in 21/22 patients with elevated baseline levels undergoing adequate CRS and IPHP, while remained elevated in 9/9 patients with persistent macroscopic disease. CA125 became positive in 12/12 patients with elevated baseline levels developing disease progression after adequate CRS and IPHP. Baseline CA125 showed borderline prognostic significance only among patients not previously treated with systemic chemotherapy.

**Conclusions:** CA125 was elevated in the majority of patients with PM in the present series. Serial marker measurements paralleled tumor growth or regression after CRS and IPHP, suggesting the need of further studies to assess the role of CA125 in this clinical setting.

**Key Words:** CA125—Peritoneal mesothelioma—Peritonectomy—Intraperitoneal hyperthermic perfusion—Serum tumor markers—Loco-regional chemotherapy.

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Peritoneal mesothelioma (PM) is an uncommon neoplasm, accounting for about 15–20% of all forms of malignant mesothelioma.<sup>1</sup> PM is a locally invasive

but rapidly fatal disease.<sup>2</sup> Different treatments have been proposed, including surgery, systemic, and loco-regional chemotherapy (CT). Nevertheless, long-term prognosis is poor, as in the literature median survival generally does not exceed 12 months.<sup>2,3</sup>

In recent years, an integrated approach to isolated peritoneal malignancies has been developed, combining aggressive cytoreductive surgery (CRS) with heated loco-regional chemotherapy.<sup>4,5</sup> It consists of complete macroscopic tumor removal by means of peritonectomy and other visceral resections. Follow-

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ing surgery, the microscopic residual disease is treated with intra-peritoneal hyperthermic perfusion (IPHP). Encouraging results have been reported in selected patients with PM.<sup>6-13</sup>

A large number of tumor related antigens are now available in oncology practice.<sup>14</sup> Unfortunately, no marker has proved to be specifically related to the cell neoplastic transformation, thus playing generally a limited role in the early identification of tumors. On the other hand, serial measurements tend to roughly reflect changes in tumor volume. Consequently, markers are increasingly used for disease staging and monitoring tumor progression or response to therapy. The role of serum markers in mesothelioma management has never been established.

We performed the present study to investigate the clinical utility of circulating tumor markers for patients with PM undergoing CRS and IPHP. In detail, primary study end-points were the following: (1) diagnostic sensitivity of baseline marker determination among the patients included in the present series; (2) correlation between post-operative marker levels and response to the comprehensive treatment; (3) marker reliability in monitoring disease progression during post-operative follow-up; and 4) long-term prognostic significance of baseline marker levels. The correlation between baseline marker levels and relevant clinicopathological variables was also assessed.

## PATIENTS AND METHODS

All the patients included in the present study were treated according to a protocol approved by the Institutional Ethic Committee and gave written informed consent. Clinical data, pathological findings, treatment performed in our center, and long-term follow-up were collected through the prospective computerized database of patients who underwent CRS and IPHP at the National Cancer Institute (Milan, Italy). Diagnosis of PM was made or confirmed in our Pathology Department for each patient, according to a protocol including hematoxylin-eosin stained sections and immunohistochemical studies, as described in a previous paper.<sup>12</sup> The following immunohistochemical panel was used to differentiate PM from other primary or metastatic peritoneal malignancies: positive calretinin, cytokeratins 5/6, Wilms' tumor 1 antigen (WT1), epithelial membrane antigen (EMA) or mesothelin, and negative polyclonal carcinoembryonic antigen (CEA), B72.3, Ber-Ep4. Tumors were histologically categorized as multicystic, well-differentiated papillary, epithelioid,

biphasic, and sarcomatoid, following the WHO classification.<sup>15</sup>

## Treatment

The details of the operative technique adopted in our center were previously described.<sup>4-6</sup> Briefly, one to six of the following procedures were performed to remove all the visible disease: (1) right parietal peritonectomy, right hemy-colectomy, greater omentectomy; (2) pelvic peritonectomy, sigmoid colectomy, hysterо-anessectomy; (3) antrectomy, cholecystectomy, lesser omentectomy, hepatic hilum dissection; (4) right sub-diaphragmatic peritonectomy, Glisson's capsule dissection; (5) left sub-diaphragmatic peritonectomy, splenectomy, left parietal peritonectomy; (6) other intestinal and/or abdominal mass resections.

IPHP was performed according to the closed abdomen technique. Perfusate volume was 4-6 Lt. Drug schedules were cis-platinum (25 ml/mq/Lt) plus mitomycin-C (3.3 mg/mq/Lt) for a perfusion time of 60 minutes (5 cases) or cis-platinum 43 mg/Lt plus doxorubicin (15.25 mg/Lt) for 90 minutes (45 cases). Perfusion was carried out at 42.5°C; average flow was 700 mL/min.

All the patients underwent postoperative follow-up as out-patients. Clinical evaluation, thoracic/abdominal CT-scan, and marker determinations were performed every 3 months during the first 2 years and every 6 months afterward.

## Serum Markers

Serum concentration of CEA, carbohydrate antigen 19.9 (CA19.9), carbohydrate antigen 15.3 (CA15.3), carbohydrate antigen 125 (CA125) were determined at a median of 3 days (range 1-3) before surgery, at a median of 3 months (range 3-4) after surgery, and routinely during long-term follow-up.

Serum for marker assessment was separated by centrifugation immediately after clotting and stored at -20°C until assay. All marker measurements were performed at the Laboratory Unit (Nuclear Medicine Division). CEA serum level was measured by immunoradiometric assay (IRMA) CEA IRMA CT supplied by Radim (Rome, Italy). CA125 serum level was measured by IRMA CA125 II<sup>TM</sup> supplied by DiaSorin (Saluggia, Italy). CA19.9 and CA15.3 serum levels were measured by IRMAs ELSA CA19.9 and ELSA CA15.3, respectively, manufactured by Cis-Bio International supplied from Shering S.p.A. (Milan, Italy). All assays were conducted according

to manufacturer instructions. Normal values were < 5 ng/mL for CEA, < 37 U/mL for CA19.9, < 35 U/L for CA125, and < 30 U/mL for CA15.3.

### Definitions

In this study, sensitivity was the percentage of patients with PM who had elevated marker levels; specificity was the percentage of patients without disease who had normal marker levels.

Tumors with papillary, cystic, or mixed papillary-cystic features were histologically scored as low-grade PM; epithelioid and biphasic variants were scored as high-grade PM.

Patient performance status was classified according to the World Health Organization (WHO) score.<sup>16</sup> The extent of peritoneal involvement was scored at surgical exploration according to the peritoneal cancer index (PCI).<sup>17</sup>

Response to the integrated treatment of CRS and IPHP was assessed according to the intra-operative evaluation of the completeness of the cytoreduction and to physical examination and CT-scan performed 3 months after the procedure. The completeness of cytoreduction (cc) was classified at the end of the surgical phase, according to Sugarbaker criteria:<sup>18</sup> cc-0 = no residual disease; cc-1 = residual disease  $\leq 2.5$ mm; cc-2 = residual disease  $> 2.5$ mm  $\leq 2.5$ cm; cc-3 = residual disease  $> 2.5$ cm. Cc-0/cc-1 cytoreduction was considered adequate. Suboptimal (cc-2/cc-3) cytoreduction, exploratory laparotomy, minor debulking, or other palliative procedures were all considered inadequate. Adequate cytoreduction and no evidence of disease at postoperative clinico-radiological work-up identified patients with complete response; failure to meet the above mentioned criteria identified patients with no response to the combined treatment.

Among patients undergoing adequate cytoreduction, post-operative disease progression was confirmed at surgical exploration or by CT-scan/ultrasound guided procedure. Alternatively, it was defined according to the Response Evaluation Criteria in Solid Tumor Group (RECIST).<sup>19</sup>

### Statistics

Survival rates were calculated according to the Kaplan-Meier method.<sup>20</sup> Overall (OS) and progression-free survival (PFS) were dated from surgery to the time of death or disease progression, respectively. Patients with uneventful post-operative course were censored at the time of last follow-up

visit. According to the intention-to-treat principle, operative death was included in the calculation of survival rates as an event occurring at month zero. Differences between curves were tested by two-tailed log-rank test. Multivariable analysis of factors deemed as statistically significant by univariable analysis was performed by Cox proportional hazard model.<sup>21</sup> Distribution of nominal or continuous variables was tested using Chi-square test with Yates correction or Mann-Whitney U-test, as appropriate. In all statistical analyses *P* value < 0.05 was considered significant.

## RESULTS

Sixty consecutive patients operated with the intention to perform adequate CRS and IPHP from June 1997 to October 2005 constituted the study population. Patient clinical characteristics are shown in Table 1.

### Baseline Serum Marker Levels

Information about pre-operative determination was available for all patients on CA125 and CEA, but only for 52 patients on CA19.9, and 33 on CA15.3. Both CA19.9 and CA15.3 were elevated in one patient; CA19.9, CA15.3, and CA125 in 1; CA125 and CA15.3 in 14; CA125 alone in 17. Therefore, baseline diagnostic sensitivity was 32/60 (53.3%) for CA125, 0/60 for CEA, 2/52 (3.8%) for CA19.9, and 16/33 (48.5%) for CA15.3.

Correlation between CA125 concentration and other clinicopathological variables is displayed in Table 2. Absolute CA125 values were significantly higher in patients with high-grade PM and PCI > 25. However, when CA125 values were expressed as positive or negative according to the 35 U/L cut-off, positive determinations were statistically related to high-grade histological subtype, PCI > 25 and no pre-operative systemic CT. Correlation with the same variables was explored also for CA15.3 but no significant association was found.

### Response to Treatment

Fifty patients underwent CRS and IPHP; the completeness of cytoreduction was scored as cc-0 in 32 cases, cc-1 in 14, cc-2 in 2, and cc-3 in 2. Ten patients underwent only laparotomy or debulking procedures, as a consequence of massive disease involvement of small bowel, mesentery, and/or he-

**TABLE 1.** Clinicopathological characteristics of 60 patients with peritoneal mesothelioma

| Variables            | Categories                 | N            | % of total |
|----------------------|----------------------------|--------------|------------|
| Sex                  | Male                       | 24           | 40.00%     |
|                      | Female                     | 36           | 60.00%     |
| Age, median (range)  |                            | 53.5 (22–75) |            |
| Histology            | Multicystic                | 5            | 8.30%      |
|                      | Papillary                  | 4            | 6.70%      |
|                      | Mixed papillary-cystic     | 2            | 3.30%      |
|                      | Epithelioid                | 43           | 71.70%     |
|                      | Biphasic                   | 6            | 10.00%     |
| Ascites              | Present                    | 38           | 63.30%     |
|                      | Absent                     | 22           | 36.70%     |
| Previous systemic CT | Not done                   | 40           | 66.70%     |
|                      | Done                       | 20           | 33.30%     |
|                      | Epirubicin + Ifosfamide    | 6            |            |
|                      | Cis-platinum + Gemcitabine | 5            |            |
|                      | Platinum based             | 7            |            |
|                      | Other                      | 2            |            |
| PCI                  | ≤25                        | 15           | 25.00%     |
|                      | >25                        | 45           | 75.00%     |
| WHO score            | 0                          | 52           | 86.70%     |
|                      | 1–2                        | 8            | 13.30%     |

CT: chemotherapy; PCI = peritoneal cancer index;<sup>15</sup> WHO score = World Health Organization performance status.<sup>14</sup>

**TABLE 2.** Correlation between CA125 levels and several clinical variables in patients with peritoneal mesothelioma

| Variables   | Categories  | N  | CA125 >35 U/L |        |        | CA125 absolute value |        |
|-------------|-------------|----|---------------|--------|--------|----------------------|--------|
|             |             |    | No.           | %      |        | Average (±SD)        |        |
| Sex         | Male        | 24 | 16            | 66.70% | NS     | 90.82 (±126.90)      | NS     |
|             | Female      | 36 | 16            | 44.40% |        | 58.87 (±85.50)       |        |
| Age         | ≤53.5 years | 30 | 15            | 50.00% | NS     | 87.97 (±139.71)      | NS     |
|             | >53.5 years | 30 | 17            | 56.70% |        | 55.23 (±46.07)       |        |
| WHO score   | 0           | 52 | 27            | 51.90% | NS     | 63.08 (±94.85)       | NS     |
|             | 1–2         | 8  | 5             | 62.50% |        | 123.88 (±145.63)     |        |
| Histology   | Low grade   | 11 | 2             | 18.20% | 0.0246 | 35.36 (±58.27)       | 0.0153 |
|             | High grade  | 49 | 30            | 61.20% |        | 55.76 (±110.36)      |        |
| PCI         | ≤25         | 15 | 2             | 13.30% | 0.001  | 20.55 (±16.49)       | 0.0014 |
|             | >25         | 45 | 30            | 66.70% |        | 88.63 (±114.95)      |        |
| Ascites     | Present     | 39 | 24            | 61.50% | NS     | 65.48 (±109.37)      | NS     |
|             | Absent      | 21 | 7             | 33.30% |        | 74.55 (±101.81)      |        |
| Previous CT | Done        | 20 | 6             | 30.00% | 0.0231 | 66.51 (±138.38)      | NS     |
|             | Not done    | 40 | 26            | 65.00% |        | 73.79 (±82.61)       |        |

CT = pre-operative systemic chemotherapy; PCI = peritoneal cancer index.<sup>15</sup> WHO score = World Health Organization performance status;<sup>14</sup> SD = standard deviation; NS = not significant.

patic hilum. Therefore, 46 patients underwent adequate cytoreduction with no or minimal residual disease, while inadequate surgery was carried out in 14. Post-operative marker assay was not available in 2 patients, due to short follow-up, and in 2, due to operative death.

Twenty-three patients with elevated baseline CA125 underwent adequate cytoreduction and IPHP; clinicoradiological work-up showed no evidence of disease three months after surgery in 22 of them (one had short follow-up). Post-operative CA125 was normal in all but one patient with a concurrent autoimmune disorder, although clinical examination and CT-scan did not detect any persistent disease.

Within this group, mean CA125 value was 118.33 (standard deviation (SD)±121.63) before and 12.94 (SD±9.28) after the treatment. The difference was highly significant ( $P = .0002$ ).

Nine patients with pre-operative CA125 level >35U/L underwent inadequate CRS. Persistent gross disease was confirmed by CT-scan three months after surgery; CA125 failed to return within normal range in seven of them (two operative deaths). Mean CA125 value was pre-operatively 142.37 (SD±150.63) and post-operatively 114.95 (SD±97.86); the difference was not significant ( $P = .6935$ ).

No patient with normal pre-operative CA125 showed elevated levels 3 months after surgery (one

had short follow-up). In the assessment of persistent disease after CRS and IPHP, marker sensitivity was 63.6% (7/11) and specificity 97.8% (44/45).

Within patients with positive baseline CA15.3, post-operative level was persistently elevated in 3/3 patients undergoing inadequate CRS. On the contrary, CA15.3 became negative in 12/12 patients following adequate CRS and IPHP (one had short follow-up).

### Disease Progression

Histologically proven disease progression was observed after a median interval of 10 months (range 5–57) in 17 of 46 patients undergoing adequate cytoreduction and IPHP. In 12 individuals with preoperative positive CA125 which normalized after the treatment, elevated marker levels were recorded by the time of disease progression. In three patients, CA125 raised above 35U/L value 2, 3, and 6 months, respectively, before they showed any clinicoradiological evidence of progression. Disease progression was treated with second CRS and IPHP in 3 patients who are presently alive after 24, 35, and 48 months. CA125 normalized after the procedure in all of them. Debulking and systemic CT were performed in 4 patients, palliative surgery in 2, systemic CT in 4, and no treatment in 4. Median survival was 5 months in this group. During post-operative follow-up, false positive CA125 tests were never recorded.

Post-operative PM progression occurred in 9 patients with elevated baseline CA15.3 and was associated with marker elevation in each of them.

Disease progression was recorded after a median of 5 months (range 1–28) in 11 of 14 patients who underwent inadequate CRS (two operative deaths). In 6 patients with elevated baseline levels, CA125 failed to return within normal range after surgery and post-operative disease progression was associated to further marker level increase.

### Prognosis

Nineteen patients died during the study period after a median interval of 7 months (range 1–52) from surgery. Median follow-up was 23 months (range 1–100) for the 41 surviving patients. Five-year overall and progression-free survival was 53.7% and 27.1%, respectively, for the complete series. OS and PFS in patients undergoing adequate and inadequate cytoreduction are displayed in Figs. 1 and 2. Univariable and multivariable analysis of factors influencing OS and PFS is displayed in Table 3 for the whole series.

High-grade histology, WHO performance status > 0, and inadequate cytoreduction were identified as independent risk factors for both OS and PFS. Baseline CA125 and CA15.3 did not correlate to survival rates. Five-year OS was 59.4% and 100.0% ( $P = .0152$ ) in 40 patients with, respectively, elevated or normal baseline CA125 not treated with preoperative systemic CT; 5-year PFS was 24.9% and 76.9% ( $P = .0092$ ). Multivariable analyses performed in this subset of patients did not recognize CA125 as an independent prognostic factor for either OS or PFS (data not shown).

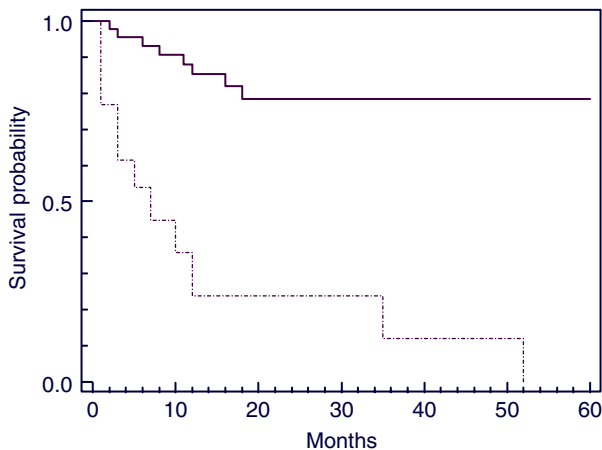
### DISCUSSION

Malignant mesothelioma is a tumor of mesenchymal origin. Serum mesothelin and osteopontin have been recently suggested as potential markers for pleural mesothelioma as well as vascular endothelial growth-factor for soft-tissue sarcoma.<sup>22–24</sup> To date, however, clinical utility of serum markers in mesenchymal tumor management has not been clearly demonstrated.

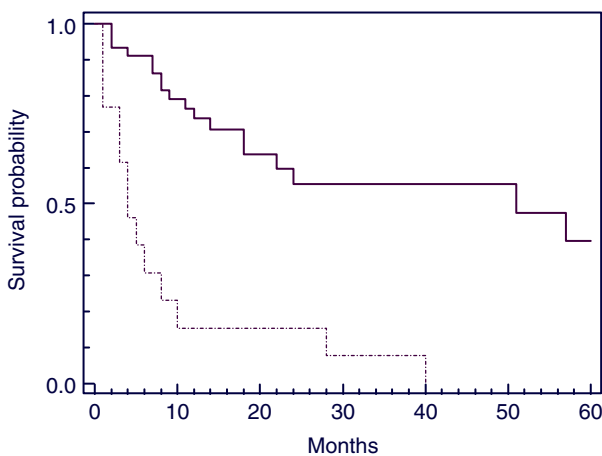
To our knowledge, this is the first study to thoroughly investigate the clinical role of circulating tumor markers in a large case series of peritoneal mesothelioma treated with cytoreductive surgery and IPHP. Surprisingly, the percentage of subjects with preoperatively increased CA125 was 53.3% in the overall series and 65% in the subset of patients not previously treated with systemic chemotherapy. Baseline diagnostic sensitivity was 48.5% for CA15.3 in a limited number of patients and irrelevant for CEA and CA19.9.

It is interesting to note that elevated CA125 levels were statistically less common among patients previously treated with systemic chemotherapy. As CA125 decrease after response to CT has been described in patients with PM, we hypothesized that CT might have determined marker normalization.<sup>25,26</sup> This could mean that the rate of 65% better represented CA125 expression in the overall PM population. This explanation, however, should be taken with caution because no major response to preoperative systemic CT was observed among our patients and marker concentrations before the onset of CT were unavailable.

CA125 is an antigenic determinant expressed on a high molecular mass mucin-like glycoprotein, produced by either normal or neoplastic derivatives of coelomic epithelium.<sup>27</sup> Determination of CA125 serum levels has become an integral part of epithelial



**FIG. 1.** Overall survival in the whole series according to treatment adequacy. \_\_\_ = adequate cytoreductive surgery with intraperitoneal hyperthermic perfusion; - - - inadequate surgery (univariate  $P$  value < .0001).



**FIG. 2.** Progression-free survival in the whole series according to treatment adequacy. \_\_\_ = adequate cytoreductive surgery with intraperitoneal hyperthermic perfusion; - - - inadequate surgery (univariate  $P$  value < .0001).

ovarian cancer management. Whereas concentrations at diagnosis seem of limited practical value, levels after cytoreductive surgery and during initial chemotherapy are independent prognostic factors.<sup>14</sup> Furthermore, CA125 half-life and the time to CA125 normalization have been proposed as prognostic indicators. Doubling of CA125 concentration, compared to baseline or nadir value, and increase of 50%, 100%, or just above the normal range are recommended objective indicators of disease progression.<sup>28</sup>

CA15.3 epitope is related to the MUC1 mucin, expressed on the apical surface of several normal and malignant epithelial cells. Clinically, it has been investigated in breast cancer management.<sup>29</sup>

Immunohistochemical staining for CA125 in mesothelioma has been described.<sup>30,31</sup> This is consistent with our observation that serum CA125 is elevated in most patients with PM, suggesting that the marker is released into serum by malignant cells, instead of being related to normal tissue reactive changes. Conversely, literature about elevated serum markers in patients with PM is limited to isolated case reports.<sup>32-34</sup> In two small series by Hedman<sup>25</sup> and Simsek,<sup>26</sup> serial CA125 measurements varied with tumor progression or response to chemotherapy. Pre-operative CA125 was elevated in 4 of 4 women with PM treated at the Roswell Park Cancer Institute and repeated essays reflected response to treatment. However, the authors did not report any detail about the treatments performed in this subset of patients.<sup>3</sup>

All the patients included in the present study had a pathologically established diagnosis of PM. The appropriate immunohistochemical tests were used to differentiate other peritoneal malignancies. The role of serum markers in diagnostic work-up is beyond the scope of this study. Analogously to most tumors, the marker profile recorded in our series is not unique for PM and consequently can not support its definitive diagnosis. The only conclusion we can draw from our data is that elevated CA125 does not exclude the diagnosis of PM. This uncommon tumor represents a diagnostic challenge, being often misdiagnosed as advanced ovarian cancer or other peritoneal malignancies.<sup>2,3</sup> Such observation might therefore be of help in the initial assessment of peritoneal dissemination of unknown origin. The need for a prompt diagnosis is underlined by recent phase I/II trials reporting prolonged survival in patients with PM undergoing CRS and IPHP.<sup>6-13</sup> The clinical outcome is predominantly dependent on adequate cytoreduction. Nevertheless, inappropriate diagnostic or surgical procedures are frequently carried out before admission to referral centers, often resulting in the loss of the peritoneal integrity that may likely hinder adequate cytoreduction and adversely affect the prognosis.

CA125 levels correlated to the extent of peritoneal involvement. CEA is increased in 5% of Dukes A colo-rectal cancers, but in about 25%, 45%, and 65% of, respectively, Dukes B, C, or distant metastases.<sup>35</sup> CA125 is elevated in over 90% of women with stage III/IV epithelial ovarian cancer, but only in approximately 50% with stage I.<sup>14</sup> Pseudomyxoma is another peritoneum spreading malignancy: van Ruth recently reported the correlation between marker values and the number of peritoneal regions involved by the tumor.<sup>36</sup>

**TABLE 3.** Univariable and multivariable analysis of factors influencing overall and progression-free survival in the whole series

| Variables     | Categories | N  | Overall survival             |                   |                | Progression-free survival    |                   |                |
|---------------|------------|----|------------------------------|-------------------|----------------|------------------------------|-------------------|----------------|
|               |            |    | Univariate<br><i>P</i> value | Multivariate      |                | Univariate<br><i>P</i> value | Multivariate      |                |
|               |            |    |                              | Hazard rate (CI)  | <i>P</i> value |                              | Hazard rate (CI)  | <i>P</i> value |
| Sex           | Male       | 24 | .0046                        |                   |                | .2952                        |                   |                |
|               | Female     | 36 |                              |                   |                |                              |                   |                |
| Age           | ≤54 yrs    | 30 | .009                         |                   |                | .0458                        |                   |                |
|               | > 54 yrs   | 30 |                              |                   |                |                              |                   |                |
| WHO score     | 0          | 52 | < .0001                      | 5.46 (1.56–19.13) | 0.0079         | < .0001                      | 5.78 (2.15–15.51) | .0005          |
|               | 1–2        | 8  |                              |                   |                |                              |                   |                |
| Histology     | Low-grade  | 11 | .0214                        | 5.22 (1.29–21.11) | 0.0203         | .0223                        | 3.61 (1.49–8.73)  | .0043          |
|               | High-grade | 49 |                              |                   |                |                              |                   |                |
| Previous CT   | Done       | 20 | .67                          |                   |                | .9468                        |                   |                |
|               | Not done   | 40 |                              |                   |                |                              |                   |                |
| PCI score     | ≤25        | 15 | .0372                        |                   |                | .0817                        |                   |                |
|               | >25        | 45 |                              |                   |                |                              |                   |                |
| Cytoreduction | Adequate   | 13 | < .0001                      | 3.66 (1.21–11.0)  | 0.0197         | < .0001                      | 3.79 (1.61–8.90)  | .0022          |
|               | Inadequate | 47 |                              |                   |                |                              |                   |                |
| CA125         | ≤35 U/L    | 32 | .3296                        |                   |                | .1564                        |                   |                |
|               | >35 U/L    | 28 |                              |                   |                |                              |                   |                |
| CA15.3        | ≤30 U/L    | 16 | .2948 *                      |                   |                | .1034 *                      |                   |                |
|               | >30 U/L    | 17 |                              |                   |                |                              |                   |                |

WHO score = World Health Organization performance status;<sup>14</sup> CT = systemic chemotherapy; PCI = peritoneal cancer index;<sup>15</sup> CI = 95% confidence interval; \* = calculated on 33 patients.

Among patients with elevated baseline levels, sensitivity of CA125 in diagnosing gross residual disease after CRS and IPHP was 100%; specificity was 95.5%. Sensitivity in assessing disease progression after adequate CRS and IPHP was 100%; false positive CA125 essay was never recorded during postoperative follow-up.

As minimal peritoneal disease may be difficult to detect by means of radiological studies, a diagnostic tool providing clinical information which might be integrated with imaging tests would be of considerable value. Theoretically, accurate assessment of response to treatment and disease progression could contribute to rationalize treatment and improve survival in patients with persistent or recurrent disease after multimodality treatment. The combination of systemic cis-platin and pemetrexed is presently the regimen of choice for unresectable or recurrent pleural mesothelioma. Preliminary results suggest efficacy also for PM.<sup>37</sup> Other possible options may be a second cytoreduction with IPHP, which was offered to selected patients of the present series, or surgical debulking. Taken together, these findings suggest the need of future prospective trials for clarifying the impact of serum marker in association with other clinico-radiological tests on PM management.

As marker diagnostic reliability was evaluated by comparison with a defined disease status, it is a relevant issue how the presence/absence of tumor was assessed. Each PM relapse was histologically

confirmed, but response to treatment was not assessed by second-look laparotomy. This could be a limitation to the quality of our data. However, although the relative contribution of IPHP to cytoreductive surgery is undetermined, it is known that hyperthermic chemotherapeutic agents can penetrate, and consequently sterilize, only few millimeters of tumor tissue. Thus, we considered patients with residual tumor nodules ≤ 2.5mm after CRS (cc0/1) as having complete response to the comprehensive treatment, unless no gross disease was detected at postoperative work-up. Marker diagnostic reliability was supported by the fact that marker levels, cc-score, and clinicoradiological findings were consistent in all patients but one. In this case, a concurrent autoimmune disorder may have been the possible cause of unspecific CA125 elevation.

Prognostic value of serum markers has never been investigated for PM. Our results provided only weak evidence that baseline CA125 was related to clinical outcome. Given the possible effect of preoperative systemic CT on marker levels, statistical analyses were repeated in the subset of patients not previously treated with CT, but elevated CA125 showed correlation to PFS and OS only at univariate analysis. The association with histological aggressiveness might explain the failure to reach statistical significance at multivariate analysis as independent prognostic factor. Other bias may have occurred in this setting. First, no reliable staging system for PM is currently

available. PCI, based on size, and distribution of tumor nodules is probably the most accurate score for peritoneal malignancies,<sup>15</sup> but it fails to focus on the involvement of critical regions, such as hepatic hilum, small bowel, and mesentery, where tumor removal is technically difficult. Second, we grouped tumors as low- or high-grade according to histological features. Other variables, in addition to traditional morphology, may be prognostically significant. As a matter of fact, deep tissue invasion has been related to prognosis, as well as mitotic count and nuclear grade, according to data from our institution.<sup>11,12</sup>

In conclusion, baseline CA125 was elevated in the majority of patients with PM included in the present series. Increase or decrease of CA125 paralleled tumor growth or regression after CRS and IPHP, suggesting that further studies should be undertaken to investigate the role of CA125 in assessing response to treatment and disease progression.

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