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USE OF TETRANECTIN, CA-125 AND CASA TO PREDICT RESIDUAL TUMOR AND SURVIVAL AT SECOND- AND THIRD-LOOK OPERATIONS FOR OVARIAN CANCER

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Tetranectin (TN), CA-125 and CASA were measured in serum prior to 63 second-look and 5 third-look operations for ovarian cancer. Patients with residual tumor had significantly lower levels of TN and higher levels of CASA and CA-125 compared with tumor-free patients. The predictive values $PV_{Pos} = 100\%$ and $PV_{Neg} = 50.9\%$ were found for TN at 9.3 mg/l. For CASA, a predictive value $PV_{Pos} = 100\%$ was found at 10 U/ml with a corresponding $PV_{Neg} = 52.7\%$. At the cut-off 35 U/ml for CA-125, the PV_{Pos} was 100% and the $PV_{Neg} = 53.6\%$. By combining the markers, PV_{Neg} increased to 61.7% with a PV_{Pos} on 100%. Significantly differences in survival were found by lifetable analysis between patients tested as positive and negative respectively for any of the markers. Using multivariate Cox analyses, it was found that every marker had an independent prognostic function for survival.

Second-look surgery in ovarian cancer patients is performed after completion of first-line therapy in order to identify two subsets of patients: those without microscopic disease where therapy can be withdrawn, and those with residual disease who theoretically could benefit from continued second-line therapy (if available). After second-line therapy the patients can be evaluated by third-look surgery. If residual tumor is found at the operation, cytoreductive tumor surgery is usually performed in order to improve the success rate of adjuvant irradiation or chemotherapy (1, 2). The findings at second-look are also of prognostic significance, since the survival rate is higher among tumor-free patients compared with patients with residual tumor. However, in some studies uncritical use of the second-look procedure has been questioned, as no improvement on survival could be found (3, 4). Therefore, from being a standard procedure in most institutions the second-look operation is nowadays often restricted to patients in clinical remission. This change in surgical indication has increased the need for non-invasive methods to predict residual tumor, whereby unnecessary second-look procedures can be avoided.

Non-invasive methods such as computerized tomography or ultrasound scanning often fail to detect the state of disease, especially in women without clinical evidence of tumor (5, 6). In the last decade many efforts have been made to identify serum markers of ovarian cancer, and so far CA-125 is the most promising of these (7, 8). In these studies an elevated CA-125 level prior to second look was a good indicator of residual tumor, but a CA-125 level within the normal range did not preclude residual disease.

Several other markers of disease status have been studied in blood from ovarian cancer patients. However, only a few seem to be clinically useful, namely the cancer-associated serum antigen (CASA) and serum tetranectin (se-

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TN) (9, 10). The CASA assay uses monoclonal antibodies that bind to an epitope on the polymorphic epithelial mucin expressed by many tumor cells, and elevated levels have been found in blood from ovarian cancer patients (11). Se-TN has been found to correlate 'negatively' with the severity of primary ovarian cancer and survival of the patients (10, 12, 13). TN is a plasminogen-kringle-4-binding protein which has been characterized as four, non-covalently linked, identical peptide chains of each of 181 amino acids with a total Mr of 20.100 (14). The source and function of TN is still unknown, but several hypotheses exist (15–18). In all likelihood TN is an important part of the proteolysis, which has been considered an important factor for malignant cells in their ability to infiltrate normal tissue and metastasize to distant sites (19). An explanation for the low se-TN in cancer patients may then be that the se-TN is taken up by the tumors and hence used for proteolysis (20–22).

The purpose of this study was to evaluate the potential of the biochemical serum markers TN, CA-125 and CASA singly and in combination, to predict residual tumor and survival prior to second- or third-look surgery for ovarian cancer.

Material and Methods

Samples and patients

Serum samples were obtained immediately before surgery in 63 second-look and in five third-look operations among 65 patients with ovarian cancer, who were treated with chemotherapy during the period 1 September 1984 to 1 June 1987. Median age on entering the study was 57.6 years, range 21.6 to 77.3 years.

The standard surgical procedure at primary surgery included laparotomy with total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy and subdiaphragmatic smears. The patients also took part in another large randomized study with the purpose of evaluating two different chemotherapy regimens. In the first regime the patients were treated with cyclophosphamide, Adriamycin and 5-fluorouracil (CAF) on days 1 and 8, every 4 weeks. In the second regime the patients were treated with CAF alternating with cisplatin and hexamethylmelamine (CIS-Hexa) every 4 weeks. The treatment regimens were continued until second look or until the onset of clinically evident progressive disease (PD). In the case of PD, the patients were treated CIS-Hexa only. Before each monthly chemotherapy course the clinical status was evaluated by general and pelvic examination and liver enzymes (plasma alkaline phosphatase, plasma lactate dehydrogenase and plasma aspartate aminotransferase). An abdominal ultrasound, a CT scan and an x-ray examination of the chest were performed before the start of chemotherapy and thereafter at 8-week intervals or when any recurrence was suspected at the monthly examinations. The patients were scheduled for second-look surgery after 10 courses of chemotherapy. At the second-look operation, subdiaphragmatic smears and biopsies from the pouch of Douglas and the right and left sides of the abdominal peritoneum were obtained. Abdominal washings were made for cytology. Debulking was perfomed whenever possible in order to reduce the residual tumor to a minimum.

The response to treatment was evaluated in accordance with the classification of the International Federation of Gynecology and Obstetrics (FIGO). Patients with no clincally detectable tumor in the time period from primary surgery to second- or third-look operation were preoperatively classified as not clinically evaluable (NE) (51 patients). Before surgery the clinical evaluation was complete response (CR) in 10 patients with a total disappearance of clinically evaluable tumor masses during chemotherapy. Partial response (PR) was observed in 3 patients, no change (NC) in one patient and progressive disease in 3 patients (PD).

TN-ELISA procedure

Tetranectin was quantitated using an avid-biotin, enzyme-linked immunosorbent assay (ELISA) as described in detail elsewhere (10, 23). For a plasma control at a TN concentration of 7.3 mg/l the intra-assay CV was 5.2% (n = 7), whereas the interassay CV was 5.8% (n = 14).

CASA analyses

A commerically available 'sandwich' ELISA kit was used for the CASA analyses (Medical Innovations Ltd., Labrador, Queensland, Australia). The analyses were performed following the manufacturer's instructions. For one patient, CASA was not performed due to a lack of sample material. The intra-assay CV was 9.3% (n = 6) for a serum control at a CASA concentration of 13 U/ml. Because only three analytical runs were used for the analyses, it was not possible to make any statistical evaluation of the interassay CV. However, from the three runs all six control samples were correctly assayed to be evaluated (median 12.5 U/ml; range 10–15 U/ml).

CA-125 analyses

The CA-125 analyses were performed using a commercially available immunoassay (EIA) (Abbott CA-125-EIA, Abott Laboratories, Chicago, IL), following the manufacturer's instructions. Intra-assay CV was 8.9% (n = 50), whereas the interassay CV was 7.8% (n = 100) at a control sample of 21 U/ml).

Statistical analysis

The Spearman rank correlation test was used in order to test for correlation between variables. Receiver operator

curves (ROC) were used for testing the different cut-offs. Median differences were identified by the Mann-Whitney test, and the Fisher exact test was used when appropriate.

The follow-up time applied for survival analysis was calculated from the last operation (third look if a patient also has a serum sample from a second look) to time of death or time of follow-up (January 1993). Patients who died of causes other than cancer were regarded as lost to follow-up from the time of death in both the univariate and the multivariate analyses. The cumulated survival rate was analyzed by the lifetable method according to Kaplan-Meier. Observed differences in survival were tested statistically by the univariate log-rank test. The multivariate Cox proportional hazards regression model was used to estimate the effect of each covariate (prognostic factor) to the survival function. CASA, CA-125 and se-TN were tested as dichotomy variables in both the univariate and the multivariate analyses. Type of histology was entered and ranked according to increasing mortality as found by univariate analyses. In a previous study we found no difference in rate of survival between patients treated with the first or second chemotherapy regimens, this variable therefore was not entered in the analyses (12). A value of $p < 0.05$ was considered statistically significant.

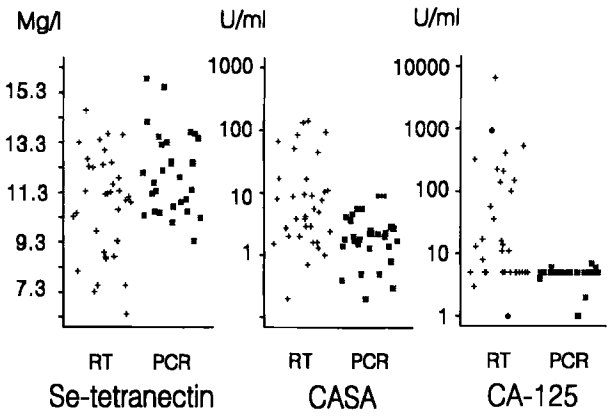

Fig. 1. Scatterplot of patients with residual tumor (RT) or complete pathological response (PCR) in relation to the three tumor markers.

Results

In 51 patients with the clinical status NE prior to the second- or third-look operation, 25 (49%) were found to have a pathologically complete response (PCR), and 26 (51%) were found to have residual tumor. Of the 10 patients evaluated to have CR before second look, only 5

Table 1

Status at second or third look in relation to the makers

Marker(s)	PCR[a]	RT[b]	SN[c]	SP[d]	PV_{Pos}[e]	PV_{Pos}[f]	P[g]
TN ⩽ 9.3 mg/l	0	9					
TN > 9.3 mg/l	30	29					
			23.7	100	100	50.9	0.007
CA125 ⩾ 10 U/ml	0	21					
CA125 < 10 U/ml	30	17					
			55.3	100	100	63.8	$<5*10^{-5}$
CA125 ⩾ 35 U/ml	0	12					
CA125 < 35 U/ml	30	26					
			31.6	100	100	53.6	0.0007
CASA ⩾ 10 U/ml	0	12					
CASA < 10 U/ml	29	26					
			31.6	100	100	52.7	0.001
CASA ⩾ 10 or CA125 ⩾ 35	0	17					
Markers negative	29	21					
			44.7	100	100	58.0	$<5*10^{-5}$
CASA ⩾ 10 or CA125 ⩾ 10	0	24					
Markers negative	29	14					
			63.2	100	100	67.0	$<5*10^{-5}$
CASA ⩾ 10 or CA125 ⩾ 35 or TN ⩽ 9.3	0	20					
Markers negative	29	18					
			52.6	100	100	61.7	$<5*10^{-5}$
CASA ⩾ 10 or CA125 ⩾ 10 or TN ⩽ 9.3	0	25					
Markers negative	29	13					
			65.8	100	100	69.0	$<5*10^{-5}$

PCR[a]: pathologic complete response RT[b]: residual tumor SN[c]: sensitivity SP[d]: specificity PV_{Pos}[e]: positive predictive value PV_{Neg} negative predictive value p[g]: Fisher's exact test TN: tetranectin.

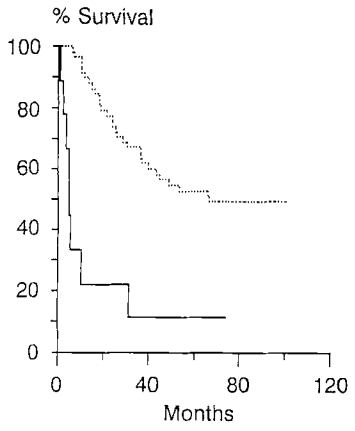

Fig. 2. Cumulated survival following second- or third-look operation in relation to plasma tetranectin (TN), all patients included (Log-rank test, $p < 10^{-5}$). ····· TN > 9.3 mg/l (n = 56); —— TN ≤ 9.3 mg/l (n = 9).

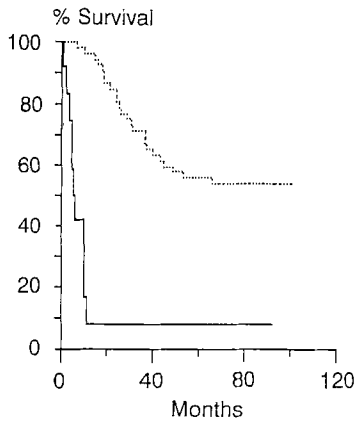

Fig. 4. Cumulated survival following second or third look operation in relation to CA 125, all patients included (Log-rank test, $p < 10^{-5}$). ····· CA 125 < 35 U/ml (n = 53); —— CA 125 ≥ 35 U/ml (n = 12).

(50%) were found to have PCR by the second-look operation. All 7 patients evaluated as having PR, NC or PD were found to have residual tumors by the second- and third-look operations.

The median se-TN level for all preoperative second- or third-look samples was 11.4 mg/l (quartiles: 10.4–12.6). For patients with PCR the median se-TN was 12.1 mg/l (quartiles: 10.7–13.3), which was significantly higher than the median se-TN at 10.9 mg/l (quartiles: 9.35–12.4) for patients with residual tumor at second look ($p = 0.003$). Significant correlations were found between se-TN and residual tumor size at operation ($R_s = -0.36$, $p = 0.003$) and between se-TN and Ca-125 ($R_s = -0.32$, $p = 0.009$). A non-significant correlation was found between se-TN and CASA ($R_s = -0.18$, $p = 0.2$). A predictive positive value PV_{Pos} on 100% (9/9) was reached by ROC analyses at the cut-off level 9.3 mg/l with a corresponding PV_{Neg} for residual tumor on 50.9% (30/59) (Fig. 1 and Table 1).

For CASA, the preoperative median was 3.0 U/ml (quartiles: 2.0–8.0) before 67 operations. The median CASA concentration for patients with PCR was 0 U/ml (quartiles 0–0), which was significantly lower than the median CASA concentration at 5.0 U/ml (quartiles: 3.0–11.0) for patients with residual tumor at second look ($p = 0.004$). A significant correlation was found between CASA and residual tumor size ($R_s = 0.55$, $p = 0.0001$). A PV_{Pos} on 100% (12/12) was reached by ROC analyses at the cut-off level 10.0 U/ml with a corresponding PV_{Neg} on 52.7% (29/55) (Fig. 1 and Table 1).

For CA-125, a PV_{Pos} on 100% (21/21) was already reached at the cut-off level 10 U/ml with a corresponding PV_{Neg} at 63.8% (30/47). When the normally accepted cut-off level 35 U/ml for CA-125 was used the PV_{Pos} was 100% (12/12) and the PV_{Neg} 53.6% (30/56) (Fig. 1 and Table 1).

A varying number of operations would not have been undertaken if the decision to perform a second- or third-look had been based solely on the levels of se-TN, CASA or CA-125, thus restricting the operation to the patients who had a marker negative test. If the decision had been based on measurements of se-TN alone, 13.2% (9/68) of the operations would not have been performed, and 17.6% (12/68) if the decision had been based on CA-125 measurements alone (cut-off 35 U/ml) (or 30% if the cut-off 10 U/ml for CA-125 was used), and 17.9% (12/67) if the measurements had been based on CASA alone (Table 1).

By using different combinations of markers, with the requirement that just one of the markers should be positive to abstain from surgery (se-TN ≤ 9.3 mg/l, CA-125 ≥ 35 U/ml (or ≥ 10 U/ml) or CASA ≥ 10 U/ml), it was found that from 22% (15/68) to 37% (25/67) of the

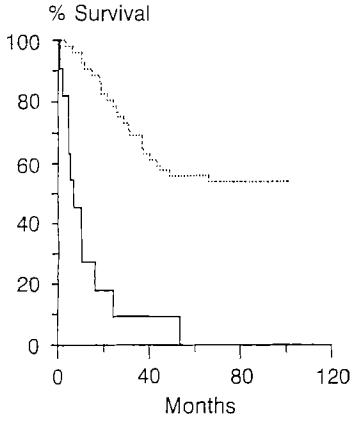

Fig. 3. Cumulated survival following second- or third-look operation in relation to CASA, all patients included (Log-rank test, $p < 10^{-5}$). ····· CASA < 10 U/ml (n = 53); —— CASA ≥ 10 U/ml (n = 11).

Table 2

Independent prognostic factors by multivariate analysis and the relative hazard (RH) of death with 95% confidence limits and the score of each prognostic factor

Prognostic factor	RH	95% confidence limits of the RH	Score	P*
CASA $\geq$ 10 U/ml	4.5	1.3–11.1	8.7	0.003
CA125 $\geq$ 35 U/ml	4.4	1.1–11.2	8.0	0.005
Tetranectin $\leq$ 9.3 mg/l	3.9	1.9–10.7	4.0	0.04
Residual tumor 0 cm vs < 2 cm vs $\geq$ 2 cm	1.4	1.1–2.2	30.1	<0.001
Stages I–IV at primary Surgery	—	—	—	0.4
Histological type	—	—	—	0.8
Age <55, 55–69 or $\leq$70 years	—	—	—	0.09

* χ^2-test.

operations would not have been performed, even with a PV_{Pos} at 100% (Table 1).

At the follow-up, 28 of the patients were still alive (median follow-up 88 months, quartiles 78–94) and 35 had died of ovarian cancer (median follow-up 19 months, quartiles 10–37). Two patients died without any signs of cancer (no autopsies). The first patient (75 years of age) died 7.1 months after the operation of respiratory failure without any signs of cancer. The other patient (59 years of age), who had a chronic psychosis of the paranoid type, died of anorexia nervosa 70 months after the operation.

Using 9.3 mg/l as the cut-off level for se-TN, a significant better survival was found by lifetable analyses for all patients with se-TN > 9.3 mg/l (51% survival at 101 months), compared with patients with se-TN $\leq$ 9.3 mg/l (11% survival at 74 months) (Fig. 2). In patients with residual tumor at the time of operation, it was found that the survival rate was 11% at 74 months for those patients with se-TN $\leq$ 9.3 mg/l and 29% at 96 months for those with se-TN > 9.3 m/gl ($p = 0.003$).

A significantly better rate of survival was found by lifetable analyses for all patients with CASA $\leq$ 10.0 U/ml (54% survival at 101 months) compared with patients with CASA $\geq$ 10 U/ml (0% survival at 66 months) (Fig. 3). For patients with residual tumor at their last operation, the survival rate was 0% at 66 months for patients with CASA $\geq$ 10 U/ml and 33% at 96 months for those with CASA < 10 U/ml ($p < 10^{-5}$). Similar variations in survival were found when the cut-off 4 U/ml was used for CASA in all patients ($p = 0.0002$) and in the subgroup of patients with residual tumor ($p = 0.01$).

The survival rate following the last operation for all patients with CA-125 < 35 U/ml was 54% at 101 months compared with a survival of 8% at 92 months for patients with CA-125 $\geq$ 35 U/ml ($p < 10^{-5}$) (Fig. 4). Also for patients with residual tumor at the last operation, a significantly better prospect of survival was found for those with CA-125 < 35 U/ml (survival 30% at 96 months), compared with patients with CA-125 $\geq$ 35 U/ml (survival 8% at 92 months, $p = 0.0001$). Similar variations were found when the cut-off 10 U/ml was used for CA-125 in the total patient group ($p = 0.0001$) and in the group of patients with residual tumor ($p = 0.01$).

In the Cox multivariate analyses all three serum markers and residual tumor size were found to be of independent prognostic value for survival (Table 2). The highest relative hazard (RH) of death was found for patients with CASA $\geq$ 10 U/ml (RH = 4.5), the second highest was found for patients with CA-125 $\geq$ 35 U/ml (RH = 4.4), followed by patients with se-TN $\leq$ 9.3 mg/l (RH = 3.9). For residual tumor the RH was 1.4. No independent prognostic function was found for any of the other variables tested. When the cut-off point for CASA was changed to 4 U/ml, the RH for CASA decreased to 2.6 ($p = 0.02$), ranking CASA as the fourth strongest independent prognostic factor.

Discussion

The present study indicates that the use of either one, or a combination of the studied markers may be of value in predicting residual tumor masses in patients scheduled for second- or third-look operations, while all patients with an elevated marker had residual tumor ($PV_{Pos} = 100\%$). Both CASA and CA-125 were found to have high predictive values when used as single markers. For CA-125, we found the highest predictive values for a single marker as well as for a marker combination, if the cut-off 10 U/ml was used. However, we fear that the positive predictive value on 100% at this cut-off may be reduced in a larger study, while ranges with values higher than 10 U/ml in tumor-free patients have been reported in other studies (8, 24). The

cut-offs for CA-125 therefore need to be reconsidered in future studies by using ROC analysis.

All three markers, alone or in combination, were unable to predict anything useful about the disease status in patients with a normal marker level ($PV_{neg} < 100\%$). A second- or third-look operation to evaluate treatment response is therefore still necessary in patients with a normal marker level.

For CASA, a PV_{Pos} of 100% was found by ROC analyses at a cut-off on 10 U/ml, which therefore was selected as our cut-off limit for CASA. This cut-off is different from earlier reports that used lower cut-off limits and reported $PV_{Pos} < 100\%$. McGuckin et al. (9), who examined another CASA kit, used 3 U/ml as the cut-off to predict residual tumor. In their study 1 out of 8 patients with PCR had a false positive CASA. Ward et al. (11, 25), who examined the same CASA kit as we did, used the cut-off 6 U/ml to predict residual tumor and found 3 out of 23 patients PCR to have a false positive CASA. Therefore, if the CASA analyses are to play a future role in selecting patients for second- or third-look operations, the choice of cut-off limit will require further investigation, which, from our point of view, means that the cut-off has to be increased to values with a PV_{Pos} of 100%.

An improvement in prediction was found when CA-125 ($\geqslant 35$ U/ml) and CASA were combined compared with the prediction when CASA or CA-125 was used alone (Table 1). This improvement was further increased by including se-TN in the combination. The explanation for the improvements is perhaps that se-TN reflects the proteolytic status of the cancer cells (19, 26) while CASA and CA-125 reflect the expression of antigens from the cancer cells. Se-TN may thus be low in a proteolytic active and growing cancer, which does not express the antigens of the other markers in blood (9, 27). Likewise, CASA will detet cancers expressing CASA and not CA-125 and vice versa.

After the introduction of second-look surgery in the management of ovarian cancer more than 20 years ago, the operation became widely established without any true test of efficacy. Therefore, the impact on survival has been critically re-evaluated in several studies with every conflicting results (1–4, 28, 29). These discrepancies may be attributable to varying patient selection criteria, small studies, and differences in effect of second-line therapies. The question of performing second- or third-look surgery will therefore remain a controversial one until larger studies reveal some general guidelines for patient selection. Until then, the decision to perform second-look surgery should only be made on a very individual basis or should in general only be performed in investigational settings. In this respect it is important to distinguish between second-look surgery and intervention surgery, which is performed after 2–3 cycles of chemotherapy in patients showing response to chemotherapy in whom primary surgical efforts have been minimal and in whom the tumor markers are not necessarily in the normal range. Whether intervention surgery has any effect on survival has to be investigated in other settings.

The question of whether a second- or third-look operation is of any benefit to the patients in terms of improvement in survival cannot be answered from this study. Potentially, some combinations of the markers, in conjunction with other diagnostic tools, may be of use in the selection of a subgroup of patients who might benefit from cytoreductive surgery. However, if the operation were restricted to patients who had a marker negative test, and the combined test were used in the actual group of patients, up to 37% would not have had any operation. We therefore find that these tests should be included as potential selection parameters in other studies evaluating the use of second-look surgery.

This study is the first one to describe se-TN as an independent prognostic marker for survival before second- or third-look surgery, a function of se-TN which has already been shown for new cases of ovarian cancer (12) and metastatic breast cancer (30). This function has already been described for CA-125 (24). Ward et al. (11) found CASA to be a non-significant prognostic factor, ranking as the second strongest prognostic factor after age in 41 patients. In that study a cut-off on 4 U/ml was chosen to discriminate between high- and low-risk patients. In our study the RH for CASA decreased from 4.5 to 2.6 when the cut-off was changed from 10 U/ml to 4 U/ml. The non-significant finding by Ward et al. (25) may thus be due to a less prognostic cut-off and fewer patients. For all three markers their prognostic values were superior to the surgical reporting of residual disease.

Surprisingly, we found relatively high se-TN concentrations in the samples taken prior to second- or third-look operations compared with the se-TN values found both in a population of normal women and in a population of patients with newly detected ovarian cancer (10, 23). One explanation may be, that larger volumes of tumor tissue exist in patients before primary surgery compared with the residual tumor size in patients scheduled for second- or third-look operations. Another explanation may be that the chemotherapy has induced a rise in se-TN through the cytotoxic effect on cell function and proliferation (13). In this respect, we found no correlation in a previous study between se-TN and the two chemotherapy regimens (12).

In conclusion, both se-TN, CASA and CA-125 are useful markers in predicting residual tumor and prognosis before second look for ovarian cancer. CASA and CA-125 are highly predictive for residual tumor when used as single markers, whereas se-TN is best when used in combination with other markers. The inclusion of the markers should be considered in future trials on the use of second-look operations and in the evaluation of new treatment strategies for ovarian cancer.

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