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CA 125 Serum Levels in the Early Post-operative Period Do Not Reflect Tumour Reduction Obtained by Cytoreductive Surgery

Cees A. Yedema, Peter Kenemans, Chris M. Thomas, Leon F. Massuger, Theo Wobbes, Rob Verstraeten, Gerard J. van Kamp and Jo Hilgers

In order to assess whether CA 125 serum levels reflect the outcome of cytoreductive surgery, CA 125 antigen levels were determined prior to and after debulking surgery in 50 ovarian cancer patients and compared to CA 125 serum levels before and after surgery in a control group of 140 patients undergoing laparotomy for various malignant or benign diseases. A significant CA 125 decrease in the first post-operative week was seen in 56% of ovarian cancer patients whereas 26% remained stable and 18% showed a significant increase after surgery. Although removal of tumour had been complete in all 14 stage I–II ovarian carcinomas, only 2 of these patients showed a subsequent significant CA 125 decrease after cytoreductive surgery, while 4 patients showed a significant increase. Such increases of CA 125 following surgery were also seen in uterine carcinomas (30%), in gastrointestinal carcinomas (75%) and in patients after laparotomy for benign gynaecological diseases (23%). CA 125 pre-treatment levels were significantly lower in patients with post-operative increases than in patients with stable or decreasing CA 125 patterns. Patients with stable CA 125 levels also had lower CA 125 pretreatment levels compared to patients with a post-operative CA 125 decrease. Post-operative increases were observed for at least 2 weeks after debulking in the case of ovarian cancer. Pre-operative levels of these patients were either within the normal range or moderately elevated. Serial measurements during surgery in partial debulking showed a rapid CA 125 decline within 24 h followed by increasing CA 125 values thereafter. Our data indicate that CA 125 serum levels in the direct post-operative period do not always reflect the outcome of cytoreductive surgery. There appears to be an effect on CA 125 levels caused by the abdominal surgical procedure itself. Consequently, CA 125 levels after abdominal surgery should be interpreted with caution.
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INTRODUCTION

MANY STUDIES have shown that CA 125 serum levels correlate well with both disease regression and progression in a majority of ovarian cancer patients (see [1] for review). However, it is largely unknown to what extent CA 125 serum levels shortly after laparotomy reflect the outcome of cytoreductive surgery. After primary surgery in stage III–IV ovarian cancer, removal of tumour tissue will be only partial in most cases. In a majority of patients macroscopical or microscopical tumour tissue will be retained in or outside the abdominal cavity. These unremoved tumour cells continue to shed the CA 125 antigen into the circulation. On the other hand, when cytoreductive surgery has been complete, which is mostly the case in patients with early stage I–II disease, CA 125 levels are expected to regress to normal levels. However, previous observations suggest this is not always the case in ovarian cancer patients without evidence of disease after intervention laparotomy [2] or second-look procedures [3]. Recent reports have shown that CA 125 elevations can occur after laparotomy in a variety of patients with a previous normal pre-treatment CA 125 level [4–6]. These patients underwent debulking surgery or second-look laparotomy for ovarian cancer. Equally, surgical intervention for gastrointestinal malignant or benign diseases can cause a CA 125 elevation [5].

The present study was initiated to investigate whether changes in CA 125 serum levels directly after first line debulking surgery in ovarian cancer reflect the outcome of cytoreductive surgery. To evaluate a possible effect of the surgical procedure itself on CA 125 serum levels we also studied patients undergoing abdominal surgery for other gynaecological malignancies (including endometrial and cervical carcinomas). Carcinomas arising from the gastrointestinal tract were also included. Finally, changes in CA 125 serum levels were studied in patients receiving abdominal surgery for benign gynaecological disorders.

PATIENTS AND METHODS

Serum samples were collected from 50 patients with ovarian cancer before and after cytoreductive surgery. All patients underwent debulking surgery as a first line treatment. Patient characteristics are listed in Table 1.

Correspondence to P. Kenemans at the Department of Obstetrics and Gynaecology, Free University Hospital, De Boelelaan 1117, 1007 MB Amsterdam, The Netherlands.
C. A. Yedema and P. Kenemans are at the Department of Obstetrics and Gynaecology at both the Free University Hospital, Amsterdam and the University Hospital of Nijmegen, Nijmegen; C. M. Thomas and L. F. Massuger are at the Department of Obstetrics and Gynaecology, University Hospital of Nijmegen; T. Wobbes is at the department of General Surgery, University Hospital of Nijmegen; R. Verstraeten and J. Hilgers are at the Department of Obstetrics and Gynaecology; and G. J. van Kamp is at the Department of Clinical Chemistry, Free University Hospital, Amsterdam, The Netherlands.
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Table 1. Characteristics of ovarian cancer patients (n = 50)

FIGO stage		Tumour grade	
I	11	Borderline	4
II	3	1	5
III	30	2	14
IV	6	3	24
		Unknown	3
Histology		**Residual tumour**	
Serous	27	0	11
Endometrioid	7	Microscopic	5
Mucinous	6	<1 cm	16
Adenocarcinoma	6	1–2 cm	3
Clear cell	3	>2 cm	15
Mixed epithelial	1		

Median age 61 years (range 38–80).

Pre- and post-operative CA 125 levels of these patients were compared to those found in 60 patients with uterine carcinomas before and after abdominal surgery. Of these, 35 patients had endometrial cancer and 25 patients had cervical cancer. Endometrial cancer patients (median age 63 years, range 40–79) comprised 22 stage I, 9 stage II, 2 stage III and 2 stage IV patients. Histologically, 29 tumours were adenocarcinomas and 6 adenosquamous carcinomas. Cervical cancer patients (median age 39 years, range 29–82) were classified as stage I and II in 21 and 4 cases, respectively. Histological examination revealed 14 squamous cell carcinomas, 3 adenosquamous carcinomas and 8 adenocarcinomas. Gastrointestinal carcinomas (median age 67 years, range 42–84) included 8 gastric carcinomas and 12 colorectal carcinomas. Staging revealed 4 stage I, 5 stage II, 10 stage III and 1 stage IV patient. Histologically, all tumours were adenocarcinomas, 10 patients were female and 10 were males.

Patients with benign gynaecological diseases included 40 patients with benign ovarian tumours (median age 47 years, range 17–78) of which 10 were mucinous cystadenomas, 8 teratomas, 6 serous cystadenomas, 5 cases of a cystoma simplex, 4 endometriotic cysts, 4 functional cysts and single cases of an ovarian abcess, a fibrothecoma and a Brenner tumour. In 12 of the remaining 20 patients of the benign group (median age 40 years, range 35–72) uterine fibroids were found. One patient had a severe dysplasia of the cervix and another patient an endometriotic cyst with uterine localisation. In 6 patients no gross specific pathology could be demonstrated.

Patients with gynaecological malignancies were studied according to FIGO recommendations [7]. Patients with gastrointestinal carcinomas were staged following AJCC criteria [8]. Patients with double tumours or with a known history of carcinoma were excluded. A pre-treatment serum sample was taken with a median time interval of 2 days before surgery (range 0–21 days) and in the post-operative period with a median time interval of 5 days after surgery (range 4–10 days). 31 ovarian cancer patients had a second sample drawn in the second post-operative week with a median time interval of 12 days from surgery (range 12–17 days). In 4 ovarian cancer patients between 4 and 8 serial CA 125 measurements were available, having been obtained within 24 h from the start of surgery.

The CA 125 assay was performed according to the instructions of the manufacturer using the immunoradiometric assay supplied by Centocor Inc. (Malvern, Pennsylvania, U.S.A.). The cut-off level used was 35 U/ml. An increase of CA 125 serum levels of 100% or more or a decrease of at least 50% compared to presurgery levels was considered to be of significant importance following the criteria used by Bast *et al.* [9].

The Wilcoxon rank sum test with continuity correction was used for statistical analysis of CA 125 levels in different patient groups.

RESULTS

Figure 1 shows the CA 125 serum levels before and after surgery in ovarian cancer patients. 43 of 50 patients (86%) showed CA 125 pre-treatment levels above 35 U/ml. 28 patients (56%) demonstrated a significant decrease following surgery. Their pre-treatment levels ranged between 140 and 21000 U/ml (median: 1800). 13 patients (26%), with pre-treatment levels ranging between 22 and 6290 U/ml (median: 140) remained stable, whereas 9 patients (18%) showed a significant increase in CA 125 serum levels with pre-treatment levels varying between 8.9 and 270 U/ml (median: 36). Median pre-treatment serum levels in patients with stable CA 125 patterns were significantly lower compared to those in patients with decreasing patterns ($P < 0.001$). Moreover, pre-surgery levels were again lower in patients with rising CA 125 levels compared to those in patients with stable CA 125 patterns ($P < 0.05$). 6 patients (12%) with pre-treatment CA 125 serum levels below the cut-off level of 35 U/ml had post-treatment CA 125 levels above 35 U/ml.

16 stage III–IV patients had residual tumour masses <1 cm and 18 patients had a residual tumour mass exceeding 1 cm in largest diameter. 2 stage III patients were completely debulked leaving no macroscopic tumour. In 26 out of these 36 stage III–IV patients surgery was followed by a decrease in CA 125 serum levels, 5 patients remained stable and 5 patients showed a significant rise. 2 of these latter 5 patients had pre-treatment levels below 35 U/ml, the others had moderately elevated CA 125 levels of 36, 47 and 270 U/ml, respectively.

In 14 stage I–II ovarian cancer patients all macroscopic

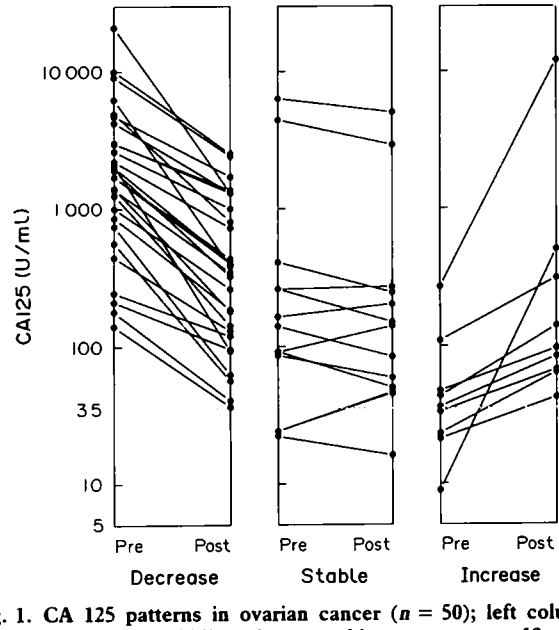

Fig. 1. CA 125 patterns in ovarian cancer ($n = 50$); left column: decreases, $n = 28$; middle column: stable patterns, $n = 13$; right column: increases, $n = 9$.

tumour tissue was removed. However, only 2 patients showed a significant decrease of CA 125 serum levels and 8 patients remained stable. 4 patients showed a significant rise of whom 2 had pre-treatment levels <35 U/ml, the others having presurgery levels of 43 and 110 U/ml.

CA 125 serum levels in ovarian cancer patients who were also sampled in the second post-operative week showed, in general, a tendency towards stabilisation in the second week following tumour debulking with only 1 patient showing a further significant decrease and 1 patient showing a continuous rise (Fig. 2).

16 patients who had a macroscopic complete debulking are shown separately in Fig. 3. Despite complete removal of all tumour deposits only 1 out of 16 patients had normalised in the first post-operative week. In the second week, 6 out of 8 patients who were sampled in this period, still had elevated CA 125 serum levels. 4 of these had shown a significant rise in the first post-operative week. Thus, some CA 125 rises persisted for at least 2 weeks.

In patients with ovarian carcinoma who had serial samples collected during the first 24 h from the beginning of laparotomy, serum CA 125 levels fluctuated strongly during the surgical procedure (Fig. 4). A rapid fall in CA 125 levels was observed in all patients with nadirs reached within 3–4 h after the beginning of surgery in 2 patients and after 24 h in the remaining 2 patients. When these lowest CA 125 values were compared to CA 125 levels at the fifth day following surgery, CA 125 values had increased again in all 4 patients. Values had more than doubled in 2 cases.

Table 2 shows tumour marker patterns in ovarian carcinomas and in control patients. In patients with uterine malignancies, 18% had pre-operative CA 125 serum levels >35 U/ml. Following surgery, 10% showed a decrease, 60% remained stable and 30% showed a post-operative CA 125 rise. 9 out of 60 patients (15%) with uterine carcinomas had post-operatively elevated CA 125 levels, whereas pre-treatment levels were within the normal range.

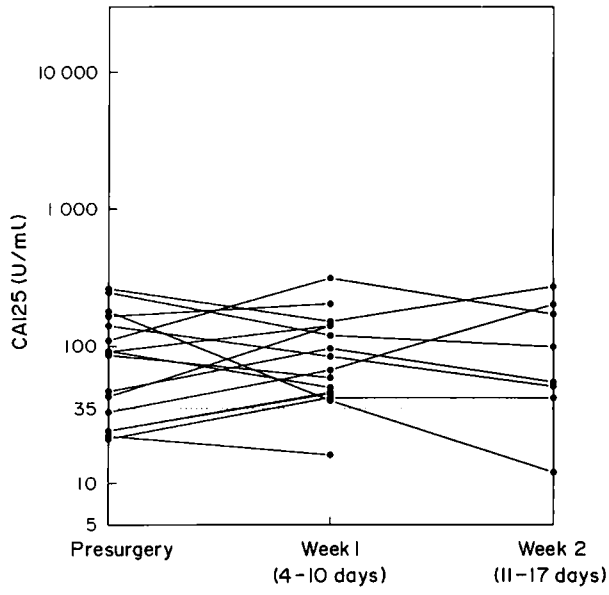

Fig. 3. CA 125 levels in ovarian cancer patients after complete debulking; left column: CA 125 levels in the first post-operative week (n = 16); right column: CA 125 levels in the second post-operative week (n = 8); CA 125 levels are clustered: 4–10 days = week 1 and 11–17 days = week 2.

None of the 20 patients with a gastrointestinal malignancy showed pre-operative CA 125 levels >35 U/ml. 25% demonstrated stable CA 125 levels while the remaining 75% showed significant increases, all exceeding the cut-off level up to a value of 380 U/ml.

Patients with benign gynaecological disorders showed elevated CA 125 pre-treatment levels in 23% of the cases. Post-operative decreases of CA 125 were only seen in one third of these patients. Furthermore, 68% of the benign disease group remained stable

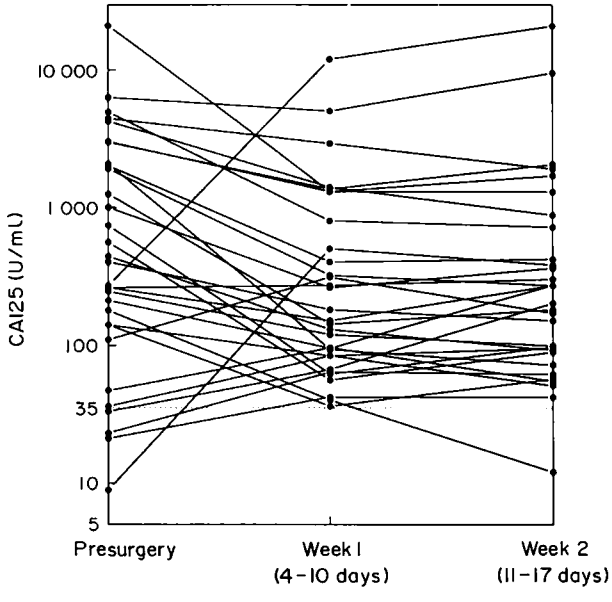

Fig. 2. CA 125 levels in ovarian cancer. Patients with a second sample taken in the second post-operative week (n = 31) are shown; left column: CA 125 levels in the first post-operative week; right column: CA 125 levels in the second post-operative week; CA 125 levels are clustered: 4–10 days = week 1 and 11–17 days = week 2.

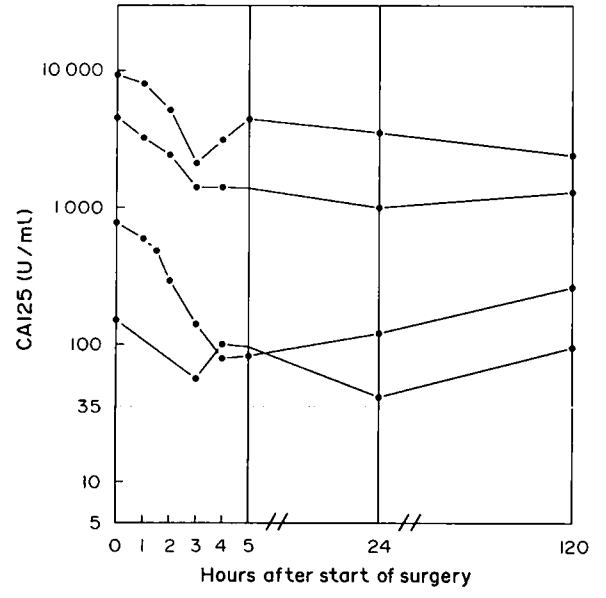

Fig. 4. CA 125 levels in ovarian cancer patients (n = 4) during surgery and in the immediate post-operative period; a: beginning of surgery; b: 24 h after partial debulking; and c: first week sample (5th post-operative day).

Table 2. CA 125 patterns in ovarian cancer (Ov. cancer), cancer of the uterus (Uterine cancer), cancer of the gastrointestinal tract (G.I. tract cancer) and in patients with benign gynaecological diseases (Benign). Numbers for each patient group are italicised.

		CA125 pattern		
Group	*n*	Decrease	Stable	Increase
Ov. cancer	50	*28*	*13*	*9*
pre-CA 125 U/ml		1800 (140–21000)	140 (22–6290)	36 (8.9–270)
post-CA 125 U/ml		361 (36–2500)	140 (16–5000)	96 (42–12000)
Uterine cancer	60	*6*	*36*	*18*
pre-CA 125 U/ml		169 (26–860)	17 (7.4–290)	11 (7.4–44)
post-CA 125 U/ml		52 (13–270)	19 (7.4–270)	54 (15–140)
G.I. tract cancer	20	*0*	*5*	*15*
pre-CA 125 U/ml		—	17 (11–26)	9.6 (7.4–32)
post-CA 125 U/ml		—	22 (11–36)	84 (38–380)
Benign	60	*6*	*40*	*14*
pre-CA 125 U/ml		169 (26–860)	17 (7.4–290)	11 (7.4–44)
post-CA 125 U/ml		52 (13–270)	19 (7.4–270)	54 (15–140)

Pre-CA 125 = pre-surgery CA 125 level; post-CA 125 = post-surgery CA 125 level. The median CA 125 levels are listed and minimum and maximum serum concentrations are given between parentheses.

and 23% showed increasing CA 125 levels. 17% demonstrated post-operative CA 125 serum levels >35 U/ml up to 140 U/ml, whereas pre-surgery levels had been within the normal range.

When ovarian cancer patients were excluded, median CA 125 levels of all patients showing decreasing, stable or increasing patterns, were 333, 23 and 14 U/ml, respectively. As in ovarian cancer, patients with decreasing CA 125 patterns had higher pre-treatment levels compared to patients with stable levels ($P < 0.001$) and those with increases after surgery also had lower CA 125 levels compared to patients with a stable CA 125 pattern ($P < 0.05$).

For the ovarian cancer group as a whole, pre-surgery CA 125 levels were significantly higher than post-operative levels ($P < 0.0001$). Those ovarian cancer patients that showed a post-operative increase had higher post-surgery CA 125 serum levels ($P < 0.01$). Furthermore, when comparing pre- and post-surgery levels in patients with gastrointestinal carcinomas or with benign diseases, CA 125 levels after surgery were found to be significantly higher than the pre-surgery baseline values ($P < 0.001$ and $P < 0.01$, respectively). For patients with uterine carcinomas, CA 125 levels following surgery were also higher than those before surgery, but this difference was not found to be statistically significant ($P = 0.09$).

Highest post-surgery increases were seen in ovarian and gastrointestinal carcinomas. For both groups, CA 125 levels following an increase were significantly higher compared to patients with cancer of the uterus and a CA 125 rise ($P < 0.05$). The same was found for ovarian cancer patients compared to patients with a CA 125 rise after laparotomy for benign disease ($P < 0.05$). In carcinomas originating from the gastrointestinal tract this latter difference was of borderline significance ($P = 0.05$).

No significant differences were found between subgroups when sampling periods after surgery were compared, with the exception of patients with gastrointestinal carcinomas. This latter group had a median sampling time of 7 days after surgery vs. 5–6 days for the other patients. In addition, no differences in sampling time were observed between patients with either increasing, stable or decreasing CA 125 patterns.

DISCUSSION

This study shows that CA 125 serum levels in the first weeks after laparotomy do not necessarily reflect residual tumour load in ovarian cancer patients. In ovarian cancer patients, after debulking surgery and removal of the main source of CA 125 production, a subsequent decline in CA 125 serum levels was only seen in patients with relatively high pre-treatment CA 125 serum levels. Remarkably, significantly rising CA 125 levels were seen especially in patients with relatively low pre-treatment levels.

In stage I and II ovarian cancer patients all macroscopic tumour tissue was successfully removed during surgery. Nevertheless a significant decrease was only seen in 2 out of 14 patients. Conversely, 4 patients showed a significant CA 125 increase post-operatively. Even in advanced stage III–IV disease 5 out of 36 patients showed a significant CA 125 increase. Apparently, removal of the major tumour load and even complete macroscopic debulking does not necessarily imply decreasing CA 125 levels. In the presence of high circulating levels of the CA 125 antigen, an initial surgical response results in rapidly falling CA 125 levels with again increasing CA 125 levels 5 days after surgery. The shortest half-life of CA 125 reported in the literature is 4.5 days [10, 11]. Thus, these rapid CA 125 falls within 24 h to a nadir between 10 and 27% of pre-surgery baseline values cannot be explained by removal of the major tumour bulk alone, but factors like haemodilution, blood transfusion and drainage of ascites will in part be responsible for this initial CA 125 decrease. This latter phenomenon can cause a substantial decrease of CA 125 serum values [12].

In addition to those in ovarian cancer, significant CA 125 increases were also seen in non-ovarian malignancies as well as in patients after laparotomy for benign diseases pointing to a causal factor related to the surgical procedure itself. As in ovarian cancer, CA 125 patterns correlated with the height of pre-treatment values. Most patients with a CA 125 rise had pre-treatment levels below 35 U/ml. Nevertheless, CA 125 elevations were also seen in the presence of pre-treatment levels up to 270 U/ml.

For the uterine carcinoma group, as well as for the gastrointes-

tinal and the benign disease group, CA 125 levels after surgery were higher than pre-surgery levels. For both latter groups this difference was significant. These data also demonstrate that surgical removal of all tumour deposits does not necessarily imply a CA 125 decrease.

A high incidence of CA 125 increases was observed in gastrointestinal carcinomas. It is known that these tumours can give rise to elevated CA 125 serum levels with percentages varying from 16 to 34% [13–16]. However, in our study all 20 patients had normal pre-surgery CA 125 levels. Equal percentages are seen in cervical cancer, endometrial cancer and even in benign ovarian tumours (see [1] for review). In the present study 18% of the patients with uterine carcinomas and 23% of the patients with benign gynaecological disease had elevated pre-treatment CA 125 serum levels. Median serum levels seen after a rise in patients with gastrointestinal tumours were higher compared to uterine carcinomas and patients with benign gynaecological diseases. Post-surgery CA 125 elevations were also higher in ovarian cancer patients. Possibly, abdominal involvement and tumour load were more pronounced in gastrointestinal and ovarian malignancies resulting in more extensive peritoneal damage and tumour manipulation which could result in a higher CA 125 rise.

The CA 125 antigen is expressed in peritoneal tissue, particularly in areas of inflammation and adhesion [17]. As a result, pelvic inflammatory disease is sometimes accompanied by elevated CA 125 serum levels [18, 19] and these CA 125 serum levels correlate with the extent of peritoneal inflammation [20]. Recently, a mesothelial cell line was shown to produce the CA 125 antigen in cell culture supernatant [21]. Apparently mesothelial cells are capable of synthesising CA 125. Extensive abdominal surgery can give rise to damage of peritoneal tissue followed by an inflammatory repair reaction. Incision of the peritoneum releases CA 125 into the peritoneal fluid thus suggesting that peritoneal trauma causes the release of CA 125 [22]. In addition to peritoneal damage, tumour manipulation during surgery may lead to an increased shedding of CA 125 into the circulation as remaining barriers between invasive carcinomas and surrounding tissue are disturbed. In benign ovarian cysts, the basement membrane and the peritoneum are believed to be natural borders preventing access of CA 125 to the circulation [23].

During surgery these barriers might be further disturbed, both in ovarian as well as in non-ovarian malignancies. Finally, since high levels of CA 125 are found in cyst fluids of malignant as well as benign ovarian tumours [23, 24], surgery in the case of ovarian neoplasms may lead to increasing CA 125 serum levels when high CA 125 levels in cystic fluids gain access to the bloodstream.

Our study does not show at what time interval after surgery CA 125 serum concentrations will indeed reflect the behaviour of remaining tumour tissue, as we observed that elevated levels were maintained up to at least 14 days after removal of all tumour tissue. Serial measurements in the immediate post-operative period indicate that after partial debulking, CA 125 serum levels can double again within a few days. Van der Zee *et al.* found the highest CA 125 levels 5–14 days after laparotomy. A gradual normalisation was seen thereafter between 3 and 4 weeks [6]. A study by Talbot *et al.* revealed maximum values between 2 and 4 weeks after surgery in malignant disease followed by an even slower normalisation up to 3 months after surgery [5]. It is concluded that CA 125 serum levels determined in the first weeks after abdominal surgery do not reflect the outcome of cytoreductive surgery since there is an operative effect on CA 125 serum levels caused by the surgical procedure itself. This occurs both in ovarian cancer patients with a partial debulking as well as in patients with a complete debulking. In the former patients a rapid CA 125 decrease shortly after surgery seems to result from a combination of tumour tissue removal, drainage of abdominal fluid and haemodilution. Post-surgery CA 125 increases are caused by a combination of peritoneal damage and tumour manipulation, the influence of which becomes predominantly apparent in patients with normal or moderately elevated pre-treatment CA 125 levels. Consequently, CA 125 serum levels after abdominal surgery should be interpreted with caution. Elevated CA 125 levels in the first post-operative weeks cannot be claimed to be indicative of residual tumour, nor to be helpful in the differential diagnosis between benign and malignant tumours.

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Short Recurrence-free Survival Associated with High Oestrogen Receptor Levels in the Natural History of Postmenopausal, Primary Breast Cancer

Susan M. Thorpe, Ib. J. Christensen, Birgitte Bruun Rasmussen and Carsten Rose

The ability of oestrogen and progesterone receptor (ER and PgR, respectively) status to discriminate recurrence-free survival (RFS) among a cohort of consecutively accrued 952 postmenopausal patients has been studied. None of the cohort members investigated were treated with adjuvant therapy. Using a graduated scale of receptor status [low, intermediate and high receptor levels (< 10 vs. 10–107 vs. ≥ 108 fmol/mg cytosol protein, respectively)] instead of the more commonly used dichotomous subdivision (positive vs. negative), ER level significantly discriminated between groups of patients with long vs. short RFS. Contrary to our expectations, patients with highest ER levels have as poor a prognosis as ER-negative patients, while patients with intermediate ER levels have longest RFS. The group of patients with ER levels ≥ 108 fmol/mg cytosol protein comprises 47% of the cohort. The independent significance of overexpression of ER as a prognostic factor among this patient group is demonstrated in multivariate analysis where ER level is more significant than either grade of anaplasia or tumour size. PgR status did not significantly predict RFS among these patients. While the highest ER levels predispose for poorer prognosis among postmenopausal patients, it is precisely this group that experiences *greatest* benefit from adjuvant treatment with tamoxifen. Thus, patients who might otherwise go untreated due to their node-negative status can be readily identified and offered adjuvant treatment.
Eur J Cancer, Vol. 29A, No. 7, pp. 971–977, 1993.

INTRODUCTION

WHILE THE majority of node-negative, primary breast cancer patients have normal life expectancies following primary surgery and do not, therefore, require adjuvant therapy, a significant proportion (20–30%) [1] will experience recurrent disease. A recent review [2] has reiterated the need to define the prognostic factors that enable distinction between these two groups of patients. Despite numerous investigations, the role of receptor status has not yet been fully clarified. Nevertheless, it has become dogma that oestrogen receptor (ER)-positive patients fare better than ER-negative patients. This paper scrutinises that belief and finds it untrue in the case of a significant, readily identifiable and biologically relevant subset of the patient population.

In the nationwide Danish Breast Cancer Cooperative Group (DBCG) trials for treatment of primary breast cancer, receptor analyses have been performed since 1979 for as many patients as possible. The design of the DBCG trials facilitates studies of the natural history of breast cancer: approximately half of the patients were evaluated to be at such a low risk of recurrent

Correspondence to S.M. Thorpe.
S.M. Thorpe is at the Department of Tumor Endocrinology, The Fibiger Institute of the Danish Cancer Society, Ndr. Frihavnsgade 70, 2100-DK, Copenhagen Ø; I.J. Christensen is at the Finsen Laboratory, University Hospital, Strandboulevarden 49, 2100-DK, Copenhagen Ø; B.B. Rasmussen is at the Department of Pathology, Roskilde County Hospital, Kogevej 7–13, Postbox 247, 4000-DK, Roskilde; and C. Rose is at the Department of Oncology R, Odense University Hospital, Sdr. Boulevard 29, 5000-DK, Odense C, Denmark.
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