Urinary Gonadotropin Fragment (UGF) Measurements in the Diagnosis and Management of Ovarian Cancer

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UGF is a small peptide present in the urines and tissues of patients with gynecologic cancers. Published research (which, at present, mainly comes from our laboratory) on the general application of UGF as a tumor marker, and on its use in the diagnosis of ovarian cancer, is reviewed, and new studies on its use, alone and with CA125, in the management of patients with ovarian cancer, are presented. In 234 healthy women, 89 with benign disease, and 79 with ovarian cancer, UGF levels were above 3 fmol/ml (low cut-off) in 12 percent, 7 percent, and 82 percent, respectively, and above 8 fmol/ml (high cut-off) in 1.7 percent, <1.1 percent, and 59 percent, respectively. Similarly, 11 percent, 14 percent, and 70 percent, respectively, had CA125 levels above 35 U/ml (low cut-off), and <1.9 percent, 1.2 percent, and 49 percent had levels above a 200 U/ml (high cut-off). Ideally, the higher UGF and CA125 cut-offs should be used for diagnostic applications, like differentiation of a benign from a malignant pelvic mass (false-positive rate: UGF, <1.1 percent; CA125, 1.2 percent), but raising the cut-offs diminishes sensitivities for malignancy (UGF, 59 percent; CA125, 49 percent). The populations detected by the two markers only partially overlap, however, so that, together, UGF or CA125 can identify 75 percent of malignant pelvic masses. Levels of UGF (cut-off, >3 fmol/ml) and CA125 (35 U/ml) were also monitored in 30 women undergoing therapy for ovarian cancer. Clinical observations were reflected at each clinic visit by UGF alone in 67 percent, by CA125 alone in 57 percent, and by UGF and CA125 together in 87 percent of cases. While separately UGF and CA125 levels predicted 71 percent and 57 percent, together they forecast 86 percent of recurrent cancers prior to clinical manifestations. UGF and CA125 should be used together in the detection and management of ovarian cancers.

BACKGROUND

Human chorionic gonadotropin (HCG) is a glycoprotein hormone composed of a common α-subunit (also found in lutropin, follitropin, and thyrotropin) and a unique β-subunit, which gives the molecule its luteotropic function. HCG is produced by trophoblast tissue and can be detected in the blood and urine of women with pregnancy or trophoblast disease. Free HCG α- and β-subunits are also present in blood and urine of women with pregnancy or trophoblast disease, at levels <1 percent to 40 percent of that of the hormone [1–12].

HCG and HCG free subunit immunoreactivities have also been detected in the serum and tissues of cancer patients [7,13–22]. Recently, Hussa [7] compiled the results of 38 separate studies of HCG detection in cancer patients. As compiled (n = 4,291, with testicular and trophoblastic cancers excluded), 19 percent of subjects with cancer had detectable serum HCG levels. We analyzed 65 serum samples from

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Abbreviations: HCG: human chorionic gonadotropin  RIA: radioimmunoassay  UGF: urinary gonadotropin fragment

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women with active ovarian, cervical, and endometrial cancers. Consistent with the compilation of Hussa [7], only 12 (18 percent) had detectable HCG levels [21]. Furthermore, the levels in the 12 HCG-positive samples (mean = 3.0 mlU/ml) were close to the limit of detection (2 mlU/ml), restricting the range of HCG levels that could be used for monitoring cancer therapy. We concurred with Hussa [7] and concluded that HCG was not a useful marker of non-trophoblastic gynecologic cancers and that other markers with higher cancer sensitivity were needed.

In 1977, Good and colleagues [5], demonstrated, using gel filtration techniques, that a small form of HCG β-subunit was present in pregnancy urines at levels higher than that of HCG. During the following ten years, similar findings were observed by several other researchers [23–29]. Chromatographic studies, and experiments with antibodies directed to different sites on HCG, indicated that this small molecule was composed of segments of β-subunit. As such, the term urinary HCG β-subunit core fragment was coined for this small molecule. In 1987–8, several laboratories generated antibodies against HCG β-subunit core fragment and established specific immunoassays. Akar and collaborators at N.I.H. generated β-subunit core fragment antisera [30]. Krichevsky and colleagues at Columbia University generated a β-subunit core fragment-specific monoclonal antibody [31] (antibody B204), as did Kardana and colleagues in London, England [32]. Using these antibodies in immunoassays, levels of HCG β-subunit core fragment were determined in pregnancy and trophoblast disease patient urines. In pregnancy urines, levels of β-subunit core fragment were shown to exceed HCG levels, by two- (first trimester) to seven- (second trimester) fold. Similarly, β-subunit core fragment levels in patients with trophoblast disease exceeded HCG levels, by as much as fiftyfold [22,30,33,34].

The gel filtration studies by Good and colleagues in 1977 also showed that the small β-subunit fragment was present in placent al tissue [5]. Recent studies by Kardana and collaborators have confirmed these observations, by demonstrating that syncytiotrophoblast cells can be specifically stained for HCG β-subunit core fragment with monoclonal antibody 2C2 [34]. Studies in our laboratory have shown that human trophoblast organ cultures (n = 10), from first, second, or third trimester pregnancies secrete HCG β-subunit core fragment at levels similar to or exceeding those of HCG [33]. Studies by Wehmann and Nisula [27] have, however, shown that when HCG β-subunit is administered to humans, β-subunit alone is detected in serum, but both β-subunit and β-subunit core fragment can be detected in urines. This result suggested the presence of an additional pathway for generating HCG β-subunit core fragment, possibly involving renal degradation of molecules.

Recently, our laboratory collaborated with that of Steven Birken at Columbia University and determined the fine peptide and carbohydrate structure of HCG β-subunit core fragment. As was shown [26], β-subunit core fragment is composed of HCG β-subunit residues 6–40 attached by four disulfide linkages to HCG β-subunit residues 55–92, with two attached N-linked sugar units. The N-linked sugar units lacked the sialic residues that are found on HCG oligosaccharides. The molecular weight of HCG β-subunit core fragment was just 10,300, or 28 percent of that of HCG (36,700). Recently, Wehmann and colleagues [35] showed that HCG β-subunit core fragment is cleared from the circulation in humans 120 times faster than HCG (if equal amounts were produced, circulating β-subunit core fragment levels would be 0.8 percent of those of HCG). The rapid clearance rate is not surprising, when the absence of sialic acid (which maintains the circulatory half-life of the glycoprotein hormones
(20]) on HCG \( \beta \)-subunit core fragment and the small size, relative to HCG, are considered. The rapid clearance rate may explain why \( \beta \)-subunit core fragment is more readily detected in urine than in serum samples (serum concentration is 70 times lower than that in urine [36]).

Kardana and colleagues [34] used antibodies 2C2, INN13 (HCG-specific), and 1E5 (free \( \beta \)-subunit-specific), with histochemical methods, to stain fixed slices of non-trophoblastic cancer tissues. While none of 83 tissue slices was stained with the HCG or the free \( \beta \)-subunit antibodies, 77 (93 percent) were stained with the fragment-specific antibody, 2C2, at a distinctly higher level than surrounding control tissue. Consistent with these findings, our laboratory has used immunoassays with antibodies B204, 1E5, and B109 (HCG-specific) and gel filtration methods to indicate the absence of HCG and free \( \beta \)-subunit, and presence of HCG \( \beta \)-subunit core fragment in five of five tissue pieces from ovarian cancer [20,36]. Other researchers have used chromatographic methods [24–26,37] or, in more recent studies, immunoassays with monoclonal antibodies 2C2 or B204 [21,22,34,38–41], to show that HCG \( \beta \)-subunit core fragment-like molecules are present in the urines of as many as 92 percent of cancer patients. The finding that HCG \( \beta \)-subunit core fragment is produced by cancer cells, in the absence of detectable HCG or \( \beta \)-subunit, indicated a detachment in their production. As such, the terms HCG and HCG \( \beta \)-subunit core fragment were detached, and the latter called urinary gonadotropin fragment (UGF) [21,34,38–41].

In the past two years, we have published several articles on UGF assays, and on applications of UGF and of UGF and CA125 measurements in the diagnosis of gynecologic cancers [21,38–41]. This article reviews our published data and supplements it with new observations on the use of UGF alone, and of UGF with CA125, in the management of ovarian cancer and on the early detection of recurrent disease.

DEVELOPMENT OF UGF ASSAY

A specific immunoradiometric assay was developed for UGF. Urine, 200 \( \mu \)l, was added to tubes coated with 900 ng monoclonal antibody B204. UGF was bound by the coated tube, and urine removed. Radiolabeled monoclonal antibody HCO514 (directed to a common \( \beta \)-subunit epitope) was then added, which labeled the bound UGF. After removing excess labeled antibody, radioactivity was determined. A linear relationship was found between UGF in urine and radioactivity. The cross-reactivity of HCG in this assay was <0.2 percent; with HCG free \( \beta \)-subunit, was 7.5 \( \pm \) 0.54 percent; and with lutropin or lutropin free \( \beta \)-subunit, was <0.1 percent. Over a six-month period the intra-assay and inter-assay coefficients of variation averaged 7.8 \( \pm \) 1.9 percent and 12.7 \( \pm \) 1.7 percent, respectively, and the sensitivity (concentration different from 0 fmol/ml standard in Student's \( t \)-test) averaged 2.1 \( \pm \) 0.31 fmol/ml. Details of these methods, and of the effects of varying antibody concentrations and incubation conditions, are published elsewhere [40].

ESTABLISHMENT OF CANCER SENSITIVITY AND SPECIFICITY, AND CUT-OFF LEVELS

UGF levels were measured in 323 control samples, from 234 healthy women, and from 89 with benign disease (Table 1). Thirty-three of the 323 women providing control urines had UGF levels which exceed 3 fmol/ml; only four, however, exceed 8 fmol/ml, or 4 standard deviations among the mean. A cut-off of 8 fmol/ml was indicated for screening-type applications, where a low false-positive rate (1.2 percent)
is critical. The higher false-positive rate, using the 3 fmol/ml cut-off (10 percent), is lower than that reported for CA125 (14 percent and 35 U/ml cut-off [41,42]) and is appropriate for application where sensitivity is less critical, such as monitoring the progress of patients with established cancer.

Similar false-positive results were observed for two groups with similar age distribution, women pre-menopause with no history of disease (0 of 94 exceed 8 fmol/ml) and women with benign gynecologic lesions (0 of 89 exceed 8 fmol/ml). The similarity of the results between these two groups indicates that benign pelvic lesions such as endometriosis, benign ovarian neoplasm, and leiomyomata uteri do not falsely elevate UGF levels. False-positive results were higher among women who were post-menopause than pre-menopause (false-positive rates 2.9 percent and <1.1 percent, respectively, at 8 fmol/ml cut-off). Recent studies have shown that some healthy post-menopausal women have low levels of HCG (0–10 mlU/ml) and HCG free α- and free β-subunits in their circulation, of pituitary origin [43,44]. We postulate that the 2.9 percent of post-menopausal women who have false-positive UGF levels in urine are those whose pituitary produces cross-reacting HCG free β-subunit.

UGF levels were examined in 156 women with proven gynecologic cancers (Table 2). While UGF levels in 102 patient samples (65 percent), exceed 3 fmol/ml, only 70 (45 percent) exceed the 8 fmol/ml cut-off. The mean UGF level in cancer patients was 44 fmol/ml, the range of levels was 3–714 fmol/ml (240-fold different), which is

### TABLE 1
Incidence of False-Positive UGF Levels in Healthy Individuals, and Women with Benign Disease

|                           | Number of Patients | Number of False-Positives |            |            |
|---------------------------|--------------------|---------------------------|------------|------------|
|                           |                    |                           | >3 fmol/ml | >8 fmol/ml |
| Healthy women             |                    |                           |            |            |
| Pre-menopause             | 94                 | 3 (3.2%)                  | 0          |
| Post-menopause            | 140                | 24 (17%)                  | 4 (2.9%)   |
| Subtotal                  | 234                | 27 (12%)                  | 4 (1.7%)   |
| Women with benign disease |                    |                           |            |            |
| Endometriosis             | 16                 | 3 (18%)                   | 0          |
| Ovarian neoplasm          | 14                 | 0                         | 0          |
| Leiomyomata uteri         | 13                 | 1 (8%)                    | 0          |
| Condyloma                 | 15                 | 0                         | 0          |
| Other                     | 31                 | 2 (6%)                    | 0          |
| Subtotal                  | 89                 | 6 (7%)                    | 0          |
| Total                     | 323                | 33 (10%)                  | 4 (1.2%)   |

### TABLE 2
Incidence of True Positive UGF Levels in Individuals with Gynecologic Cancer

|                | Number of Patients | Number of True Positives |
|----------------|--------------------|--------------------------|
|                |                    | >3 fmol/ml | >8 fmol/ml |
| Ovary          | 71                 | 58 (82%)  | 42 (59%)   |
| Endometrium    | 33                 | 20 (61%)  | 12 (36%)   |
| Cervix         | 52                 | 24 (46%)  | 16 (31%)   |
| Total          | 156                | 102 (65%) | 70 (45%)   |
similar to that of CA125 (35–9,000 U/ml, 260-fold different [45]). The organ specificity of UGF, as a cancer marker, was also similar to that of CA125 (Table 2). While 82 percent, 61 percent, and 46 percent of ovarian, endometrial, and cervical cancers, respectively, were detected by UGF (cut-off >3 fmol/ml), 76 percent, 59 percent, and 18 percent were reported to be detected by CA125 (cut-off 35 U/ml [45]); however, the tissue specificities of UGF and CA125 for ovarian cancers were markedly different. While UGF is impartial and detected a similar proportion of serous (81 percent) and endometrioid/mucinous/other (82 percent) ovarian cancers (Table 3), CA125 had a distinct preference for detecting serous malignancies (sensitivity 79 percent, vs. 57 percent for other ovarian malignancies). We conclude that UGF is a marker of gynecologic cancers. Like CA125, UGF levels preferentially mark ovarian malignancies. The sensitivity and specificity of UGF (81 percent and 10 percent, cut-off >3 fmol/ml) and CA125 (79 percent and 14 percent, cut-off 35 U/ml) are similar for serous ovarian cancers. While CA125 has reduced sensitivity for other types of ovarian cancer, however, the sensitivity of UGF remains the same (82 percent).

**APPLICATION 1: IN DIFFERENTIATING BENIGN AND MALIGNANT PELVIC MASSES**

The distinction of a benign from a malignant pelvic mass is a difficult problem for the gynecologist. Physical examination may be of little use, and ultrasound, while distinguishing an adnexal mass from a uterine mass, has limited use in differentiating a benign pelvic mass from a malignancy [46–49]. Tumor markers, such as CA125, are also insufficiently accurate to help in the differential diagnosis of benign and malignant disease. In studies at Yale–New Haven Hospital (Table 3), CA125 detected 79 percent of serous malignancies, but also detected 14 percent of patients with benign pelvic masses. Studies at other centers show that CA125 detects 76 percent to 91 percent of serous malignancies, but also 6 percent to 40 percent of benign pelvic lesions [42,50–52].
New methods are needed to distinguish masses and to identify malignancies pre-operatively. With these methods, appropriate additional studies could be arranged which may influence the type of surgery scheduled. If a malignancy is expected, then a bowel prep and the necessary surgical expertise can be scheduled pre-operatively. In this way, accurate staging procedures and complete tumor removal can be done, both of which are very important for selection of the appropriate post-operative management program.

We investigated the levels of UGF in patients with pelvic masses and its ability to complement CA125 results. As shown in Table 3, UGF at a cut-off of >3 fmol/ml, like CA125 at 35 U/ml, falsely detected a high proportion (9.3 percent and 14 percent, respectively) of benign pelvic masses. When the UGF and CA125 cut-off levels were raised to >8 fmol/ml and to 200 U/ml, respectively, the number of benign pelvic masses detected was significantly reduced (to <2.3 percent and 1.2 percent, respectively). The cancer sensitivities of UGF and CA125 were reduced also (59 percent and 49 percent, respectively). The populations detected by the two markers only partially overlap, however, so that, together, UGF or CA125 can identify 79 percent of serous and 68 percent of other malignant pelvic masses.

The latter finding indicated new procedures for the evaluation of patients presenting with a pelvic mass. A urine specimen should be collected for UGF measurements and a parallel plasma sample collected for CA125. Using two assay results, with UGF at a cut-off of >8 fmol/ml and CA125 at a cut-off of 200 U/ml, 75 percent of malignancies should be detected. The false-positive rate is 1.2 percent for CA125 alone, <2.3 percent for UGF alone, and <1.2 percent when, as in the majority of cases, UGF and CA125 are detected. These false-positive rates may be low enough for use in the evaluation of pelvic masses. If elevated levels are detected (>8 fmol/ml or ≥200 U/ml), cancer should be assumed and appropriate measures taken.

APPLICATION 2: IN MONITORING THE THERAPY OF OVARIAN CANCER

The clinical evaluation of tumor burden in ovarian cancer patients undergoing therapy and follow-up is problematic. Currently, second-look surgical procedures are commonly used to determine whether therapy should be halted or modified, or new procedures instituted. The discovery of sensitive tumor markers which accurately reflect the tumor burden may help to monitor clinical status better, alleviate the necessity of second-look surgery, and possibly permit the detection of recurrent disease prior to the appearance of clinical signs, when therapy may be too late to be of value.

CA125 is found in the plasma of a high proportion of patients (reports vary from 76 percent to 91 percent) with serous ovarian cancers [42,50–52]. Several centers have examined the use of plasma CA125 measurements in monitoring therapy of ovarian cancer. Early reports showed that CA125 levels diminished and became undetectable as ovarian cancer patients responded to treatment [53–55]. This finding suggested that CA125 levels reflected tumor burden, and applications for CA125 in monitoring the efficacy of therapy and in the early detection of recurrent disease [53–55]. More recent studies have found limitations in the use of CA125 in ovarian cancer management. For instance, reports indicate that >40 percent of patients who are clinically free of disease, with CA125 levels (<35 U/ml) in the normal range, have persistent cancer when evaluated by second-look surgery procedures [45,56,57]. Furthermore, it has been suggested that diminishing CA125 levels in ovarian cancer patients do not
necessarily indicate diminishing disease [58]. Additional markers are needed to back up CA125 and to detect non-serous ovarian malignancies.

As described earlier, UGF is also produced by a high proportion of serous ovarian carcinomas. In our experience (Table 3), CA125 (cut-off, 35 U/ml) detects in plasma 79 percent, and UGF (cut-off, >3 fmol/ml) in urine a similar proportion (81 percent) of serous cystadenocarcinomas. Like CA125, UGF sensitivity, and levels [41], increase with advancing stage (Table 4). This finding suggests that UGF levels, like those of CA125, may reflect tumor burden. UGF, however, unlike CA125, similarly detects serous, mucinous, and endometrioid malignancies and, as described earlier, complements CA125 detection of serous cystadenocarcinoma (Table 3: UGF, 81 percent; CA125, 79 percent, and together they detect 95 percent of serous cancers). The use of UGF alone, and of UGF and CA125, was investigated, in following the therapy of patients with ovarian cancer.

Levels of UGF and CA125 were monitored in 30 women undergoing therapy for ovarian cancer. Twenty-one of the group (70 percent) had true positive UGF (>3 fmol/ml) and 19 of the group (63 percent) had true positive CA125 levels (>35 U/ml) at entry into the study or when cancer became clinically evident. Levels of UGF accurately (at each clinic visit) reflected clinical observations during therapy in 20 of the 21 (95 percent) true positives, or 67 percent of the 30 patients (Table 5). CA125 levels reflected clinical observations in 17 of the 19 (89 percent) true positives, or 57 percent of the 30 patients. Interestingly, UGF levels reflected the clinical course in a similar proportion of the 19 CA125 true positives (64 percent) and 11 CA125 true negatives (68 percent), suggesting the independence of the two markers. While CA125 levels were most useful in monitoring patients with serous cancers (levels were concordant with clinical observations in 67 percent of women with serous and 33 percent of those with other ovarian malignancies), UGF levels were best in the management of those with endometrioid and other ovarian malignancies (levels reflected clinical observations in 62 percent of those with serous and 77 percent of patients with other cancers). These results further indicate that the two markers complement each other, and the appropriateness of using them together, to back up each other's false-negatives. Using UGF and CA125 together, therapy was appropriately monitored at each clinic visit in 26 of the 30 (87 percent) patients.

We investigated the use of UGF alone, CA125 alone, and the two markers together in the early detection of recurrent disease. Rising UGF and rising CA125 levels each separately predicted four of seven recurrences in patients clinically free of disease.

### TABLE 4
Detection of UGF and CA125 Levels in Parallel Urine and Plasma Samples from Patients with Malignant Pelvic Masses: Breakdown by Stage (F.I.G.O.)

| Stages I and II | UGF >3 | UGF >8 fmol/ml | CA125 35 | CA125 200 U/ml |
|----------------|--------|----------------|----------|-------------|
| Stages III     | 40     | 75%            | 50%      | 60%         | 43%         |
| Stage IV       | 10     | 100%           | 70%      | 90%         | 60%         |
| Stage X        | 4      | 100%           | 100%     | 100%        | 100%        |
| Recurrence     | 12     | 83%            | 75%      | 92%         | 67%         |
| Total          | 71     | 82%            | 59%      | 70%         | 49%         |
| Case | Histology | Stage/Grade | Therapy and Clinical Observations$^a$ | UGF Levels (fmol/ml) at Visits 1 through 9 | CA125 Levels (U/ml) at Visits 1 through 9 | Clinical Correlation |
|------|-----------|-------------|--------------------------------------|------------------------------------------|------------------------------------------|----------------------|
| 1    | Endometrioid | II/2 | S→C|C•C•C•C• | 30, 2, 0, 0, 0 | 5, 6, 6, 5, 5 | + - + |
| 2    | Endometrioid | III/3 | C→C→N•N•N↑ | 5, 3, 4, 6, 8 | 33, 8, 5, 6, 22 | + - + |
| 3    | Endometrioid | III/3 | S→C|C•C•C•C↑ | 15, 0, 0, 0, 4, 13 | 27, 8, 5, 8, 4, 6 | + - + |
| 4    | Imm. teratoma | III/3 | C→C→C|C|C•C•C•C• | 9, 10, 10, 0, 0, 0, 2 | 1, 7, 1, 10, 5, 5, 5 | + - + |
| 5    | MMT | III/3 | S|C|C↑ | 19, 0, 3 | 33, 5, 1 | - - - |
| 6    | Mucinous | X | C|C|C↑ | 7, 4, 6 | 1,580, 1,430, 1,360 | + - + |
| 7    | Mucinous | X | S|C|C↓ | 80, 9, 8 | 600, 210, 21 | + + + |
| 8    | Serous | III/2 | S|C•C•C•C•C• | 11, 3, 4, 4, 0 | 1,7, 8, 10, 6 | + - + |
| 9    | Serous | III/2 | S•C•C|C↑ | 2, 2, 6, 21 | 6, 84, 56, 84 | + - + |
| 10   | Serous | II/1 | ↑C|C•N•N•NS↓ | 5, 0, 0, 4, 4 | 1, 5, 5, 25, 5, 5 | + - + |
| 11   | Serous | IV/3 | S|C|C|C•C• | 13, 10, 8, 0 | 6, 7, 7, 6 | + - + |
| 12   | Serous | R/3 | C→C|C↑ | 5, 10, 15 | 40, 350, 360 | + + + |
| 13   | Serous | X | C→C•C•C•C↑ | 12, 6, 8, 7, 56 | 200, 180, 190, 270, 1,220 | + + + |
| 14   | Serous | III/3 | S→C|C•C•C↑ | 2, 9, 8, 14 | 66, 57, 250, 860 | + + + |
| 15   | Serous | III/3 | ↑S|C|C•C•C• | 6, 0, 0, 0, 0 | 1,000, 40, 7, 7, 7 | + + + |
| 16   | Serous | III/3 | C→C→C|C|N•N•N•N• | 6, 4, 2, 0, 2, 3 | 490, 24, 15, 11, 12, 13 | + + + |
| 17   | Serous | R/2 | ↑S|C|C•C• | 9, 11, 0, 0 | 40, 56, 32, 30 | + + + |
| 18   | Serous | III/2 | ↑S|C|C→C•C• | 29, 19, 7, 22, 12 | 4,880, 100, 100, 850, 180 | + + + |
| 19   | Serous | R/3 | ↑S|C|C•N•N•↑ | 20, 13, 0, 0, 10 | 2,000, 5, 6, 6, 60 | + + + |
| 20   | Serous | III/2 | C•C•C•C•C•S|C|C•C•C↑ | 0, 0, 0, 0, 3, 0, 5, 3, 9 | 5, 5, 7, 5, 21, 0, 34, 55, 98 | + + + |
| 21   | Theca cell | II/2 | S|C|C•C•C• | 6, 3, 0, 0 | 40, 8, 8, 7 | UGF True Positives 95% 52% 95% |
| Patients with False-Negative UGF Levels |
|----------------------------------------|
| Endometrioid | R/3 | C↑R↑C→ | 0, 0, 2 | 300, 1,300, 870 | – | + | + |
| Serous | III/1 | C→C↑C→ | 0, 0, 0 | 125, 150, 83 | – | + | + |
| Serous | III/3 | C→C↑C↑ | 0, 0, 0 | 230, 580, 1,750 | – | + | + |
| Serous | R/3 | C↑C→C↑ | 0, 12, 5 | 2,050, 3,430, 5,260 | – | + | + |
| Serous | III/3 | S→C→C↑C↑ | 0, 0, 0, 0 | 410, 400, 460, 1,860 | – | + | + |
| Serous | IV/3 | S→C↑C↑C→C↑ | 0, 5, 0, 0, 3 | 220, 700, 1,300, 990, 3,760 | – | + | + |
| Serous | III/3 | S→C→C→ | 0, 0, 0 | 23, 11, 3 | – | – | – |
| Serous | III/3 | C→C↑C↑C↑ | 0, 0, 0, 41 | 7, 31, 35, 27, 1,200 | – | – | – |
| Serous | III/3 | S→C→C→C→S→ | 3, 3, 0, 0, 6 | 5, 2, 6, 9, 25 | – | – | – |
| UGF False-Negatives | | | 0 | 67% | 67% |
| Overall | | | 67% | 57% | 87% |

*A brief patient history is presented for the study period. The symbols ↑, →, ↓, and * mark the clinical observations at each visit/sample collection and represent progressive, stable, and decreasing tumor mass, and no evidence of disease, respectively. Therapy between clinic visits/sample collections is indicated by the letters S, C, R, and N, which refer to surgery, chemotherapy, radiotherapy, and no therapy, respectively. The time between clinic visits/sample collections averaged 32 days (range, 5–210 days). The symbols in the clinical correlation columns indicate whether changing levels of UGF, CA125, or both are (+) or are not (−) concordant with clinical observations (at all clinic visits).*
Using either marker, however, seven of seven recurrences were detected when first clinically evident, and six of seven at a clinic visit prior to that.

We conclude that UGF is a good back-up marker for CA125 and that it should be used in monitoring all patients with ovarian cancer. For mucinous and other non-serous ovarian cancers, UGF should be the marker of choice, and, for serous malignancies, the use of both UGF and CA125 is recommended. In our experience while following the progress of 21 patients with serous cancer, changes in CA125 and UGF levels do not conflict with each other, so that, in patients clinically free of disease, an elevation of either CA125 or UGF indicates a recurrence, and the need to start appropriate therapy.

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