Clinico-Pathological Measures and Management of Mucinous Ovarian Cancer: Single Institutional Study

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ABSTRACT
Background: Mucinous ovarian cancer is less common and less aggressive epithelial ovarian cancer, which represents 3% of epithelial ovarian cancer.
Patient and methods: A retrospective descriptive analysis involving all patients with mucinous ovarian cancer who underwent surgical management or referred to National Cancer Institute (NCI), Cairo University (CU), from January 2010 to January 2020. Of 46 cases reviewed. 16 cases were excluded (10 cases had metastatic and 6 cases had incomplete data). **Results:** forty-six cases reviewed with median age of 48.3±18.1 years. Half of patients were in premenopausal status. Patients presented with distention with or without pain were 70% of cases, 10% of patients with abdominal mass and 6.7% of patients with bleeding. Most of cases 63.30% were diagnosed at late stages (1C and beyond). Patients had unilateral disease were 70% of cases and had elevated tumor markers were 53.3 % of cases. The most commonly elevated tumor marker was CA 125 (26.7%). Patients had comorbidities were 30% of cases.
Surgery was the main line of management. Total abdominal hysterectomy and bilateral salpingo-oophorectomy plus infracolic omentectomy were done in 73.3% of patients, 6.7% underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, 3.3% underwent cytoreductive surgery and 3.3% underwent cytoreductive surgery and 13% of patients underwent fertility sparing surgery. The role of pelvic lymphadenectomy was limited (13.3% underwent pelvic lymphadenectomy and only one patient had positive lymph node metastasis).
Conclusion: The most important prognostic factors were disease stage, laterality, tumor markers and performance status.
Key words: Mucinous ovarian cancer (mEOC), Surgery.

INTRODUCTION

Epithelial ovarian cancer (EOC) is the most lethal gynecological malignancy. Epithelial ovarian cancer is not a single disease but is composed of a diverse group of tumors which includes serous, mucinous, endometrioid and clear cell tumor [1].

Mucinous ovarian cancer is a less common epithelial ovarian cancer which represents approximately 3% of epithelial ovarian cancers. Mucinous ovarian cancer (mEOC) seems less aggressive than other histologic types and require more conservative treatment [2]. Mucinous EOC most commonly presents in women between 39 and 50 years' old which is younger age range than other histological types. Almost 83% of mEOCs are stage I at the time of diagnosis [3].

Many patients are premenopausal, and most mucinous tumors are unilateral, allowing for fertility preservation. In early-stage illness, preservation of the normal-appearing uterus and contralateral ovary is possible [4].

Because lymphatic dissemination is uncommon in primary mucinous ovarian cancer, pelvic and/or para-aortic lymphadenectomy as part of the staging method is not required in patients with primary mEOC that is grossly confined to the ovary [5].

Early stage mEOC has a better overall prognosis than non-mucinous forms. The majority of tumors are detected at an early stage, and the prognosis after surgery is favorable. Mucinous carcinoma of the ovary that is advanced or recurring responds poorly to current cytotoxic therapies, and the prognosis is unfavorable [6].

PATIENTS AND METHODS

A retrospective descriptive analysis involving all patients with mucinous ovarian cancer who underwent surgical management or referred to National Cancer Institute (NCI), Cairo University (CU) in Department of Surgery from January 2010 to January 2020. Patient of all age groups and all stages who underwent surgical management for primary mucinous ovarian cancer were included. They were excluded if they met the following criteria:
1- Primary mEOC, tumors that had metastasized to the ovaries were excluded
2- Insufficient data and medical records. Patients were excluded when data on pathological review were not available

Medical records and data:
A. Medical records:
Data from National Cancer Institute Hospital-based registry were used to generate a list of all patients diagnosed with mucinous ovarian cancer at the period from January 2010 to January 2020. Records were scrutinized at archives of biostatistics and Surgery and Pathology Departments.

B. Data:
A pre-determined sheet was used to fulfill objectives of the study. All patients' files were reviewed to obtain all available data as follows:

Preoperative data: Patient's name and age, chief complaint, medical comorbidities, risk factors, performance status, tumor markers: preoperative CA 125, CEA, CA19-9 and fertility status before surgery

Operative data: Surgical approach, surgical procedure, lymphadenectomy or not.

Postoperative and follow up data: FIGO stage, adjuvant chemotherapy, recurrence if detected: date of diagnosis, site and disease free survival

Ethical Committee approval:

The study was approved by Institutional Review Board (IRB) before start of the study (1381). The data of the patients were presented anonymously with protection of privacy and confidentiality. All given data were used for the current medical research only. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.
Statistical methods

Data management and analysis were performed using Statistical Package for the Social Sciences (SPSS) vs. 23. Numerical data were summarized using means and standard deviations or medians and ranges, as appropriate. Categorical data were summarized as numbers and percentages. Numerical data were explored for normality using Kolmogorov-Smirnov test and Shapiro-Wilk test. Kaplan-Meier method was used to estimate recurrence free survival. Predictor and prognostic variables were related to survival using log rank test. All tests were two-sided. P-values < 0.05 was considered significant.

RESULTS

Six cases had incomplete or missing medical records and 10 cases were metastatic from the start. Therefore, they were excluded from the study. As a result, 30 cases were subjected to statistical analysis.

The age of our patients ranged between 18-84 years with a mean of 48.3±18.1 (Table 1).

Table (1): *Demographic and preoperative characteristics*

		No	%
Age(yrs.)	Mean ± SD	48.3±18.1	
	Range	18-84	
Family History	No	23	76.7
	Yes	7	23.3
Menstrual Status	Pre-menopausal	15	50.0
	Post-Menopausal	15	50.0
Comorbidities	No	21	70.0
	Yes	9	30.0
Type of comorbidity (n=9)	HTN	7	77.8
	DM	6	66.7

Regarding the menstrual status, there were 15 premenopausal patients (50%), while the other 15 patients (50%) were postmenopausal Most of the patient with MOC who underwent surgery had performance status 1 (76.7%) (Table 5). About the comorbidities, there were 21 patients (70%) had no co-morbidities, while the other 9 patients (30%) had hypertension or diabetes mellitus or both (Table 1).

There were 7 patients who had family history of ovarian cancer (23.3%), while the other 23 patients had no family history of ovarian cancer (76.7%)(Table 1).

About the clinical presentation, 21 patients (70%) presented with distention (whether distension only or associated with pain) . There were 11 patients (36.7%) presented with early stage MOC, while the majority of patients 19 (63.3%) presented with late stage MOC Table (2).

Table (2): *Staging and clinical presentation*

		No	%
Stage	Early (1A and 1B)	11	36.7
	Late (1C and Beyond)	19	63.3
Clinical Picture	Distention	21	70.0
	Pain	18	60.0
	Bleeding	2	6.7
	Mass	3	10.0

16 patients representing (53 .3 %) of our patients had elevated tumor markers. The most commonly elevated tumor marker among our patients was CA 125 (26.7%) Table (3).

Table (3): *Tumor markers*

Tumor Markers	All Normal	14	46.7
	Elevated	16	53.3
Tumor Markers	All normal	14	46.7
	↑ CA125	8	26.7
	↑ CA125 and CA19-9	1	3.3
	↑ CEA	1	3.3
	↑ CEA and CA 19-9	1	3.3
	All elevated	5	16.7

Regarding the surgical management, the results are shown in table 4. Analysis of data showed that; most of our patients underwent non-fertility sparing surgery (Radical surgery) in the form of total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO) plus Infracolic omentectomy (73.3%) (Table 4).

Table (4): *Analysis of surgical management and chemotherapy*

		No	%
Operation	Unilateral Oophorectomy	1	3.3
	unilateral salpingo-oophorectomy	3	10.0
	TAH and BSO	2	6.7
	TAH and BSO + infracolic omentectomy	22	73.3
	CRS	1	3.3
	CRS and HIPEC	1	3.3
Lymphadenectomy	No	26	86.7
	Yes	4	13.3
LN Status	No	3	75.0
	Yes	1	25.0
Chemotherapy	No	11	36.7
	Yes	19	63.3
Chemotherapy Type	Neoadjuvant	4	21.1
	Adjuvant	18	94.7

TAH; total abdominal hysterectomy, and BSO; bilateral salpingo-oophorectomy CRS; cytoreductive surgery, HIPEC; hyperthermic intraperitoneal chemotherapy.
Bilateral tumors were found in 9 patients (30%), while 21 patients (70%) had a unilateral tumor (Table 5).

Table (5): *Laterality and Performance status*

Laterality	Unilateral	21	70.0
	Bilateral	9	30.0
Performance Status	1	23	76.7
	2	5	16.7
	3	2	6.7

The overall median disease-free survival (DFS) for all patients was 48 months. Also, we found that the median DFS for early stage was 72 months, while it was 12 months for late stages at diagnosis (p value 0.001) (Table 6).

Table (6): *The relation between different factors and DFS*

Factors	n	6 m	1 yr.	3 yrs.	5 yrs.	Median in Months (95% CI)	P value
		DFS%				**Median in Months**	
All	30	83.3	63.3	51.4	44.9	48.0 (0.5-96.8)	NA
Age							
<50 yrs.	15	93.3	80.0	70.0	70.0	NA	**0.020**
≥ 50 yrs.	15	73.3	46.7	33.3	25.0	12.0 (1.6-22.4)	
Family History							
No	23	87.0	65.2	49.7	42.6	30.0 (0.5-74.0)	0.977
Yes	7	71.4	57.1	57.1	57.1	NA	
Menstrual Status							
Premenopausal	15	93.3	80.0	70.0	70.0	NA	**0.020**
Postmenopausal	15	73.3	46.7	33.3	25.0	12.0(1.6-22.4)	
Stage							
Early	11	90.9	90.9	90.9	90.9	72.0	**0.001**
Late	19	78.9	47.4	25.9	13.0	12.0(4.3-19.7)	
Tumor Markers							
All Normal	14	100	85.7	68.6	68.6	72.0(0.2-143.8)	**0.018**
Elevated CA 125	16	68.8	43.8	35.0	23.3	12.0(5.5-18.5)	
Lymphadenectomy							
No	26	84.6	61.5	51.6	51.6	72.0(12.0-131.9)	0.377
Yes	4	100	100	50	NA	18.0(0.5-48.7)	
Chemotherapy							
No	11	81.8	81.8	81.8	81.8	72.0	**0.044**
Yes	19	84.2	52.6	32.1	21.4	18.0(9.2-26.7)	
Laterality							
Unilateral	21	85.7	71.4	65.9	57.7	72.0(37.3-106.7)	**0.038**
Bilateral	9	77.8	44.4	14.8	NA	12.0(4.7-19.3)	
Performance Status							
I	23	95.7	78.3	62.5	53.5	72.0	**0.007**
II-III	7	71.4	14.3	14.3	14.3	6.0(3.4-8.6)	
Comorbidities							
No	21	90.5	81.0	75.6	66.1	72.0(37.6-106.4)	**<0.001**
Yes	9	66.7	55.6	NA	NA	12.0(7.9-16.1)	

NA: not applicable, CI confidence interval, P<0.05 is statically significant.

Regarding tumor markers and chemotherapy, we found that the median DFS in patients with normal tumor markers was 72 months, while it was 12 months in patients with elevated CA 125 (p value 0.018). Also we found that the median DFS in patients who did not receive chemotherapy was 72 months, while was 18 months in whom received chemotherapy either neoadjuvant or adjuvant or both (p value 0.044).

Regarding the laterality of the tumor and lymphadenectomy, study found that the median DFS in patients presented with unilateral tumors was 72 months, while it was 12 months in patients presented with bilateral tumors (p value 0.038). Also we found that the median DFS in patients who underwent lymphadenectomy was 18 months, while was 72 months in whom did not undergo lymphadenectomy (p value 0.377).

Regarding performance status and comorbidities, on analysis 0f data; we found that the median DFS in patients who had performance status I was 72 months, while was 6 months in patients presented with performance status II-III (p value 0.007). Also we found that the median DFS in patients who had comorbidities was 12 months, while it was 72 months in those who did not have any comorbidities (p value < 0.001).

DISCUSSION

The mean age of our patients at the time of surgery was 48.3±18.1 years. **Hart** and **Brown and Frumovitz** have stated that mucinous ovarian cancer is a rare epithelial ovarian cancer that accounts for around 3% of all epithelial ovarian cancers. mEOC is most frequent in women between the ages of 39 and 50, which matches our findings [2, 3].

There were 15 patients (50%) premenopausal, while the other 15 patients (50%) were postmenopausal. This is different from what **Ledermann** *et al.* reported in his study that the majority of individuals with mucinous ovarian cancer are premenopausal at the time of diagnosis [4].

Regarding the family history, there were 7 patients who had family history of ovarian cancer (23.3%), while the other 23 patients had no family history of ovarian cancer (76.7%). This emphasized the results of **Jordan** *et al.* who found that mucinous ovarian tumors, on the other hand, appear to have a weaker link to reproductive factors [7, 8].

Regarding the clinical presentation, 21 patients (70%) presented with distention (whether distension only or associated with pain). this was similar to what was stated by **Marko** *et al.* and **Seidman** *et al.* that in mucinous tumors of the ovary, clinical signs and symptoms of a large unilateral pelvic mass are typical [9, 10].

Seventy percent of our patients presented with unilateral tumor at time of presentation which is similar to what **Ledermann** *et al.* stated that at the time of diagnosis, the majority of MOC patients had a unilateral tumor [4].

Only 16 patients (53 .3 %) of our patients had elevated tumor markers and the most commonly elevated tumor marker among our patients was CA 125 (26.7%). This is different from the results of **Brown and Frumovitz** who have stated that the CEA is the most helpful circulating tumor marker for detecting mEOC before surgery and following the progress of a patient with mEOC after surgery, and CEA is high in nearly one-third of all ovarian carcinomas. It is much more likely to be elevated in mEOCs than in non-mucinous ovarian carcinomas (88 % vs. 19 %) [3].

Surgery either radical or fertility sparing is the main line of management. Most of our patients underwent non-fertility sparing surgery (Radical surgery); 73.3% underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy plus Infracolic omentectomy, 6.7% underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, 3.3% underwent cytoreductive surgery (CRS) and 3.3% underwent cytoreductive surgery; CRS and HIPEC were done, while 13% underwent fertility sparing surgery, while **Morice** *et al.*, **Gouy** *et al.*, **and Bentivegna** *et al.* had stated that the most common operation for young patients who need to preserve fertility is unilateral salpingo-oophorectomy with peritoneal staging procedures (cytology, peritoneal biopsies, and omentectomy). While Only the elderly is subjected to bilateral salpingo-oophorectomy [11,12,13].

This difference can be attributed to the more advanced stage and older age of our patients at presentation. Only 4 of our patients underwent pelvic lymphadenectomy (13.3 %) while the rest (86.7%) didn't undergo pelvic lymphadenectomy in addition to their surgical management. Among those who underwent pelvic lymphadenectomy, only one patient had positive lymph node metastasis.

Babaier et *al.* and **Hoogendam** *et al.* have similarly stated that in early-stage MOC, the role of routine pelvic lymphadenectomy is still debatable. The probability of lymph node involvement is 0.8 percent and 1.2 percent, respectively, when lymph node sampling or lymphadenectomy is performed in apparent stage I and II disease [14, 15].

In this study; 19 patients (63.3 %) received chemotherapy, most of them (18 patients) received adjuvant chemotherapy whether alone or in addition to neoadjuvant. this was similar to NCCN (National Comprehensive Cancer Network) guidelines, surgery alone is recommended for stage IA or IB mucinous ovarian cancer, while adjuvant platinum-based chemotherapy is recommended for stage II or more advanced disease [7,16].

We can conclude that the overall median disease-free survival (DFS) for all patients was 48 months and the median DFS for early stage was 72 months, while it was 12 months for late stages at diagnosis. This was similar to **Marko** *et al.* , **Babaier** *et al.* and **Zaino** *et al.* results who had stated Early-stage MOC has a favorable prognosis, with DFS of about 60 months in more than 90% of patients, whereas metastatic disease has a 12-to-30-month survival rate [9 14, 17].

CONCLUSION

Surgery either radical or fertility sparing is the main line of management. The role of pelvic lymphadenectomy is limited. Some cases may require adjuvant or neoadjuvant chemotherapy. Disease-free survival was shorter in patients with late stages at time of surgery, in patients who received chemotherapy, bilaterality and comorbidities. Overall disease-free survival (DFS) was 48 months. The most important prognostic factors were disease stage.

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