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Prognostic significance of elevated pre-treatment serum CA-125 levels in patients with stage I ovarian sex cord-stromal tumors

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ABSTRACT

Objective: To investigate the prognostic significance of elevated pre-operative serum CA-125 values for patients with early stage ovarian sex cord – stromal tumors (SCSTs).
Methods: Patients diagnosed between 2004 and 2015 with a SCST were drawn from the U.S National Cancer Database. Those with stage I disease, and normal or elevated CA-125 values were selected for further analysis. Overall survival (OS) was evaluated for patients diagnosed between 2004 and 2014 with Kaplan-Meier curves, and compared with the log-rank test. A multivariate Cox analysis was performed to control for known confounders.
Results: A total of 1156 patients met the inclusion criteria; 486 (42%) had elevated pre-treatment CA-125 values. Patients with elevated pre-treatment CA-125 (n = 417) had worse OS compared to those with normal values (n = 588), p < 0.001 from log-rank test; 5-yr OS rates were 86.8% and 94.8% respectively. After controlling for patient age (<50 vs >= 50 yrs), the presence of medical co-morbidities, tumor histology (granulosa vs non-granulosa), size (<10 vs >= 10 cm vs unknown) and the performance of lymphadenectomy, elevated pre-treatment CA-125 levels were associated with a worse survival (HR: 1.80, 95% CI: 1.15, 2.82, p = 0.01).
Conclusions: In a large cohort of patients with early stage SCSTs elevated preoperative CA-125 levels were associated with worse survival.

Introduction

CA-125, also known as MUC16, is a well-established biomarker aiding in the diagnosis and surveillance of women with ovarian cancer [1]. Serum CA-125 levels are typically evaluated in the initial work-up of peri-menopausal and postmenopausal women with a suspicious pelvic mass [2]. CA-125 is most commonly elevated in patients with epithelial ovarian tumors, especially of serous histology. Several retrospective studies have also correlated pre-operative serum CA-125 levels with the survival of patients with epithelial ovarian cancer [3].

Sex cord – stromal ovarian tumors arise from primitive sex cords or stromal cells and represent approximately 7% of all malignant ovarian tumors [4]. Upon presentation, they are most commonly confined to the ovary and are characterized by a relatively indolent course [4]. For patients with granulosa cell tumors, late recurrences, even ten years following initial presentation, are not uncommon [5]. Inhibin B and anti-Mullerian hormone (AMH) are surveillance biomarkers used in the management of patients with granulosa cell tumors (GCTs). If elevated upon presentation, a sharp decrease is observed after surgical treatment; a subsequent increase signifies a relapse, even before the presence of clinical symptoms or any radiological evidence [6,7]. Abnormal serum CA-125 levels are also found in patients with sex cord-stromal tumors. In a retrospective study of 115 women with granulosa cell tumors almost half of them had abnormal CA-125 levels [8]. However, in that study, CA-125 in conjunction with imaging did not have any value in the pre-operative diagnosis of a granulosa cell tumor. In another study that included 135 samples from patients with granulosa cell tumors, 25% had elevated CA-125 levels [9].

The aim of the present study was to evaluate the prognostic significance of elevated pre-operative serum CA-125 values for women with SCSTs confined to the ovary, using a multi-institutional, hospital-based database.

Materials and methods

A cohort of patients diagnosed with a microscopically confirmed malignant ovarian sex cord -stromal tumor (ICD-O-3 histology codes 8590–8671 as grouped by the International Agency

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for Research on Cancer,) [10] was selected from the National Cancer Data Base (NCDB). The NCDB, established jointly by the American Cancer Society and Commission on Cancer of the American College of Surgeons, is a hospital-based database capturing approximately 70% of all malignancies diagnosed in the United States. Patient data are prospectively collected from participating commission-accredited cancer programs and are frequently audited to ensure their high-quality [11]. All data are de-identified and available for research purposes. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytical or statistical methodology employed, or the conclusions drawn from these data.

Patients with pathological stage I disease were identified and those with known pre-treatment serum or blood CA-125 values (categorized as normal or elevated by the coding schema, based on the reference values of the laboratory at the reporting facility) were selected for further analysis while patients with borderline or unknown values were excluded. Demographic, clinico-pathological, and treatment variables were extracted from the de-identified NCDB dataset. Patient race, when available, was recoded into White, and non-White while age was grouped as <50 and >=50 years. Based on ICD-O-3 histology codes, cases were categorized into two histology groups: granulosa-cell tumos (including juvenile granulosa cell tumors) and non-granulosa cell tumors (including sex cord-stromal, not otherwise specified). Based on available information, tumor size was categorized into <10 cm and >=10 cm. Disease sub-stage was determined from the extend of disease variable available at the collaborative staging field and categorized into IA/IB and IC. Performance of hysterectomy and bilateral salpingo-oophorectomy (BSO) was assesed from site-specific surgery codes.

Frequency of distribution of categorical variables was compared with the chi-square test or Fisher's exact test and continuous variables with Mann-Whitney *U* test. Overall survival (OS) was defined as the months elapsed from tumor diagnosis to the date of death or last-follow up. Patients with less than one month of follow-up were excluded from the survival analysis. Five-year OS was determined following generation of Kaplan-Meier curves and compared with the log-rank test. A Cox proportional hazard analysis was performed to evaluate mortality after controlling for a priori selected confounders. Survival analysis was limited to patients who underwent surgical treatment. A sensitivity analysis was performed by excluding patients with a history of another primary tumor. All statistical analysis was performed with the SPSS v.24 statistical package (IBM Corp. Armonk, NY) and the alpha level of statistical significance was set at 0.05.

Results

A total of 1156 patients met the inclusion criteria. Median patient age was 51 years (IQR: 20) while the majority were of White race (72.5%). A total of 224 (19.4%) patients had medical co-morbidities as assessed from the Charlson-Deyo index. The majority of patients had granulosa cell tumors (84.2%) and stage IA or IB (811/1130, 71.8%) disease. The rate of lymph node sampling/dissection was 56.7%, while 65.6% (688/1048) had a hysterectomy and 41.3% (450/1089) had omentectomy. Based on available information, a total of 248 patients (22.2%) received chemotherapy.

A total of 486 (42%) patients had elevated pre-treatment CA-125 values. These patients were more likely to have non-granulosa tumors (18.5% vs 13.9%, p=0.033) that were larger than 10 cm (68.3% vs 40.1%, p<0.001). Table 1 summarizes the demographic and clinico-pathological characteristics of patients with a malignant sex cord-stromal tumor confined to the ovary stratified by pre-treatment CA-125 levels.

Table 1
Demographic and clinico-pathological characteristics of women with malignant sex crod-stromal tumor confined to the ovary stratified by pretreatment serum CA-125 levels.

	Normal	Elevated	p-value
Age (yrs)			0.22
<50	328 (49%)	220 (45.3%)	
>=50	342 (51%)	266 (54.7%)	
Race			0.53
White	481 (71.8%)	357 (73.5%)	
Non-White/Unknown	189 (28.2%)	129 (26.5%)	
Comorbidities			0.98
No	540 (80.6%)	392 (80.7%)	
Yes	130 (19.4%)	94 (19.3%)	
Histology			0.033
Granulosa	577 (86.1%)	396(81.5%)	
Non-granulosa	93 (13.9%)	90 (18.5%)	
Size			<0.001
<10 cm	367 (59.9%)	142 (31.7%)	
>=10 cm	246 (40.1%)	306 (68.3%)	
Substage			0.12
IA/IB	483 (73.5%)	328 (69.3%)	
IC	174 (26.5%)	145 (30.7%)	
LND			0.43
No	297 (44.3%)	204 (42%)	
Yes	373 (55.7%)	282 (58%)	
Hysterectomy			0.13
Yes	391 (63.8%)	297 (68.3%)	
No	222 (36.2%)	138 (31.7%)	
Omentectomy			0.07
Yes	250 (39.1%)	200 (44.5%)	
No	390 (60.9%)	249 (55.5%)	
BSO			0.034
Yes	234 (60%)	170 (68.3%)	
No	156 (40%)	79 (31.7%)	
Chemo			<0.001
Yes	109 (16.8%)	139 (29.6%)	
No	538 (83.2%)	330 (70.4%)	

Missing values: substage 26 cases, size 95 cases, chemotherapy 40 cases, BSO 571 cases, hysterectomy 108 cases.

According to the reverse Kaplan-Meier method, median follow-up was 59.03 months (95% CI: 53.87, 60.19). Based on Kaplan-Meier curves, patients with elevated pre-treatment CA-125 (n=417) had worse OS than those with normal values (n=588), p<0.001 from log-rank test; 5-yr OS rates were 86.8% and 94.8% respectively (Fig. 1). After excluding patients with a history of another primary tumor, those with elevated pre-treatment CA-125 values (n=357) had worse OS compared to those with normal values (n=526), p=0.006; 5-yr OS rates were 89% vs 96% respectively. Following stratification by tumor histology, for patients with granulosa cell tumors, those with elevated pre-treatment CA-125 (n=335) had worse OS than those with normal values (n=503), p<0.001 from log-rank; 5-yr OS rates were 86.5% and 96% respectively (Supplemental Fig. 1). However, for patients with non-granulosa cell tumors there was no difference in OS between those with elevated (n=82) and normal pre-treatment CA-125 (n=85), p=0.87 from log-rank; 5-yr OS rate was 88% in both groups (Supplemental Fig. 2).

After controlling for patient age (<50 vs >=50 yrs), the presence of medical co-morbidities, tumor histology (granulosa vs non-granulosa), size (<10 vs >=10 cm vs unknown) and the performance of LND, elevated pre-treatment CA-125 levels were

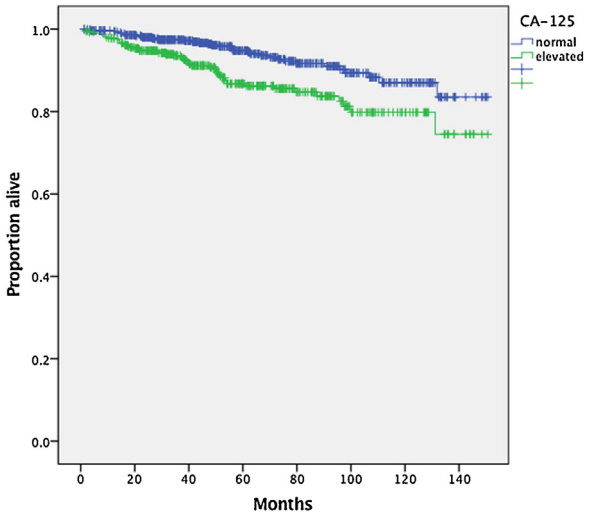

Fig. 1. Overall survival of women diagnosed with a malignant sex cord-stromal tumor confined to the ovary stratified by pre-treatment serum or blood CA-125 levels (n = 588 for normal and n = 417 for elevated, p < 0.001 from log-rank test).

associated with a worse survival (HR: 1.80, 95% CI: 1.15, 2.82, p = 0.01).

Discussion

CA-125 is a membrane-bound protein present in bodily fluids and cells that can metaplastically change into Mullerian-type epithelium [12]. CA-125 is known to have a prognostic role in epithelial ovarian carcinoma (EOC), but its relevance in the management of patients with SCSTs has not been elucidated. In a large cohort of women with early stage SCSTs, elevated pre-treatment CA-125 values were observed in approximately 40% of patients. Those with abnormal levels exhibited a worse survival even after controlling for major confounders. However, following stratification by histology the prognostic significance of elevated CA-125 was limited to patients with granulosa cell tumors.

The percentage of patients with elevated CA-125 in our cohort is consistent with previous reports. Stine et al. reported an elevated CA-125 level in 43% (18/42) of GCT patients [8]. However, in that study combination of CA-125 and preoperative imaging did not have any value in the preoperative diagnosis of GCTs. In another study that included 82 GCT patients, only 25% had elevated CA-125 levels [9]. Although CA-125 is known to be expressed on the ovarian epithelium, it can also be elevated in nonmalignant disease like endometriosis, pelvic inflammatory disease and ovarian cysts and other malignancies [13]. The source of CA-125 among patients with SCSTs is unclear.

Previous studies have demonstrated that CA-125 is a prognostic indicator of overall survival and progression free survival (PFS) for patients with EOC [3]. CA-125 serum levels are used to monitor response to chemotherapy and to detect possible recurrence and progressive disease [3]. Postoperative CA-125 levels have proved to be independent prognostic factors for future recurrence. Decreasing CA-125 levels following treatment generally indicate an appropriate response, while rising levels signify recurrence and worsened outcomes [14]. Additionally, Nagele et al. reported an increased preoperative CA-125 levels in stage I EOC is an independent prognostic factor; women with higher levels had worse outcomes and an increased mortality risk of 6.37 [15]. These findings were validated by Cooper et al., who found elevated preoperative CA-125 levels to be an independent risk factor for mortality regardless of disease stage [16]. However, in that study, CA-125 level was not an accurate marker of optimal tumor debulking. Elevated preoperative levels were found to be associated with serous histology (p = 0.02), higher stage (p < 0.001), tumor grade 3 compared to 1 or 2 (p < 0.001) and with the presence of ascites (p < 0.001). Lastly, Zorn et al.'s GOG study found that CA-125 to be an independent risk factor for PFS, and a 1-fold increase in pretreatment CA-125 was associated with a 7% increase in progression risk among patients with advanced EOC. The authors also reported that the CA-125 levels had more prognostic value for patients with favorable clinical factors such as microscopic residual disease and serous and endometrioid histology [17]. A prognostic role of preoperative CA125 has been recently demontrasted in patients with germ cell tumors as well [18].

Inhibin-B and AMH are the most commonly used biomarkers for the management of SCSTs. In 2009, Nosov et al. reported a predictive role for increased inhibin levels for diagnosis patients with GCTs, however elevated levels were not predictive of disease recurrence [19]. Haltia et al.'s study reported inhibin-B as the most accurate biomarker for the preoperative diagnosis of SCST and reported that elevated levels could adequately distinguish an AGCT from gynecologic carcinomas [9]. Färkkilä et al.'s longitudinal cohort study of 123 GCT patients found strong evidence of the use of AMH in association with inhibin-B to strengthen the detection of GCTs [7]. Rey at al. reported increased levels of AMH in GCT patients [20]. In 9 patients with extended follow-up, elevated AMH was detected in 8 out of 9 patients with a progressive tumor, and AMH levels were noted to be elevated at least 11 months before clinically evidence recurrence was seen.

Several limitations of the present study should be mentioned. Firstly, due to the lack of central pathology report and the absence of specific details on the staging procedures performed, possible tumor and stage misclassifications cannot be excluded. Also, the lack of information on tumor relapse precluded us from analyzing progression free survival. Lastly, the NCDB database classifies CA-125 as elevated or normal without providing any information on the exact value.

This study is the first to demonstrate a potential prognostic significance of elevated CA-125 among patients with early stage SCSTs especially for those with granulosa cell tumors. The present report should be regarded as hypothesis generating and further studies are greatly warranted to validate our results. Potentially these patients may benefit from enhanced surveillance or administration of targeted therapy.

Conflicts of interest

No conflicts of interest to report.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ejogrb.2019.05.002.

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