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ORIGINAL ARTICLE

Analysis of Morbidity, Mortality and Survival Pattern Following Surgery for Borderline Ovarian and Malignant Ovarian Tumour in Tertiary Care Centre

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Abstract

Backgrounds To analyse the morbidity, mortality and survival pattern following surgery for borderline ovarian and malignant ovarian tumours.

Methods The medical records of 57 consecutive patients with invasive and borderline epithelial ovarian cancer patients registered and operated in our tertiary centre between 2015 to 2017 were reviewed. Patients were followed up for a minimum of 18 months to maximum of 42 months at an interval of 3 months with CA125 values. Various prognostic factors were analysed. The data descriptive statistics of frequency and percentage analysis were used for categorical variables and mean and standard deviation were used for continuous variables.

Results The most common age group was 51 years and above with the majority (56.2%) of women belonging to postmenopausal age group (32/57). In our study, 30 out of 57 women (52.6%) had stage III disease, 17 women had stage I disease (29.8%) and 7 women had stage 2 disease (12.3%). Majority of the women had serous epithelial ovarian tumour (47 out of 57 patients), which contributed to 82.4%. Grade 1 and 2 morbidity was encountered in 8 patients. Six patients had wound infection (grade 1), and 2 patients required blood transfusions (grade 2). One patient had grade 3 morbidity requiring relaparotomy. Borderline tumours and early-stage epithelial ovarian tumours had good prognosis, less morbidity and good survival. The overall median survival was 25 months.

Conclusions With meticulous perioperative care, surgery for ovarian cancer in the primary and interval setting can be done with minimal morbidity and no postoperative mortality, especially in patients with co-morbidities. Grade is an important prognostic factor affecting the survival of patients with epithelial ovarian cancers undergoing surgery. Lymph node dissection helps achieve local control but may not improve the survival.

Keywords Malignant ovarian tumour · Morbidity · Clavien–Dindo classification · Grade · Cytoreductive surgery

Introduction

Annually, ovarian cancer (OC) accounts for an estimated 239,000 new cases and 152,000 deaths all over the world [1]. The highest rates are seen in Eastern and Central Europe (11.4 per 100,000 and 6.0 per 100,000, respectively). China has a relatively low incidence rate (4.1 per 100,000), but the large population translates to an estimated 52,100 new cases and 22,500 related deaths in 2015 [2]. During the same year, 21,290 cases and 14,180 related deaths were estimated to occur in the USA [3]. Optimal cytoreduction is achieved when the areas of residual tumour are less than 1 cm and maximal surgical effort is done to remove all gross disease [4, 5]. Here we present the analysis of morbidity, mortality

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and survival pattern following surgery for borderline ovarian and malignant ovarian tumours in a tertiary care centre.

Materials and Methods

The medical records of 57 consecutive patients with invasive and borderline epithelial ovarian cancer patients registered and operated in our tertiary centre between 2015 and 2017 were reviewed after obtaining institutional review board approval. The ethics approval and copy allotted number were CSP-MED/18/JAN/41/07. Informed written consent was obtained from all the patients and next of kin. Patients with non-epithelial ovarian tumours and stage IV epithelial ovarian tumours were excluded.

The data acquired included the age at diagnosis, medical co-morbidities, preoperative Ca125, type of surgery, number of lymph nodes examined and involved, histology and grade of tumour, stage of disease, morbidity (according to Clavien–Dindo classification), mortality and follow-up Ca125. Patients were staged according to the International Federation of Gynecology and Obstetrics (2009 FIGO) system. All pathology specimens were reviewed by an onco-pathologist of our institute and graded. The standard operative protocol in our institute was staging laparotomy for early-stage disease where peritoneal wash for cytology, total abdominal hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy with pelvic and paraaortic lymphnode dissection was done. Optimal cytoreduction was done either primarily or following neoadjuvant chemotherapy (interval cytoreduction) as per the disease burden in advanced epithelial ovarian tumours. The chemotherapy regimen of carboplatin or cisplatin with paclitaxel was given. Patients, who underwent surgery for borderline and malignant epithelial ovarian tumours, were followed up for a minimum of 18 months to maximum of 42 months at an interval of 3 months with CA125 values. Further imaging was done if CA125 showed increasing trends. The morbidity, mortality and survival pattern were analysed with each prognostic factor.

Results

Data descriptive statistics of frequency and percentage analysis were used for categorical variables and mean and standard deviation were used for continuous variables. Chi-square or Student's T test was used to analyse difference in distribution of co-factors between groups. The Kaplan–Meier curve was used to find overall survival analysis on comparison of survival to the duration of months in survival.

In our study, most common age group was 51 years and above, which contributed to 61.5% of the cases. Forty-seven out of 57 women enrolled are still surviving, 10/57 women who died belonged to age > 50 years and 4 women died of natural cause which was statistically insignificant ($p = 0.429$). The majority of women belonged to postmenopausal age group (32/57)—56.2%.

Among all the co-morbidities, diabetes mellitus was most common (15/57 patients), followed by hypertension (12/57), but few women had both diabetes and hypertension (8 patients).

Staging was done as per the FIGO classification. In our study, 30 women out of 57 (52.6%) had stage III disease, 17 women had stage I disease (29.8%) and 7 women had stage 2 disease (12.3%). Three women had borderline ovarian tumour (5.3%). All women with borderline tumours and early stages (stages I and II) are free from disease. All women who died belonged to stage III disease (10/27 patients) 3 women were alive with recurrence on second-line chemotherapy, 3 women died due to recurrence despite treatment and 4 women died due to other cause. However, the correlation of stage of disease with survival had no statistical significance ($p = 0.314$). Preoperatively, Ca125 was done for all patients; details are mentioned in Table 1.

Preoperative Ca125 level was highest in patients with stage III serous epithelial ovarian tumour. Borderline ovarian epithelial tumours and stage II disease had a low mean CA125. The p value was 0.268 and not statistically significant.

Primary cytoreduction was performed in 40.3% of women (23/57). Interval cytoreduction was done in 54.4% of women (31/57). Three women with borderline ovarian tumours diagnosed on frozen section underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH with BSO).

Majority of the women had serous epithelial ovarian tumour (47 out of 57 patients), which contributed to 82.4% of cases. Table 2 correlates the histology of the tumour with survival. All women who had recurrence or death (either due to disease or due to other cause) belonged to this group. There was 100% survival in patients with histology reports of non serous epithelial tumors.

Table 1 Preoperative Ca125 in all patients

Ca125	Total no. of women ($N = 57$)	PREOP Ca125 (Mean)	PREOP Ca125 (Range)
BORDERLINE	3	34.6	(27—50)
STAGE 1	17	688.1	(39—6221)
STAGE 2	7	284.2	(5—682)
STAGE 3	30	1684	(5—9632)

Table 2 Various histologies and their recurrence and survival pattern

HISTOLOGY	*N* = 57	Alive	Recurrence and alive	Death due to recurrence	Death due to other cause
SEROUS	47	37	3	3	4
MUCINOUS	1	1	–	–	–
CLEAR CELL	1	1	–	–	–
ENDOMETRIOID	3	3	–	–	–
MIXED	2	2	–	–	–
BORDERLINE#SEROUS#MUCINOUS	1 2	1 2	–	–	–
TOTAL	57	47	3	3	4

All the women who died due to recurrence had high-grade tumours. The p value was 0.04, which was statistically significant.

Out of 57 women, 50 women underwent lymphnode dissection. Nine of them had pathological positive lymphnode involvement. Positive lymph node diagnosed on final pathology report did not affect the survival.

After completion of treatment, CA125 values decreased in all stages, when repeated 3 months (at first follow-up) and 18 months after surgery (Table 3).

Postop morbidity as assessed by Clavien–Dindo Classification is shown in Table 4. Grade 1 and 2 morbidity was encountered in 8 patients. Six patients had wound infection (grade 1), and 2 patients required blood transfusions (grade 2). One patient had grade 3 morbidity requiring re-laparotomy.

Discussion

Chiang et al. [6] reported that the peak age at diagnosis changed 60 to 50 years from 1979 to 2008. In our study, the peak age at diagnosis was 50 years and above. Between age of 50 to 60 years, 20.9% (4/57) had recurrence and 15.7% (3/57) died due to disease. We had better survival outcomes (93.7%) (15/16) in women > 60 years. Only one patient died but not due to disease. In our study, women who were < 50 years had 100% survival, and survival rate in women of age 50 and above was 61.4%. However, p value was 0.429, which is statistically insignificant, proving that age was not a prognostic indicator of survival.

Comorbidity (ASA > 1) as a predictor of mortality at 0–180 days after surgery was shown by Orskov et al. [7], in concordance with studies by Grann et al. [8] and Sperling et al. [9]. Diabetes mellitus was the predominant comorbidity in our study followed by hypertension. None of our patients with comorbidity had mortality probably due to better control of comorbid conditions before surgery.

Table 3 Clinicopathological factors of all patients

Age groups (years)	Number of patients	Percentage
< 40	7	12.2
40–50	15	26.3
50–60	19	33.4
> 60	16	28.1
Stage		
Borderline	3	5.3
Stage 1	17	29.8
Stage 2	7	12.3
Stage 3	30	52.6
Preop Ca 125 with stage (mean)		Range
Borderline	34.6	27–50
Stage 1	688.1	39–62
Stage 2	284.2	215-682
Stage 3	1684	5–9632
Histology		
Serous	47	82.4
Mucinous	1	1.7
Endometrioid	3	5.3
Clear cell	1	1.7
Mixed	2	3.6
Borderline		
Serous	1	1.7
Mucinous	2	3.6
Past surgery		
Yes	26	47.4
No	31	52.6
Type of surgery		
TAH + BSO	3	5.2
Primary cytoreduction	23	40
Interval cytoreduction	31	54
Lymphnode involvement		
Positive	9 out of 50 patients	18
Preop scan + HPE positive	5	10
Postoperative ca125	3 month (mean) 18 month	
Borderline	15.3 12.6	
Stage 1	26.9 20.6	
Stage 2	39 30	
Stage 3	47.13 178.9	

Table 4 Postoperative morbidity

Morbidity	Number of women	Percentage
Grade 1	6	10.5%
Grade 2	2	3.5%
Grade 3	1	1.75%

While staging facilitates treatment planning, a lower stage at diagnosis generally converts into a superior clinical outcome and improved survival [10]. As the disease increases, mortality due to disease recurrence is higher. Seven patients with stage III died during the study period. However, 4 women died of other causes not related to disease. Thus, only 3/57 women died due to disease. Stage as a prognostic factor for survival was not statistically significant (p value 0.34).

Recent studies indicate that low-grade serous carcinoma has a significantly better prognosis than high-grade serous carcinoma [11, 12]. In our study, all the recurrences and deaths occurred in patients with high-grade lesion. There was neither recurrence nor death in patients with low-grade and borderline tumours. Thus, grade of tumour affected survival with *p* value of 0.04, which was statistically significant. Histologic subtype outperforms the tumour grade in prediction of survival, especially when combined with molecular markers [13].

Wei et al. [14] showed that in early-stage EOC, clear cell carcinoma had poorer outcomes than serous carcinoma. However, Ye et al. [15] observed that there was no statistically significant difference in the survival of patients between these EOC in early stages, which is similar to our study. The p value with regard to histology in our study was 0.832, which was not statistically significant.

Tumour cell type is shown to be the most relevant histologic prognostic factor in advanced ovarian cancer treated with platinum/paclitaxel [8]. In our study, serous tumours contributed to 78% of all patients. All the serous tumour patients belonged to stage III, whereas clear cell carcinoma (1.7%) was early stage. Ten out of 57 women in our study had non-serous and borderline tumours detected in early stages and had 100% survival.

Du Bois et al. [16] retrospectively analysed the data from three randomized clinical trials (AGO-OVAR) to evaluate the role of systemic retroperitoneal lymphadenectomy in patients with advanced ovarian cancer. In patients with residual tumour up to 1 cm, the lymphadenectomy showed no statistical difference. For patients with small residual nodules and clinically suspicious nodes, lymphadenectomy improved survival from 17 to 28%. LION STUDY (Lymphadenectomy In Ovarian Neoplasm), a prospective randomized controlled trial, studied the potential benefit of systemic pelvic and paraaortic lymphadenectomy and its outcome. They concluded that in patients with advanced ovarian cancer who underwent macroscopically complete resection did not benefit from systemic lymphadenectomy [17]. In our study, out of 57 patients, 50 patients (87.7%) underwent lymphnode dissection. Nine patients (18%) had pathological positive lymphnode involvement. However, it did not affect survival as p value was 0.429, which was statistically insignificant.

Disease-specific survival in our study is shown in Fig. 1 where survival is plotted against the duration in months and median survival was 25 months which is at par with international data (Table 5).

The EORTC study and CHORUS were included in Cochrane review and meta-analysis, long-term follow-up data substantiate previous results, showing neoadjuvant chemotherapy and upfront debulking surgery result in similar overall survival in advanced tubo-ovarian cancer. Further analysis showed neoadjuvant chemotherapy has valuable role in stage IIIc and IV disease [18, 19]. In our study, we excluded stage IV disease; however, 27 women with stage III had interval cytoreduction with good survival. There was overall 17.54% mortality and 82.45% survival in carcinoma ovary patients operated with primary optimal or interval cytoreduction.

Postoperative morbidity was assessed by Clavien–Dindo Classification, which showed low morbidity in patients who underwent cytoreductive surgery. There was no postoperative mortality. In our study, various prognostic factors were analysed, and only grade of tumour was statistically significant.

Conclusion

With meticulous perioperative care, surgery for ovarian cancer in the primary and interval setting can be done with minimal morbidity and no postoperative mortality, especially in patients with comorbidities. Grade is an important prognostic factor affecting survival of patients with epithelial

Fig. 1 Disease-specific survival

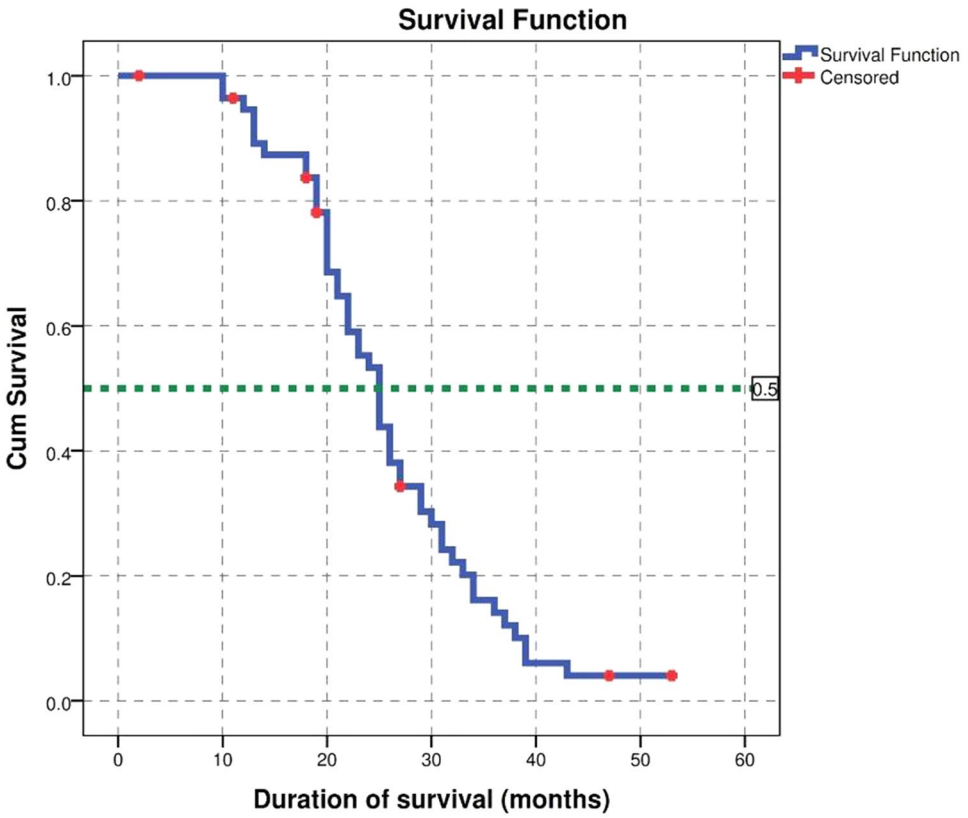

Table 5 Comparative survival across various studies

Study	No. of patients	Stage of disease	Surgical expertise	Surgery done	Median overall survival (in months)
CHORUS (18)	Patients from 87 hospitals in U.K. and New Zealand from March 2004 to August 30, 2010. 550 Patients were eligible	STAGE III–IV Ovarian cancer	Not specified	PDS#NACT-IDS	22.6 months 24.1 months Median follow-up:5.9 yrs
Vergote et al., 2010 (EORTC 55,971) (19)	59 Institutions from September 1998 to December 2006. 670 patients	Stage IIIC–IV ovarian, fallopian tube, or peritoneal cancer	Not specified	PDS NACT-IDS	30.2 months Median follow-up:7.6 yrs
OUR STUDY	57 patients	Stage I to III and borderline ovarian tumours	Surgical oncologist	PDS NACT-IDS	25 months Median follow-up: 42 months

ovarian cancers undergoing surgery. Lymph node dissection helps achieve local control but may not improve the survival.

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Compliance with Ethical Standards

Conflict of interest None declared.

Ethical approval The medical records of all invasive and borderline epithelial ovarian cancer patients registered and operated in our tertiary centre between 2015 and 2017 were reviewed after obtaining institutional review board approval. The ethics approval and copy allotted number were CSP-MED/18/JAN/41/07. Confidentiality and patient anonymity were maintained.

Informed consent Informed consent was obtained.

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