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ORIGINAL ARTICLE

Evaluation of CA-125 as an Indicator of Imaging During Follow-up of Carcinoma Ovary: Original Research

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Abstract

Background Women with response to primary treatment for advanced ovarian cancer are said to have progression if CA125 increases more than double the upper normal limit (70 IU/L) on follow-up. It was, however, noted that large section of women with CA125 > 35 IU/L had disease on imaging.

Objective To compare values of CA125 rise at which radiological recurrence can be detected.

Methods This is a retrospective observational study where women with advanced epithelial ovarian cancer who underwent interval debulking surgery and completed treatment at Tata Medical Center, Kolkata, India, from 2012 to 2016, and were followed up with Ca125. If CA125 doubled or exceeded 35 IU/L or increased to ≥ 70 IU/L, women were subjected to imaging.

Results Among 142 women who underwent treatment, 64 women with response to primary treatment had recurrence. Recurrence was noted in two (3%) patients with doubling of Ca125 but ≤ 35 IU/, 18 (24%) patients with CA125 > 35 IU/L and 41 (64%) patients when CA125 was ≥ 70 IU/L. Three patients (5%) with normal CA125 had recurrence. Among the recurrence group, 45 women had R0 during surgery of which 27 (60%) had CA125 ≥ 70 IU/L and 14 (31%) had CA125 > 35 IU/L during recurrence. Sensitivity and specificity of value > 35 IU/L were 30.51% and 33.33%, respectively, with accuracy of 32.03%, while sensitivity and specificity at > 70 IU/L were 69.49% and 66.67%, respectively, with accuracy of 67.97%.

Conclusion CA125 value of ≥ 70 IU/L is a better predictor of recurrence; however, imaging done when value rises > 35 IU/L would be able to detect significant recurrences early thus allowing early treatment.

Keywords Ovarian cancer · Recurrence · CA125 · Imaging

Introduction

Serum tumor marker CA125 has been used during follow-up of patients treated for carcinoma ovary in order to detect recurrence. Gynae-Cancer Intergroup group (GCIG) states that ovarian cancer patients with elevated CA-125 and normalization of CA125 after completion of treatment must show evidence of CA125 greater than, or equal to, two times the upper normal limit on two occasions at least 1 week apart, as a sign of recurrence [1, 2]. The OV05/EORTC 55955 trial compared the benefits of early treatment on the basis of increased CA125 concentrations alone with delayed treatment on the basis of clinical recurrence [3]. The trial showed that there was no evidence of a survival benefit with early treatment of relapse on the basis of biochemical recurrence alone. Hence, they suggested that the value of routine measurement of CA125 in the follow-up of patients with ovarian cancer who attain a complete response after first-line treatment is not proven.

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There is no general consensus as to when an imaging should be done on follow-up based on CA125 rise to detect clinical recurrence. In a low-resource country like India where imaging is expensive, it adds to the financial burden on the inflicted who has already incurred a huge expenditure in the primary treatment. CA125 thus is a cheap and a very good follow-up tool for women who have completed treatment for carcinoma ovary. Though the OV05/EORTC 55955 trial did not show benefit of early treatment in the biochemical recurrence group, there was benefit in women who had clinical disease [3]. Thus, imaging such as computed tomography (CT) scan done after the rise of CA125 can detect visible disease early and will help initiate treatment early in the clinical recurrence group.

However, now the question arises—"when should an imaging be advised in women having a rise in CA125 value on follow up?" We, therefore, conducted this retrospective analysis among women with recurrence to know the level of rise in CA125 after which one could advise for imaging. This would prevent repeated imaging thus reducing cost and anxiety among women suspected of having recurrence, also knowing the right time of imaging would detect disease early to initiate early treatment. This study was thus conducted to understand the best time for imaging during follow-up of women who completed primary treatment for carcinoma ovary and is suspected to have recurrence based on rise of CA125 level.

Materials and Methods

Trial Design

A retrospective cohort study was conducted among women with advanced carcinoma ovary/fallopian tube/primary peritoneal cancer (Stage III and IV) who underwent interval debulking surgery and completed their adjuvant chemotherapy by 2012–2016 at Tata Medical Center, Kolkata, India. Only women who had their CA125 return to normal after completion of primary treatment were included in the study. Follow-up of patients with CA125 was done routinely three monthly for 2 years then six monthly after completion of treatment. Computed tomography (CT) scan to detect recurrence was done in these women when there was rise in CA125. Women under study who had recurred during the study period were divided into four groups: First group were women who had doubling of CA125, but the value was below the upper normal limit (≤35 IU/L). Second group of women were those who had rise in CA125 > upper normal limit (36–69 IU/L) with or without doubling; third group were those women who had rise in CA125 more than double upper normal limit (≥70 IU/L) as stated by the Gynae-Cancer Intergroup group. The last group included women who had no rise in CA125 but had clinical or radiological recurrence only.

Results

There were 146 women with advanced ovarian malignancy who had undergone neoadjuvant chemotherapy followed by interval debulking surgery at Tata Medical Center, Kolkata, India, and completed their adjuvant chemotherapy from January 2012 to December 2016. Twenty-five women were excluded from the study as 12 patients did not complete treatment and 13 were lost to follow-up. Among the remaining 121 patients, 46 patients did not have recurrence during the study period, while 75 had recurrence. Among the 75 recurred patients, 64 had complete response to primary treatment as stated by Gynae-Cancer Intergroup group criteria, i.e., these women had raised CA125 prior to treatment which had come back to normal after completion of treatment; hence, these were the group of women selected for the study.

Among these 64 patients who had response to primary treatment, following observations were made during follow-up with CA125:

Group one There were two patients with doubling of Ca125 but ≤ upper normal limit who had recurrence, all of whom had R0 during interval debulking (Table 1, Fig. 1).
Group two Recurrence was confirmed radiologically in 18 (28%) patients whose CA125 was 35–69 IU/L (with or without doubling) out of which 14 (78%) patients had R0 and four (22%) patients had R1 disease during interval debulking surgery (Table 1, Fig. 1).
Group three When CA125 was ≥ 70 IU/L, 41 patients (64%) had recurrence detected on imaging, out of these 27 (66%) had R0, 11 (27%) had R1, and three (7%) patients had R2 disease on interval debulking surgery (Table 1, Fig. 1).
Group four Three patients (5%) with normal CA125 had recurrence of which one (33%) patient had clinical recurrence (abdominal disease detected during ileostomy reversal), and this patient had R2 disease during surgery,

Table 1 CA125 levels at the time of recurrence ($N=64$)

Group	CA-125	Recurrence on imaging $N=64$ (%)
1	Double but ≤ 35 U/mL	2 (3)
2	36–69 U/mL	18 (28)
3	≥ 70 U/mL	41 (64)
4	Normal	3 (5)
	Total	64

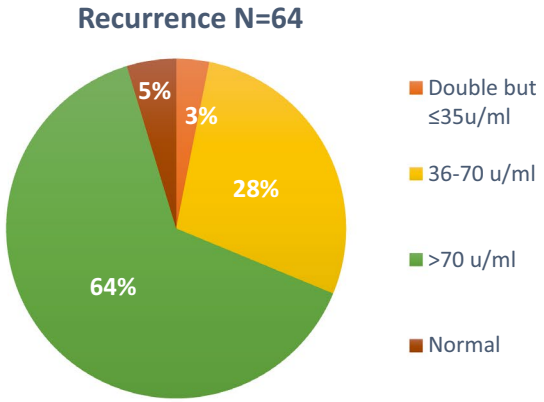

Fig. 1 CA125 levels at the time of recurrence on imaging

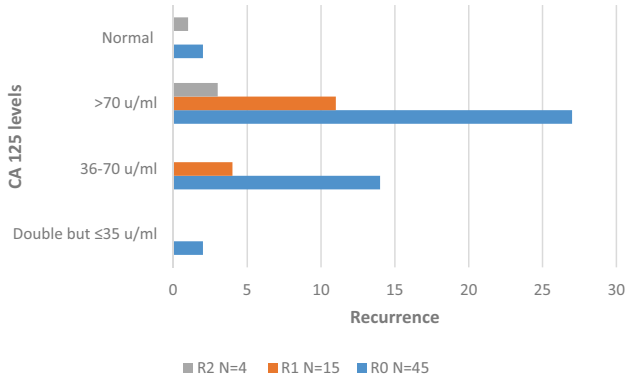

Fig. 2 Residual disease and Ca125 level on recurrence

while two patients (67%) had recurrence on imaging only, and they had R0 during surgery (Table 1, Fig. 1).

Recurrence was noted in 45 women who had no residual disease (R0) during surgery out of which 27 (60%) patients had CA125 ≥ 70 IU/l on recurrence; however, 14 (31%) women with R0 disease had recurrence detected when CA125 > 35 IU/L (Table 2, Fig. 2).

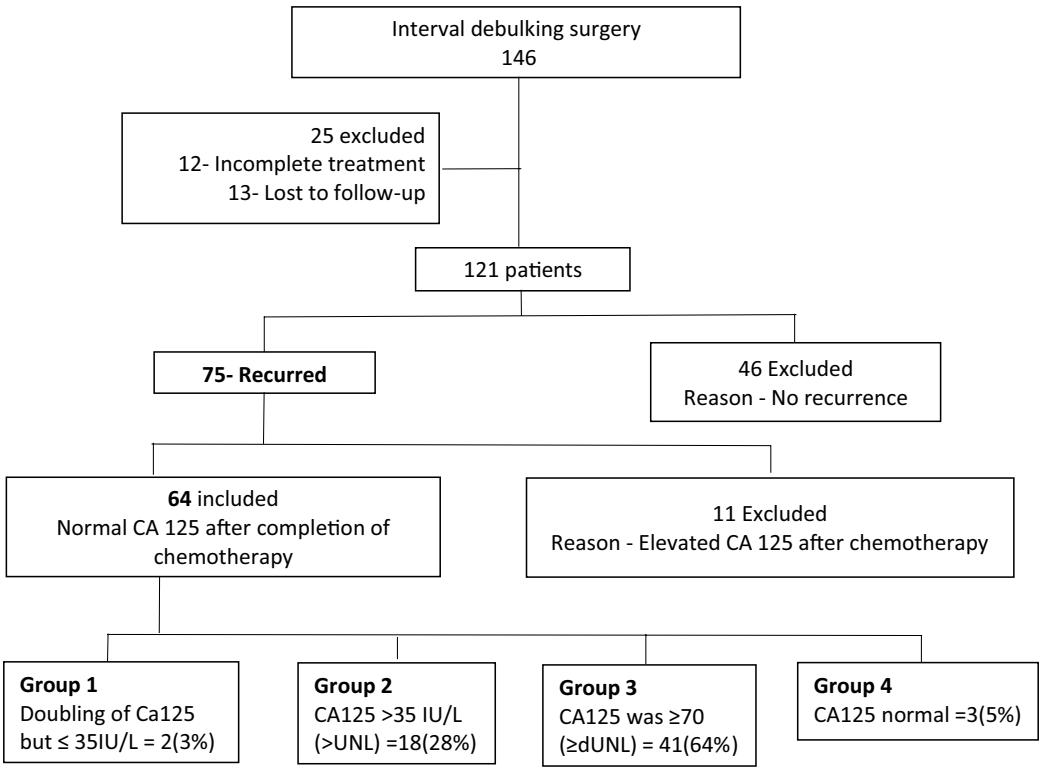

Table 2 Residual disease during IDS and Ca125 levels during recurrence

CA125 on recurrence	R0 (%) $N=45$	R1 (%) $N=15$	R2 (%) $N=4$
Double but ≤ 35 U/mL	2 (4.5)	0	0
36–69 U/mL	14 (31)	4 (27)	0
≥ 70 U/mL	27 (60)	11 (73)	3 (75)
Normal	2 (4.5)	0	1 (25)
Total	45	15	4

Sensitivity and specificity of value > 35 IU/L were 30.51% and 33.33%, respectively, with accuracy of 32.03%, while sensitivity and specificity at > 70 IU/L were 69.49% and 66.67%, respectively, with accuracy of 67.97%. Though CA125 value of ≥ 70 IU/L is a better predictor of recurrence, however, imaging done when value rises > 35 IU/L would be able to detect significant early recurrences thus allowing early treatment.

Discussion

CA125 is a very efficient tumor marker for detection of recurrence of carcinoma ovary. An elevated and rising CA125 level of ≥ double upper normal limit (70 IU/L) is indicative of progression in the vast majority of patients. Gynae-Cancer Intergroup group states that patients with elevated CA125 pre-treatment and normalization of CA125 must show evidence of CA125 greater than, or equal to, two times the upper normal limit (70 IU/L) on two occasions at least 1 week apart, as a sign of recurrence [1]. In 56–94% of cases, rise in serum CA125 levels is detected before the clinical detection of relapse, with a median lead time of 3–5 months [4]. However, as per OV05/EORTC 55955 trial, there was no evidence of a survival benefit with early treatment of relapse based on biochemical recurrence alone [3]. They suggested that the value of routine measurement of CA125 in the follow-up of patients with ovarian cancer who attain a complete response after first-line treatment is not proven; thus, CA125 should not be prescribed to all patients with ovarian cancer during follow-up. Despite the statement following the OV05/European Organisation for Research and Treatment of Cancer 55955 trial regarding the non-requirement of routine serum CA125 on follow-up after treatment of carcinoma ovary, we believe that CA125 measurement during follow-up can help select women who require imaging to detect early disease. Independently from the results of the MRC/European Organisation for Research and Treatment of Cancer trial, patients with radiological evidence of disease progression should start treatment without waiting for symptom onset. Fleming et al. in a study noted that a shorter time interval between CA125 elevation and secondary cytoreductive surgery correlated with a greater incidence of optimal resection, resulting in a longer median disease-free interval and overall survival (47 vs. 23 months, $P \leq 0.0001$) [5]. It was also noted in his study that for patients who ultimately underwent surgery (median time interval of 16.4 weeks from the time their CA125 started to increase), each week delay after the first CA125 rise led to a 3% increased chance that the resection would be suboptimal [5].

In recurrent setting, patients who undergo complete secondary cytoreduction have a clear advantage in terms of progression-free survival and overall survival, as underlined in several retrospective studies [6, 7]. A meta-analysis also suggested that optimal resection of recurrence at secondary cytoreductive surgery could prolong survival [8]. AGO DESKTOP 3 trial suggested that surgery in patients with first relapse after a treatment-free period of more than 6 months resulted in a clinically increase in progression-free survival [9]. Until the overall survival data reveal the role of secondary cytoreductive surgery in an early relapse setting, it should at least be considered as valuable option.

Imaging such as MRI (magnetic resonance imaging), CE (contrast enhanced)/CT or PET (positron emission tomography)/CT can be used efficiently to detect disease on recurrence. Evis Sala et al. stated in their study that CT and PET/CT may have similar accuracy in detection of recurrent ovarian cancer [10]. Hence, if the cost of imaging is considered, then CE/CT would be a better option for detection of disease during follow-up as it is cheaper than PET/CT. There is no general consensus as to when an imaging should be done on follow-up based on CA125 rise to detect disease. In a study done by Antonio Santillan et al., to evaluate the risk of epithelial ovarian cancer recurrence in patients with rising CA125 levels that remain below the upper limit of normal (≤ 35 U/mL) showed that patients in complete clinical remission, a progressive low-level increase in serum CA125 levels is strongly predictive of disease recurrence [11]. In our study, we noticed that there was no advantage in advising CT scan in these women with value ≤ 35 IU/L as a very small number of women (3%) would have visible disease on imaging (Table 1). AbuShain et al. further conducted another larger retrospective study to evaluate if three progressively rising CA125 values, doubling of CA125, and an absolute rise of 5 U/mL from the nadir, all while remaining in the normal range were associated with disease recurrence among women with stages IIIC and IV epithelial ovarian cancer treated with primary surgery and adjuvant chemotherapy [12]. They concluded that rising CA125 levels within the normal range that meet any of the above criteria are

highly predictive (86%) of recurrence within 12 months and closer observation is warranted in these populations. In our study, we noticed that majority of women had disease on imaging when CA125 was > double upper normal limit as per the Gynae-Cancer Intergroup group criteria, but we could not neglect the fact that a significant number of women had disease detected on CE/CT when CA125 was 36–69 IU/L (64% and 28%, respectively).

The goal of cytoreductive surgery for advanced ovarian malignancy should be to achieve a reduction in microscopic disease or disease < 1 cm in maximum diameter. Studies have shown that no residual disease (R0) has a better survival benefit than women having residual disease (R1 = < 1 cm and R2 = > 1 cm) during surgery [13, 14]. It was also noted in our study that 45 women who had no residual disease (R0) during surgery had recurred during the study period. Majority of women in the group of population with no residual disease had CA125 ≥ 70 during recurrence; however, we could not reject the fact that a significant number of women had CA125 > 35 IU/L during recurrence (60% and 31%, respectively).

Strength and Limitation of the Study

This study was done including only the interval debulking group; hence, the sample size is small. If patients undergoing primary debulking surgery could have been included, it would have increased the study population. However, majority of the women with advanced carcinoma ovary underwent interval debulking surgery during the study period; hence, this population represents the study group well. This study was done only to identify the early recurrence group based on CA125; hence, the overall survival has not been mentioned in this study.

Conclusions

Serum CA125 may not be a necessity during follow-up, but it does help in guiding the timing of imaging and planning management. An elevated and rising CA125 level of ≥ 70 IU/L is indicative of progression in the vast majority of patients as per Gynae-Cancer Intergroup group [1]. In our study, Ca125 ≥ 70 IU/L had better sensitivity, specificity and accuracy compared to CA125 level of 35–69 IU/L. However, a significant amount of women were found to have disease when imaging was done at rise of CA125 > 35 IU/L. Early imaging if done, based on the rise of CA125 > 35 IU/L, can identify women who are likely to have visible disease even before she develops symptoms, which may be in a lesser bulk. A single maximal debulking attempt which makes a clinically important difference in patients with recurrence can be possible only if detection of disease is early. Many studies have shown that secondary debulking surgery is a clinically beneficial treatment option for selected patients with recurrent platinum-sensitive ovarian cancer (DESKTOP 3) [9]. Thus, imaging if done when CA125 rises to > 35 IU/L, disease can be detected early and will benefit patients with early successful treatment.

In the era of research and management of patients in the setting of recurrence, CA125 is likely to resume its importance in guiding management. It is hoped that future trials will resolve the important question of how to triage patients to the appropriate sequence of surgery and chemotherapy to achieve the best possible outcome.

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Compliance with Ethical Standards

Conflict of interest There is no conflict of interest among the authors.

Ethical Committee The study has been approved by the institutional ethics committee (Tata Medical Center) for publication.

Ethical Clearance IRB waiver No: EC/WV/TMC/010/19.

Informed Consent This was a retrospective cohort study and hence did not require consent.

Research Involving Human Participants and/or Animals This is an observational study and did not involve any interventional research involving Human participants and/or Animals.

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