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Research Article

Follow-Up of Ovarian Cancer: Correlation Between Imaging Findings and CA 125 Serum Value

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Abstract

Objectives: To assess the correlation between imaging findings and Cancer Antigen (CA) 125 serum value in the follow-up of ovarian cancer.

Methods: We included 41 consecutive patients with malignant ovarian epithelial cancer who underwent surgical debulking at our institution (Jan 2014–Dec 2018). Computed Tomography (CT) / Positron Emission Tomography (PET)-CT images obtained during follow-up were reviewed for the presence of disease (yes/no). Imaging findings were compared with the CA 125 serum values at the time of examination.

Results: Of the 211 imaging studies, 117 (55.5%) were negative for the presence of disease, whereas 94 (44.5%) were positive. The median CA 125 value was 87 U/mL in patients with positive imaging findings and 10 U/mL in patients with negative ones (Mann-Whitney U test, $p<0.0001$). Of the 129 examinations performed in patients with normal CA 125 serum value, 110 (85.3%) were negative for disease, whereas 19 (14.7%) were positive; the median CA 125 serum value of the latter were 10 U/mL in patients with negative imaging findings and 23 U/mL in patients with positive ones (Mann-Whitney U test, $p<0.0001$). Only 3/129(2.3%) patients with normal CA 125 serum value, no CA 125 increasing trend and no clinical suspicion of progression showed positive imaging findings.

Conclusion: A strict correlation between CA 125 serum value and imaging finding was observed. Imaging should be avoided in patients with normal CA 125 serum value and no clinical suspicion of disease progression.

Keywords: CT, PET-CT, CA-125 Antigen, Follow-up, Ovarian Cancer

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Ovarian cancer is the fifth most common cause of cancer death among women both in Europe and in the USA.[1, 2] About 90% of ovarian cancers are of epithelial origin and can be histologically subdivided into serous, endometrioid, clear cell, mucinous, transitional cell, mixed epithelial, and undifferentiated carcinomas of various grades. According to molecular, genetic, and morphologic characteristics, these neoplasms can be subdivided into two major subtypes: relatively indolent type 1 tumors, including low-grade serous, low-grade endometrioid, mucinous,

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transitional, and clear cell carcinomas, and more aggressive type 2 tumors, including high-grade serous or endometrioid carcinomas and undifferentiated cancers.[3]

Preoperative staging is typically performed with contrast-enhanced Computed Tomography (CT). Positron Emission Tomography (PET)-CT and Magnetic Resonance Imaging (MRI) can be considered as problem solving techniques in case of unclear CT findings.[4] Serum markers, including Cancer Antigen (CA) 125 and Human Epididymis Protein 4 (HE4), are also routinely evaluated during preoperative diagnostic workup.[5]

Surgical debulking is the treatment of choice if all macroscopic diseases can be safely resected according to preoperative imaging, whereas neoadjuvant chemotherapy must be considered if potentially unresectable lesions (e.g., multiple implants in small bowel root, diffuse implants on the small bowel) are detected on imaging. Adjuvant chemotherapy is indicated in most of the cases.

Ovarian cancer recurs in 70%–80% of patients. Although there is no strong evidence that routine follow-up improves survival, most patients undergo a strict follow-up that is based on a variable mix of clinical evaluation, pelvic examination, serum marker assessment, and imaging.[6–8] CA 125 is the most accurate serum marker for assessing treatment response or progression in ovarian cancer, and the Gynecologic Cancer InterGroup has published a consensus statement indicating how to interpret CA 125 variations for diagnosing recurrence in clinical trials.[9, 10] On the other hand, the 2018 European Society for Medical Oncology – European Society of Gynecologic Oncology consensus conference stated that the CA 125 criteria for response and progression should always be used in combination with radiological and clinical assessment in routine practice and that imaging should be performed only according to symptoms, clinical suspicion, or rising CA 125 values.[11] Other scientific societies suggest to routinely perform imaging studies, independently from clinical or biochemical suspicion, to diagnose and treat tumor recurrence at an early stage.[12] According to both the American College of Radiology and the European Society of Urogenital Radiology, contrast-enhanced CT of the abdomen and pelvis, eventually extended to the thorax, is the imaging modality of choice for assessing disease extension in suspected or known ovarian cancer recurrence, whereas PET-CT might be considered in selected cases.[4, 13]

This study aimed to assess the correlation between imaging findings and CA 125 serum value during the follow-up of patients treated for ovarian cancer.

Methods

In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

Patient Population

The Institutional Review Board approved our retrospective observational study; the need for informed consent was waived. We considered for inclusion 64 consecutive female patients who underwent primary debulking surgery for epithelial ovarian cancer at our institution between January 2014 and December 2018. The exclusion criteria were oncological follow-up performed elsewhere (11/64 patients), history of other abdominal malignancies (8/64), absence of postoperative imaging studies in our institutional database (3/64 patients), and incomplete laboratory data (1/64 patients) (Fig. 1). Therefore, our study population included 41 women with a mean age of 60±14 years.

Clinical and Laboratory Data Collection

Clinical and laboratory data of each patient at diagnosis and during follow-up were retrieved from the institutional database by one gynecologist. Follow-up included variable combinations of clinical visit, tumor marker assessment, and imaging studies. Clinical suspicion of disease progression was defined as new symptom onset and/or symptom worsening. CA 125 serum values, determined via an electrochemiluminescence immunoassay, and trend were annotated, considering significant variations exceeding 20% over a 30-day period.

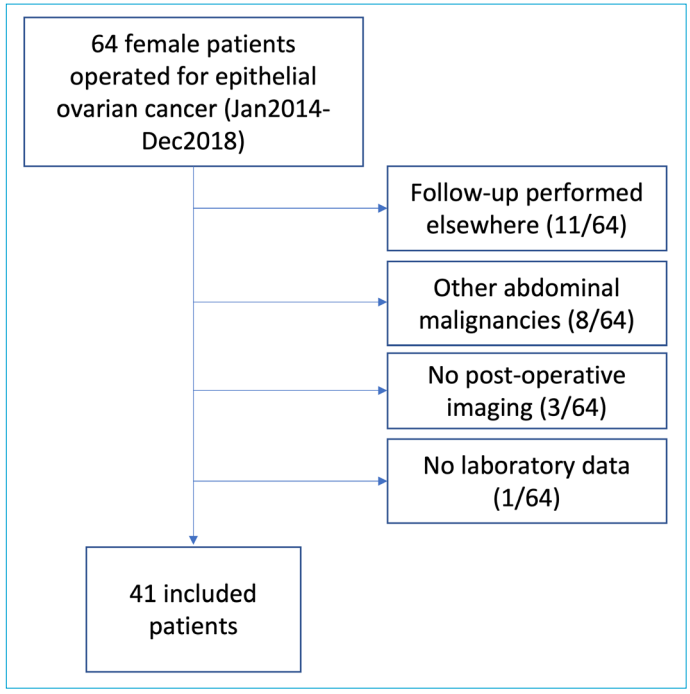

Figure 1. STARD flowchart showing patients' population building.

Imaging Protocol and Evaluation

CT scans were acquired on a 2 × 64 detector rows dual-source CT scanner (Somatom Drive, Siemens). Every examination comprised at least one portal venous phase acquisition of the chest and abdomen, acquired 70 s after injecting 1.6 mL/kg of 350 mgI/mL iodinated contrast medium.

PET, low-dose CT, and fusion images were obtained 60 min after injection of 18F-FDG (3 MBq/kg) using PET-CT scanner (Gemini TF 16, Philips).

Image analysis was conducted for all the examinations for which a CA 125 serum value obtained within 10 days from the study date was available in the institutional database; therefore, 211 imaging studies were reviewed (139 CTs and 72 PET-CTs). CT images were reviewed on a workstation (Syngo.via VB60A, Siemens) by two radiologists (with 13 and 5 years of experience in gynecological imaging, respectively) in consensus, whereas PET-CT studies were reviewed on a dedicated workstation (IntelliSpace Portal 11 PHILIPS Healthcare) by one nuclear medicine specialist and one radiologist (18 and 13 years of experience in gynecological imaging, respectively) in consensus. The readers were unaware of the patients' clinical status and CA 125 serum value. First, every imaging study was classified as positive or negative for the presence of disease, including peritoneal carcinomatosis, nodal metastases, and distant hematogenous metastases. Then, after comparison with previous imaging studies, the disease trend was assessed by evaluating the evolution of both target and non-target lesions and classified as progressive disease (PD), stable disease (SD), partial response (PR), or complete response (CR). Finally, imaging findings were compared with the CA 125 value (normal or abnormal, according to our laboratory cutoff value of 35 U/mL) and the CA 125 trend (decrease, stable, or increase).

Statistical Analysis

Continuous variables are expressed as mean (±standard deviation) or median (range) and categorical variables as numbers and percentages. Data distribution was verified using the D'Agostino–Pearson omnibus K2 normality test. Comparison between subgroups was performed using the Mann-Whitney U test for continuous variables, whereas qualitative data were compared using Fisher's exact tests. All statistical analyses were conducted using GraphPad Prism version 8.00 for Mac OS X (GraphPad Software). P values were considered significant when ≤0.05.

Results

The median preoperative CA 125 serum value was 187 (21–7674) U/mL; only 2 out of 41 patients had normal (< 35 U/mL) preoperative CA 125 serum value. Of the 41 patients, the histological subtype was serous carcinoma in 28 (68.3%), endometrioid carcinoma in 7 (17.1%), clear cell carcinoma in 3 (7.3%), and mucinous carcinoma in 3 (7.3%); furthermore, the tumor grade was G3 in 27 (65.9%), G1 in 11 (26.8%), and G2 in 3 (7.3%). Therefore, 26 out of 41 (63.4%) tumors were classified as type 2 and 15 (36.6%) as type 1; the median preoperative serum CA 125 values were 353 (21–7674) U/mL and 81 (26–542) U/mL in type 2 and 1 lesions, respectively. Of the 41 patients, 20 (48.8%) were classified as FIGO stage III, 11 (26.8%) as stage I, 8 (19.5%) as stage II, and 2 (4.9%) as stage IV. After surgery, abdominal cavity was classified as "No Evident Disease" in 34 out of 41 (82.9%) cases and as R1 in 7 (17.1%). Of the 41 patients, 27 (65.9%) received adjuvant chemotherapy.

The median follow-up time was 48 (2–96) months. Of the 41 patients, 26 (63.4%) were still alive at the time of data collection (January 2022). During the follow-up period, the patients performed a total of 139 CTs and 72 PET-CTs, with a median of 5 (1–15) examinations per patients, leading to a median of 1 imaging study/patient/year. Imaging studies were requested by oncologists in 103 of 211 (48.8%) cases, by gynecologists in 83 (39.4%), by general practitioners in 15 (7.1%), and by emergency doctors in 10 (4.7%). At the time of imaging, the median CA 125 serum value was 19 (2–1616) U/mL. Of the 211 cases, the CA 125 serum value was normal in 129 (61.1%), whereas it was elevated in 82 (38.9%). The CA 125 trend was stable in 88 out of 211 (41.7%) cases, increasing in 63 (29.9%), and decreasing in 60 (28.4%). Of the 211 examinations, 50 (23.7%) were performed in patients with clinical suspicion of disease progression. Out of 211 examinations, 82 (38.9%) were performed as a control after chemotherapy, whereas 58 (27.5%) were performed in the absence of clinical/biochemical alterations nor of recent chemotherapy conclusion.

Out of 211 imaging studies, 117 (55.5%) were negative for the presence of disease and 94 (44.5%) were positive. Positive imaging findings were significantly more common in type 2 than in type 1 neoplasms (47.9 vs. 31.0%, p<0.0001, Fisher's exact test), in R1 than in NED patients (66.7 vs. 39.5%, p<0.0001, Fisher's exact test), and in FIGO III–IV vs. I–II (56.4 vs. 21.1%, P < 0.0001 Fisher's exact test). The positivity rates were 50.4% among CTs and 33.3% among PET-CTs. In patients with positive imaging findings, the median CA 125 value was 87 (7–1616) U/mL, whereas in patients with negative findings, it was 10 (2–620) U/mL (Mann-Whitney U test, p<0.0001). After comparison with previous studies, 54 out of 94 (57.5%) positive cases were classified as PD, 21 (22.3%) as PR, and 19 (20.2%) as SD.

Among the 129 examinations performed in patients with

normal CA 125 serum values, 110 (85.3%) and 19 (14.7%) showed negative and positive findings, respectively. The median CA 125 value was 10 (2–33) U/mL in patients with negative imaging findings and 23 (7–32) U/mL in patients with positive ones (Mann-Whitney U test, p<0.0001). Among the 19 patients with normal CA 125 serum values and positive imaging findings, 16 showed CA 125 increasing trend and/or clinical disease progression suspicion; consequently, positive imaging findings were present in only 3 out of 129 (2.3%) patients with normal CA 125 serum value, no CA 125 increasing trend, and no new symptom onset.

Among the 82 examinations acquired in patients with abnormal CA 125 serum values, 75 (91.5%) showed positive imaging findings, whereas 7 (8.5%) had negative imaging findings. The median CA 125 value was 111 (36–1616) U/mL in patients with positive imaging findings and 63 (38–620) U/mL in patients with negative ones (p=ns).

An increasing trend of the CA 125 serum value was observed in 57 out of 94 (61%) cases with positive imaging findings, whereas a stable or decreasing trend was observed in 111 out of 117 (95%) cases with negative imaging findings (Fisher's exact test, p<0.0001). Furthermore, an increasing CA 125 trend was associated with positive imaging findings with 61% sensitivity, 95% specificity, 90% PPV, and 75% NPV (LR=11.82).

An abnormal CA 125 serum value was observed in 46 out of 54 (85%) cases of PD, whereas a normal value was found in 121 out of 157 (77%) cases of CR, PR, or SD (Fisher's exact test, p<0.0001). An abnormal CA 125 serum value was associated with PD with 85% sensitivity, 77% specificity, 56% PPV, and 94% NPV (LR=3.715). An increasing CA 125 trend was observed in 48 out of 54 (89%) cases of PD, whereas a stable or decreasing trend was found in 142 out of 157 (90%) cases of CR, PR, or SD (Fisher's exact test, p<0.0001). An increasing trend was associated with PD with 89% sensitivity, 90% specificity, 76% PPV, and 96% NPV (LR=9.304). A combination of abnormal CA 125 serum value and increasing trend was observed in 42 out of 54 (78%) cases with PD, whereas a stable or decreasing trend with or without normal CA 125 value was observed in 144 out of 157 (92%) cases with CR, PR, or SD (Fisher's exact test, p<0.0001). A combination of increased CA 125 serum value and increasing trend was associated with PD with 78% sensitivity, 92% specificity, 76% PPV, and 92% NPV (LR=9.393).

Discussion

To date, the optimal follow-up strategy for patients who underwent primary surgery for ovarian cancer is unclear and still debated.[6, 10, 14] Although a strict follow-up, including routinary use of imaging, to detect and treat clinically asymptomatic relapses at an early stage did not seem to bring advantages in terms of survival and is not recommended by most gynecological and oncological societies [15, 16], laboratory tests and imaging studies are routinely required by most of the clinicians in everyday practice.[17] In our series, 23.7% of imaging studies were performed due to clinical suspicion of disease progression, 38.9% as a control after chemotherapy ending, whereas the remaining 37.4% were performed as "routinary" follow-up, without any clear clinical or serological indication.

The imaging modality of choice for the detection of ovarian cancer recurrence is contrast-enhanced CT of the abdomen and pelvis, eventually extended to the thorax, which has relevant economical and biological costs. PET-CT can be considered an option in patients allergic to iodinated contrast media or in case of equivocal CT findings, but it is more expensive than CT and even implies radioprotection issues. On the other hand, serum CA 125 assessment and clinical evaluation are cheap, widely available, do not show any relevant contraindication, and are able to detect disease progression.[17] In our series, more than a half (55.5%) of the performed imaging studies were negative for the presence of disease, with a positivity rate of 50.4% among CT and 33.3% among PET-CT. We have not been able to find a clear explanation of the difference in the positivity rate between CTs and PET-CTs, but we observed that the PET-CT positivity rate was significantly higher among the ones requested by oncologists (20/40, 50%, similarly to that of CT) than among those requested by gynecologists (3/20, 15%). At the time of imaging, the serum CA 125 value was abnormally high in 38.9% of the cases, whereas it was within the normal range in 61.1%. We observed a strict correlation between serum CA 125 values and imaging findings, with the CA 125 values significantly higher among patients with positive imaging findings than among those with negative ones (median CA 125 value 87 vs. 10 U/mL, p<0.0001).

In our series, the performed imaging studies had a negativity rate of 85.3% in patients with normal CA 125 serum value, which increased to 94.8% when considering patients with normal CA 125 serum value and no new symptom onset. The three cases (5.2%) of isolated imaging positivity in patients without clinical or serological alterations, which were also described in the original radiological reports, did not determine any change in the patients' management. These findings indicate that routine imaging utility is of no practical utility in the absence of clinical and/or serological suspicion of disease. Moreover, false-positive imaging findings in clinically symptomatic patients without serum CA 125 increase might determine unnecessary therapeutic consequences (Fig. 2).

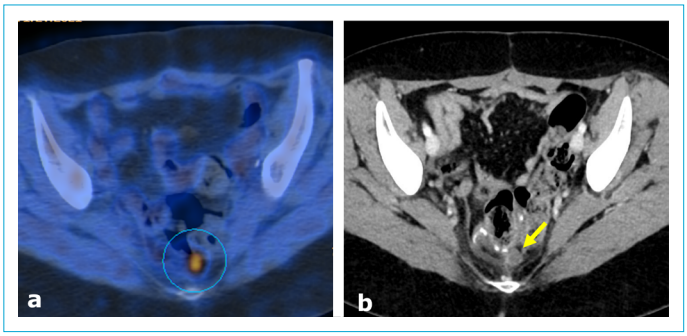

Figure 2. False-positive case. Patient radically operated for G3 serous carcinoma of the ovaries, stage IIIC, CA 125 at diagnosis 1142 U/mL, adjuvant chemotherapy performed. Routine follow-up PET-CT **(a)** performed in complete well-being, with normal and stable CA 125 value (11 U/mL at the time of examination, 10 U/mL 3 months before), showed a focal area of increased glucose uptake adjacent to the posterior rectal wall (circle), suspicious for tumor recurrence. The patient did not undergo any further treatment. Contrast-enhanced CT **(b)** performed 6 months later (CA 125 10 U/mL) showed lesion stability (arrow); given its para-anastomotic location and hypoattenuating core, the lesion has been considered an inflammatory fluid collection.

The positivity rate of imaging studies conducted in patients with elevated CA 125 serum values was 91.5%, and an increasing CA 125 trend was significantly associated with progressive disease at imaging ($p<0.0001$). The negative imaging findings in patients with increased CA 125 serum values are probably mainly due to the paucity of tumoral implants (Fig. 3) and mandate of strict follow-up.

Our study has some limitations, mainly due to its retrospective nature. Most of the included patients (93%) had elevated CA 125 serum value at the time of diagnosis (median 187 U/mL). We know that the expression of CA 125 varies among different ovarian cancer subtypes, and thus, the sensitivity/specificity of the marker during follow-up should probably be assessed for each histologic subtype.[17] In our series, this subanalysis was not possible given the relatively small number of included patients; therefore, larger cohort studies should be planned to confirm our results. Moreover, we do not have a gold standard for effectively confirming the positivity/negativity of imaging studies; therefore, false-positive and false-negative cases might be present.

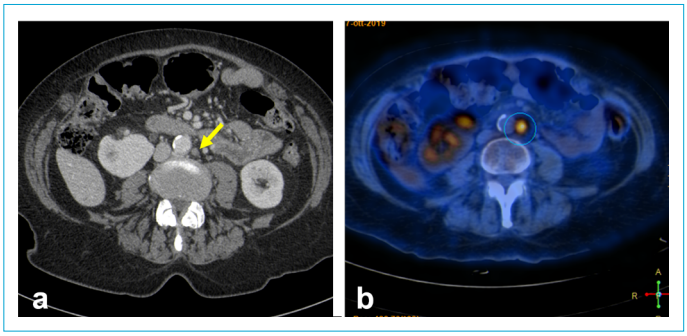

Figure 3. False-negative case. The patient was radically operated for G3 serous carcinoma of the ovaries, stage IIb, CA 125 at diagnosis 55 U/mL, adjuvant chemotherapy performed. At routine follow-up CT **(a)**, performed in complete well-being, but with increasing CA 125 serum value (63 U/mL at the time of examination, 13 U/mL 3 months before), a 6-mm large, rounded para-aortic lymph node (arrow) was overlooked. On PET-CT **(b)** performed 3 months later because of further CA 125 increase (86 U/mL), the lymph node (circle) increased in size and showed increased glucose uptake, indicating tumor relapse.

Conclusion

In conclusion, our study demonstrated a strict association between CA 125 serum values and imaging findings during follow-up of ovarian cancer. Our findings indicate that imaging studies might be avoided in patients with normal and stable CA 125 serum values and no clinical suspicion of disease progression; however, these observations need to be confirmed by larger, prospective trials. Besides economical and biological costs, excessive use of imaging might increase the risk of false-positive and false-negative findings, with subsequent treatment dilemmas and psychological implications.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.B., R.V., M.F., G.A.; Design – M.B., F.L., G.A.; Supervision – M.B., G.N., M.S., G.D.M.; Materials – M.B., F.L., M.F.; Data collection &/or processing – T.T., G.N., M.S., M.S.; Analysis and/or interpretation – F.L., G.A.; Literature search – M.B., R.V., T.T.; Writing – M.B., G.A.; Critical review – M.B., R.V. F.L., G.N., T.T., M.S., G.D.M., M.S., G.A.

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