Improving ovarian cancer outcome by studying the clinicopathological characteristics at a tertiary care hospital

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Abstract

Objectives: to optimize the outcome of malignant ovarian tumour via evaluation of the management procedures and protocols in Mansoura university hospitals and how far they are from the international standards.

Method: This descriptive, observational analytical study was conducted at Mansoura University Hospital, oncology unit of the department of Obstetrics & Gynaecology from January 2016 to December 2017 and included 94 patients. The participants were chosen from those attending the gynaecology outpatient clinic and diagnosed clinically and proven by investigations as having ovarian cancer. History, clinical examination and data obtained by abdominal and vaginal ultrasound as well as reports received from MRI and CT scanning we rereserved. Tumour markers were estimated by the same laboratory and technicians and treatment interventions provided with one year follow up results were collected.

Results: demographic patients' data recorded the mean age estimated for all patients is 45.28 ± 15.5 years, 42.5% of which are more than 50 years, and 6.4% younger than 18 years. Patients with low gravidity and parity included near half of the cohort (48.9 % and 44.7 respectively).Family history of ovarian, breast and colon cancers were positive in 9 patients only. Premenopausal ones recorded the highest number. From all of the cohort 6 cases gave a history of infertility. The main complaint was abdominal discomfort (40 cases), followed by abdominal swelling (24). Epithelial ovarian cancers were the most common (74.5%), with serous cyst adenocarcinoma constituting the majority (68.6 %) followed by granulosa cell tumour (10.6%) then border line and germ cell tumours(6.4%) for each group. The least reported subclass was immature teratoma (1%). Two cases were found to be Krukenbergmetastasis from colonic cancer. CA125 mean was+SD 510.41 ± 131.42 IU/ml. AFP and HCG were elevated in germ cell tumour and sex cord tumour. Most of the patients (74.5%) presented with advanced stage disease III and IV, whereas 25.5% of patients presented with stage I and II. Eighty-eight patients did primary debulking surgery. Two patients received neoadjuvant chemotherapy followed by secondary debulking surgery. The majority of patients (68%) had a combined surgery and chemotherapy.25.5% of the patients had the chance of fertility preserving surgery as they underwent unilateral oophorectomy. Estimated cancer mortality in our cohort proved 18 cases died (19.1%) within a year after treatment, 76 patients (80.9%) survived beyond a year after the initial treatment. The stage of the disease at presenta-

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tion was strongly correlated to survival beyond a year after treatment ($p < 0.001$).

Conclusion: mproving the health care system and promoting effective clinical management of ovarian cancer is an important issue to eliminate the survival disparities in our locality that requires improvement in guidelines adherent care.

Keywords: ovarian cancer, tertiary care.

INTRODUCTION

Ovarian cancer is a highly aggressive neoplastic disease in women with a high mortality rates [1]. Being diagnosed usually in advanced stage, the treatment is usually less valuable[2]. Symptoms reported for ovarian cancers include abdominal discomfort, bloating, nausea, and urinary urgency are vague and often mistaken with other minor diseases. Currently, the best available way for screening and detecting early stages ovarian cancer are transvaginal sonography (TVS) and elevated CA-125 [3].Histologically, over 90% of ovarian neoplasm arise from the surface epithelium, the rest from germ cells or stromal cells. The epithelial neoplasms are subsequently classified as serous(30-70%), endometrioid (10-20%), mucinous (5-20%), clear cell (3-10%), and undifferentiated (1%) with a 5-year survival rates recorded are 20-30%, 40-63%, 40-69%, 35-50%, and 11-29%, respectively. The subtypes differ with regard to risk factors, biological behaviour, and treatment response [3].Ovarian malignancies are surgically staged according to International Federation of Gynecology and Obstetrics (FIGO) staging system through staging laparotomy [4]. Treatment of ovarian cancer depends on the extent of metastasis at the time of diagnosis. Therefore, surgery is necessary for diagnosis, staging, and primary treatment and the goals of initial surgery is to provide the therapeutic benefit with cytoreduction. On the other hand, systemic treatment or adjuvant therapy, needs a precise histologic diagnosis and accurate staging [5, 6].The current study was held to optimize the management of malignant ovarian tumours via evaluation of the management procedures/protocols at Mansoura University hospitals and how far they are from the international standards.

PATIENTS AND METHODS

This prospective, descriptive, observational and analytical study was conducted at Mansoura University Hospital, oncology unit of the department of Obstetrics & Gynaecology from January 2016 to December 2017. The study protocol was reviewed and approved by the department of obstetrics and gynaecology, Faculty of Medicine, Mansoura University, Mansoura, Egypt and approved by local ethical committee, institutional research board [IRB number R/16.11.11].The participants number was 94 and were chosen from those attending the gynaecology outpatient clinic and diagnosed clinically and proven by investigations as having ovarian malignancy. All women selected were subjected to verbal and written informed consents after explaining the basics of the study with her own rights to withdraw at any time. Patients who had associated endometrial carcinoma with ovarian malignancy were excluded together with those having incomplete data available verifying diagnosis or refusing participation. Full history taking and examination were recorded for all cases. All patients were subjected for trans abdominal and transvaginal ultrasound (TAS, TVS) by the same machine(Canon / Aplio500) and with the same sonographer. Also; it should be noted that, MRI and CT scanning being a part of malignancy workup pre and postoperatively were evaluated by the same radiologist (MRI: 1.5 T, sequences included conventional T1 and T2-WI, T2 fat sat images and CT:Inginia , Philips, Netherland, slice acquisition 3mm). Expected ovarian tumour markers including CA125, AFP and HCG were estimated by the same laboratory and technicians. These clinical data were collected together with investigations done or treatment interventions given; whatever the type or planned for the patients, then tabulated and subjected for statistical analysis. Follow up of patients was by clinical examination and transabdominal ultrasonography, vaginal ultrasonography and CT.

Statistical analysis

Data were collected, tabulated and statistically analysed by IBM computer using the Statistical Package for the Social Sciences (SPSS version 22). Chi- square test was used to compare the association between categorical variables between

groups and Fisher exact test was used where the cell count is less than 5. Student t-test was used to compare means± SD of quantitative variables in parametric data. P value <0.05 was set significant.

Results

The majority of cases(42.5%) were more than 50 years, 36.2 % from 30-50, 14.9 % from 19-30 years meanwhile about 6.4% of patients are younger than 18 years. The mean age estimated for all patients was 45.28 ± 15.5 years with a range from 9-83 years. Patients with low gravidity and parity included near half of the cohort (48.9 % and 44.7 respectively). About a half of the patients were premenopausal. Family history of ovarian, breast and colon cancers were positive in 9 patients only, who represent 9.5 % of all patients. Premenarchal tumours reported in2 cases (2.1%), premenopausal ones recorded the highest number being 48 (51.1%) while postmenopausal patients were 44 cases (46.8%). The family history for ovarian cancer was found in 9 cases (9.5) whereas 6 cases (6.4) gave a history of infertility.

Patient's clinical data in addition to surgical staging, histopathological types and associated tumour markers were represented in table (2).

Table (1): Distribution of cases according to main clinical presentation, surgical staging and histopathological grading and tumour markers.

Variable			No (%)
Main clinical presentation:			
Pelvic pain			12 ((12.8)
Abdominal discomfort			40 (42.6)
abdominal swelling or mass			24 (25.5)
GIT symptoms			10 (10.6)
Urinary symptoms			2 (2.1)
Histopathology types:			**No %**
1- Granulosa cell tumor			**10 (10.6)**
2- EOC:			**70 (74.5)**
Serouscystadenocarcinoma			48/70 (68.6)
Mucinous cystadenocarcioma			12/70 (17.1)
Undifferentiated adenocarcinoma			8/70 (11.4
clear cell carcinoma			2/70 (2.9)
3- Germ cell tumor			**6 (6.4)**
Immatureteratoma			1/6 16.6
Yolksac tumor			3/6 50.0
Dysgermenoma			2/6 33.4
4- krukenbergtumor			**2 (2.1)**
5- Borderline tumor			**6 (6.4)**
Stage:			
Stage I			10 (10.6)
Stage II			14 (14.9)
Stage III			44 (46.8)
Stage IV			26 (27.7)
Grade:			
GI			14 (14.9)
GII			34 (36.2)
GIII			40 (42.5)
Tumour markers	**Positive**	**Range (IU/ml)**	**Mean ± SD**
CA125	84/94 (89.3%)	11.00 – 7621.00	510.41 ± 131.42
AFP	14/18 (77.7%)	3 – 1811	282.63 ± 576.89
HCG	2/16 (12.5%)	3 – 637	51.13 ± 159.49

Data presented in number (%), EOC = epithelial ovarian cancer.

Analysis of EOC patients alone showed a mean age of 47.5 ± 11.7 years and that all age groups were represented within this group. On the other hand, at the age of 19-50 years Germ cell tumour represent 11.1% and Granulosa cell tumour 18.5%. Simple linear regression showed that age at presentation was strongly correlated to histopathology at presentation ($p < 0.05$), table 2.

Table (2): Correlation between histopathology types and age of the patients,

Variables	19-50y (n=54)	>50y (n=40)	P value
Granulosa cell tumour	10 (18.5)	0 (0%)	□2 (23.486) P < 0.05*
EOC Serous cystadenocarcinoma Mucinous cystadenocarcioma Undifferentiated adenocarcinoma clear cell carcinoma	**32 (59.3)** 22 (40.8) 6 (11.1) 4 (7.4) 0 (0)	**38 (95%)** 26 (65%) 8 (20%) 4 (10%) 2 (5%)	
Germ cell tumour Immature teratoma Yolk sac tumour Dysgermenoma	**6 (11.1)** 1 (3.7) 3 (5.5) 2 (3.7)	0 (0) 0 (0) 0 (0) 0 (0)	
krukenbergtumor	2 (3.7)	0 (0)	
Borderline Tumor	4 (7.4)	2 (5)	

Data presented in number (%), EOC = epithelial ovarian cancer* Significant P < 0.05

Table (3) shows the different modalities of treatments used and their related mortality.

More than 95% of patients had surgery during their treatment course. The majority of the patients (68) had a combination of surgery and chemotherapy,

Out of those who underwent primary debulking surgeries, 6 (6.3 %)had secondary debulking surgery either due to residuals or tumour recurrence (table (3).

Table (3): The different modalities of treatments used and their related mortality.

Variables	No (%)
Type of Surgery as treatment: **Primary Surgery** Unilateral adenexectomy TAH+BSO Debulking (GIT metastasis) **Interval debulking surgery**	 **88 (93.6)** 24/88 (27.3) 55/88 (62.5) 9/88 (10.2) **6 (6.3)**
Chemotherapy: No chemotherapy Postoperative chemotherapy Neoadjuvant Range of cycles needed	26 (27.7) 62 (65.9) 6 (6.4) 1-17 (Mean ±SD 5.66± 2.82)
Response rate of 6 months follow up of chemotherapy: Stage I (8 cases) Stage II (12 cases) Stage III (32 cases) Stage IV (16 cases)	 8 (100%) 12 (100%) 23 (71.8%) 6 (37.5%)

Mortality rate during 1 year follow up in relation to stage:	
Negative mortality: (N = 76)	
Stage I	10 (13.1)
Stage II	12 (15.8)
Stage III	38 (50)
Stage IV	16 (21.1)
Positive mortality: (N = 18)	
Stage I	0 (0)
Stage II	2 11.1
Stage III	6 33.3
Stage IV	12 66.6
	[□2 18.798; P <0.001*]

Data presented as number (%), mean ± SD. P value is set significant when <0.05.

T AH+BSO = total abdominal hysterectomy and bilateral salpingoopherectomy, GIT= gastrointestinal tract.

Discussion

The study cohort included 94 women diagnosed with various types of ovarian cancer. Ovarian cancer is the 7thmost common cancer and 8thmost common cause of cancer death among women [7] and it is predominantly a disease of older postmenopausal women with the majority of cases being diagnosed in women over 50 years [8].In this study the majority of our cohort were below 50 years (57.5%) including about 6.4% of patients younger than 19 years meanwhile those diagnosed above fifties included 42.5 %. The mean age of all patients was 45.28 ± 15.5 years and for EOC alone, being the commonest appeared to be 47.5 ± 12.7 years. Actually, this postulated more than a decade lower in the mean age of our patients than what is seen in Western populations[6, 7]but appearing similar to a study from our locality at Alexandria University by Mostafaa et al., 2012 [9] who proved the age was around 48 years and another one population-based cancer registry study from Gharbia governorate which estimated the mean age at diagnosis was 47.2 years [10].Also, Abdel Aziz et a 2014[11] reported that the mean age of patients in Menoufia study was 53.4 years and this despite slightly higher than our findings but still also recognizing a decade lower than what is seen in Western populations and supporting our findings. Compared to recent studies done outside Egypt [12], the middle east cancer consortium (MECC) evaluated the incidence of ovarian cancer among four countries, namely Turkey, Israel, Cyprus, and Jordan compared to the US SEER database and noted that, the highest age of patients diagnosed with ovarian cancer were in US women followed by Israeli Jews, Cyprus and Izmir (Turkey) as having nearly 10 years more and lowest in Jordanians being almost below the age of 50 years and this comes very close to our result. Therefore, the age incidence of our patients is similar to that of other parts of Egypt and Jordan, while it is nearly 10 years younger than those published from developed counters [11].This might be connected to the average life expectancy in Egypt that is shorter than reported in the developed countries but this needs to be further studied.The majority of the studied patients (51.1%) were premenopausal, despite the notion that ovarian cancer is a disease of post-menopause, and this appeared similar toHong Kong study where 49.5% were premenopausal [13] and a Nigerian study where 60%were premenopausal [14].The high incidence within the premenopausal age in this study may suggest a shift to an earlier age of occurrence in the population which is a worrisome development and in contrast with international studies done in the United States, United Kingdom and Australia which showed higher incidence in the postmenopausal age [15].

A large proportion of the women in this study were nulliparous (25.5%) and this is consistent with the incessant ovulation theory; (Fathalla 1971) where autorsugesstednulliparity as a risk factor for ovarian cancer due to repeated cycles of ovulation, resulting in an increased trauma and scar tissue formation on the surface epithelium of the ovary thereby an increasing risk of malignant transformation (16).

In our study, positive family history to cancers was present in 9.5% of case and this comes similar to the percentage in Pakistanian study (Sarwar et al., 2006)(17) and still lower than those with proved higher incidence in other localities especially when the patient had BRCA1 and BRCA2 Mutation Carriers. Really this point is not included in our investigations and considered as a shortcoming in our work [18].Studying clinical presentation of our patients, most of patients (74.5%) presented at late stage disease (III and IV) with vague abdominal bloating or distension. Our results were similar to results presented by Malik, 2002 and Sarwar et al., 2006 [17.19] but lower than that proved by Peas et al 2011 and Fatiregun et al., 2015 [20. 21]. The atypical presentation mentioned should suggests that clinicians must have a high index of suspicion when patients present with vague abdominal symptoms and signs and it is important for women and medical practitioners and health care providers to know the symptoms of ovarian cancer so that early diagnosis could be made as screening in general population is not yet effective. In our results, simple linear regression showed that stage at presentation was strongly correlated to age at presentation ($p < 0.001$) and showed that younger patients are more likely to present early with slight better prognosis.

In our study, EOC predominates constituting 74.5% of cases with higher incidence of serous followed by mucinous subtypes and this come in agreement of some other results [9, 11, 12, 19, 22). Also, in our study the percentages of granulosa cell tumor and germ cell tumors, 10.6% and 6.4 % respectively, appeared similar to results published by Freedman et al., 2001 [22].

CA 125 is generally recommended for clinical use in the diagnosis and follow up treatment of ovarian cancer. In our study, CA-125 was elevated in more than 89% of all cases and this comes similar to Alexandria study where CA-125 was elevated in all epithelial tumors [9], while in the study done by Sarwar et al [17],CA-125 was elevated only in 70% of epithelial ovarian cancer.

The standard care for ovarian cancer is proper surgical staging with optimal cytoreduction and chemotherapy. The aim of surgical effort in ovarian cancer is to reduce the burden of residual tumor to a point at which the chemotherapy will be optimally effective. The recommended surgical procedure is total hysterectomy, bilateral salpingo-oophorectomy and omentectomy aimed at radical cytoreductive treatment. Actually, this was the rule in this study where nearly 93.6 % of patients were managed initially with primary debulkimgsurgery. Many studies proved similar results [23]. On the other hand, a study done by Thrall et al., 2011 [24], reported that surgery was performed initially in 58.8% of the women with advanced ovarian epithelial carcinoma. The gynecology oncology group has defined optimal debulking as residual implants up to 1 cm to give a positive hope for postsurgical survival and such measurements are subjectively determined at the completion of surgery [25, 26].

Of those who underwent surgery, 36.4% of cases had optimum cytoreduction (no residual or residual less than 2 cm) and despite this comes near to figures found by Gerestein et al., 2011 [27] but much lower than figures proved by Brand, 2011[28] being 45 % and 65% respectively. It is obvious from the comparison that in this study, optimal cytoreductive surgery is performed in a much less frequency than done in Western countries and this can be explained by; the very late presentation in most of our cases and non-availability of multidisciplinary team evaluating all the cases before surgery. Therefore, the authors advice here is to increase the efficacy of adjuvant chemotherapy and success of surgery for ovarian cancer is patient's selection and stabilizing a skilled surgical team to achieve a survival benefit.

Different response rates to chemotherapy in ovarian cancers were seen in the literature with different percentages of complete responses. It was found to be 51% for cisplatin by Thigpen et al., 1994 [29] meanwhile for paclitaxel followed by either cisplatin or carboplatin it ranged between 64–74%[29]. In other studyused paclitaxel plus cisplatin versus paclitaxel plus carboplatin the response rate recorded, 46% vs. 53% respectively [30].After comparing our results to those of the large international studies, we found that the response rate including clinical complete response in our patients is closely similar to those of the international studies.

Regarding the type of chemotherapy regimen used, Paclitaxel-carboplatin was the most frequently

used regimen as a first line in 62.3%, followed by carboplatin single agent in 24.1% of cases. The response rate to the first line chemotherapy (including both neo-adjuvant and following surgery) after three cycles was seen in 72 % of the cases. In our study there was a statistically significant correlation between response and stage ($P < 0.001$). FDA recently approved the use of Bevacizumab, a monoclonal antibody, in the management of platinum resistant ovarian cancer[31], but this had no role in our patients because of the limitation of the resources.

The follow up period for our patients was 12 months and the progression free survival after first line chemotherapy was 10.8 months and this comes slightly lower than some international studies as this found to be ranged between 11 and 21 months [32].The possible explanation of that difference could be explained by; first; the number of the patients in our study was relatively small in comparison to those studies, second; no standard chemotherapy protocol was given among all patients in our study, and third; the high frequency of chemotherapy under-dosage and frequent interruption of the treatment were due to limited resources and at sometimes unavailability of the drugs specially paclitaxel. Further research on outcomes of implementing quality improvement programs in ovarian cancer care will improve the ability to implement centralized care and further identify factors improving outcomes in ovarian cancer care. Hence, the authors' advice for further study involving a large number and better to be multicentric for obtaining results near or similar to that listed international.

In conclusion

Accurate and annual studies on patients with ovarian cancer will help improving the health care system and promote effective clinical management to eliminate the survival disparities, and thereby improved the clinical outcome.

Conflict of interest

the authors declare that there is no conflict of interest.

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