Clinical Behaviour, Pathological Findings, Survival and Prognostic Factors in Young Woman in Comparison to Menopausal Women with Epithelial Ovarian Malignancy

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ABSTRACT

Objective: The purpose of this study was to evaluate the clinical behaviour, pathological findings, survival and prognostic factors in young women in comparison to menopausal women with epithelial ovarian malignancy. **Methods:** A retrospective analysis of 141 patients (67 for age below 40 years and 74 menopausal) treated between 1980 and 2000 was conducted. **Results**: Irrespective of the stage, the most common clinical presentation was abdominal distension in both young (78%) and menopausal women (66%). In young women, 52% presented at an early stage of the disease and in menopausal women this was seen in 22% (p-value <0.05). The most common histological type of carcinoma in young women was mucinous cystadenocarcinoma (36%) and in menopausal women, it was serous cystadenocarcinoma (47%) (p<0.05).The overall 5-year survival rates in each group were 54% in young women and 41% in menopausal women. The 5-year survival rate appeared to be influenced by the stage of disease and tumour debulking surgery from univariate analysis in both young and menopausal women. In the final multivariate Cox proportional hazard model analysis, the optimal tumour debulking surgery was a significant (0.25; 95% CI (0.1-0.3) p <0.01) independent prognostic factor for survival probability in both young and menopausal women **Conclusion:** There are limited reports in the literature comparing the outcomes of younger and menopausal women with epithelial ovarian malignancy treated by any gynaecology oncologist from a single academic institution. Our results showed that the proportion of epithelial ovarian malignancy in young women was 30% from the total identified numbers of patients treated for epithelial ovarian malignancy. Although different types of carcinoma occurred in the young and menopausal women, the stage of the disease at presentation and optimal debulking surgery are important prognostic factors to ensure better survival rate.

Keywords: Epithelial ovarian malignancy, menopause, prognostic factors, survival probability, young women

INTRODUCTION

Ovarian carcinoma is the leading cause of death from gynaecological malignancies in a great majority of developed countries;[1] however, it is low in the developing countries and

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Asia.[2] In a National Cancer Registry survey in 2002, ovarian cancer was the fourth most common cancer among women in Peninsular Malaysia.[3] This accounted for 5.0% of the total female cancers and the incidence was 7.4 per 100,000 population in Peninsular Malaysia.[3] The age standardised incidence was 8.6 per 100,000 population and the disease occurred most commonly amongst the Chinese with 10.4 per 100,000 population.[3] Malaysian vital statistics in 1998 showed that there were 122 certified deaths due to ovarian cancer which was 2.7% of all deaths from cancer.[4] Currently, there is very limited data about epithelial ovarian malignancy in Malaysia especially in young women. Therefore this study was conducted in order to evaluate the clinical behaviour, pathological findings, survival and prognostic factors in young women as compared to menopausal women with epithelial ovarian malignancy.

A retrospective study of young and menopausal patients treated in the University Malaya Medical Centre (formerly known as University Hospital Kuala Lumpur) for epithelial ovarian malignancy over the past 20 years was conducted to assess indicators that could have an impact on overall survival in these two groups. Prognostic factors in patients with epithelial ovarian malignancy need to be determined to accurately predict outcome and tailor treatment according to individual risks and potential benefits. Several studies had shown that clinico-pathological factors (tumour stage, histologic grade, residual disease after primary surgery) had prognostic significance.[5,6,7]

The symptoms and clinical presentations in both groups of women might also give information in evaluating a patient at presentation and to recommend a particular modality of treatment, as well as to give patients a more realistic idea of their overall prognosis.

METHODS

Between 1January 1980 and 31December 2000, 258 women with epithelial ovarian malignancy were treated in the Department of Gynaecology University of Malaya Medical Centre (previously known as University Hospital Kuala Lumpur). The names of patients diagnosed with epithelial ovarian malignancy were retrieved from the histopathological examination (HPE) records in Department of Pathology University Malaya Medical Centre. Eighty-five patients were not evaluated in the study group as they were not menopausal (peri-menopausal) and their age was above 40 years old because the objective of this study was to evaluate the clinical behaviour, pathological findings, survival and prognostic factors in young women (age 40 years and below) in comparison to menopausal women with epithelial ovarian malignancy.

Menopause is the state in women's life where there have no menstrual periods for 12 consecutive months and peri-menopause is the time in a woman's life when physiological changes occur that begin the transition to menopause.

Thirty-two patients' clinical records could not be traced and they were excluded from the study. The records could not be traced as all the clinical records of more than 10 years in duration were destroyed by the hospital as the copies were kept in the form of microfilm or compact discs (CD) and there was a possibility that the records were lost during this process.

A hundred forty-one (141) patients were left for inclusion in the final analysis. They were studied by using their clinical records, that is, various forms including the microfilms, CD and histology request forms. Their presentation symptoms and clinical findings were evaluated including the results of various investigations such as ultrasound and CT scan. Their age at diagnosis, (International Federation of Gynecology and Obstetrics) (FIGO) stage, and cytology of peritoneal fluid were defined. All operative and histo-pathological findings were reviewed to classify tumour stages according to FIGO 1985.

The standard operative procedure included total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendicectomy and if judged necessary, segmental bowel resections. Lymph node sampling and peritoneal biopsies were performed in the presence of palpable abnormality. The size of the residual tumour was evaluated after surgery. Initial cytoreductive surgery was classified as optimal if no residual tumour of less than 1cm was left behind and suboptimal if residual tumour was more than 1cm. If a total abdominal hysterectomy and bilateral salpingo-oophorectomy was not performed for stage beyond 1c, the operation was considered suboptimal. A cystectomy or biopsy was also considered as suboptimal surgery.

In borderline malignant tumours, unilateral salpingo-oophorectomy was considered as optimal surgery.

Included in the study were patients (age 40 years below and menopausal) who had initial surgery elsewhere and the diagnosis were confirmed by histopathological examination and were subsequently managed at our centre.

The histolopathology was classified according to histologic type (serous, mucinous, endometriod, clear cell, others (undifferentiated, unclassified, Brenner and mixed) and grading by carcinoma and borderline malignancy. The details of the histologic grade in carcinoma cases were not evaluated as the detailed grading was not defined in most of the HPE results. Serum CA 125 was not evaluated as the test was not done in all patients especially from 1980 to 1990 as the technique was not well established. Adjuvant chemotherapy was given to patients with FIGO stage 1c onwards.

Re-laparotomy was performed for suboptimal primary surgery, recurrence of cancer or for second look- exploration.

Statistical Analysis

Survival, defined in years from primary surgery to date of death or to date of the last follow-up, was evaluated on December 2002. All data were analysed using SPSS version 11.5. Kaplan-Meier survival curves were calculated using univariate survival analysis. The log-rank test was used to compare survival curves by obtaining a x^2 value. Statistical significance was considered when $p<0.05$. Cumulative survival curves were calculated separately for age group, young and menopause, FIGO stage, peritoneal fluid cytology, histologic type and grade, extent of primary cytoreductive surgery, size of residual tumours and chemotherapy treatment for each group of patients. A multivariate proportional hazard model (Cox) was used to test the prognostic value of various features.

RESULTS

Patients' Demographic Data

The patients' mean age was 46 years (range 13-86); 67 patients were 40 years or less (range 13-40 years) and were included in young age criteria. Seventy- four were menopausal. Of the total identified numbers of patients (141 cases) treated for epithelial ovarian malignant tumours, 47.5% were young women while 32.7% were menopausal women.

Table 1 shows the clinical, stage and histo-pathological characteristics of the 141 patients with epithelial ovarian cancer and borderline malignancy.

Clinical Presentation

The symptoms observed in the young aged group and in the menopausal women were almost similar. Irrespective of the disease stage, the most common presentation was abdominal distension (78% in young and 66% in menopausal) and abdominal pain (30% in young and 34% in menopausal) in both groups. However, this was not statistically significant (p=0.1).

In young women, 39 patients (58%) had palpable mass per abdomen while for menopausal women, it was 42 patients (56%). There were only 3 patients in young women and 5 patients in menopausal women who were asymptomatic. All were in early stage (stage I and II).

In young women, 52% presented at an early stage of the disease, while in menopausal women, 54% presented at advanced stage of the disease (p value <0.05).

Ascites was observed in 16.4% of young women; in 5.9% of these patients, the ascites was massive. On the other hand, ascites was present in 36.9% of post-menopausal women; 48.1% was massive (p<0.05).

As shown in Table 1, pleural effusion was seen in 2% of young women compared to 13.6% in post menopausal women and all these patients were in the advanced stage of the disease.

Histology

The most common histological type of carcinoma in young women was mucinous cystadenocarcinoma (36%), whilst the most common type of carcinoma in post menopausal women was serous cystadenocarcinoma (47%) (p<0.05).

Management

Figures 1 and 2 show the management modalities given to both young and menopausal women. Optimal surgery was performed in 45 (67%) young aged group of patients and 49 (66%) in menopausal women. Sixteen out of 22 young aged women had suboptimal surgery as the first surgery was not done in this centre. Eighteen of them needed to undergo a second surgery in this centre to standardise or complete the procedure.

In menopausal women, 18 (52%) patients had suboptimal surgery as the first surgery was not done in this centre. Eleven patients needed to undergo a second surgery to make it complete. In 21of them, the disease was very extensive.

Table 1. Clinical, stage and histopathological characteristics of the 141 patients with epithelial ovarian malignancy

Characteristics	No. of patients (%)		*P*-value
Age	Young(n=67)	Menopause(n=74)	<0.001
Mean age (years)	31	59	
40 years and below	67 (48)		
40-50 years		13 (9)	
Above 50 years		61 (44)	
FIGO Stage			0.003
Stage I	35 (52)	16 (22)	
Stage II	10 (15)	15 (21)	
Stage III	15 (22)	25 (34)	
Stage IV	7 (10)	16(20)	
Histologic type			0.04
Serous	19 (28)	35 (47)	
Mucinous	24 (36)	11 (15)	
Endometriod	3 (5)	8 (11)	
Clear cell	4 (6)	8 (11)	
Borderline malignancy	13 (19)	8 (11)	
Others	4(6)	2 (3)	
Symptoms			0.5
Abd.distension	52 (78)	49 (66)	
Abd.pain	20 (30)	26 (34)	
Menstrual abnormality	9 (13)	9 (12)	
Weight changes	10 (15)	17 (23)	
Loss of appetite	6 (9)	11 (15)	
Bowel symptoms	1 (1)	3 (7)	
Urinary symptoms	2 (3)	5 (4)	
Others	7 (10)	18 (23)	
Asymptomatic	3 (4)	5 (7)	
Signs at presentation			0.5
Palpable mass perabdomen	39 (58)	42 (56)	
Palpable mass pervaginum	16 (24)	23 (32)	
Bilateral masses	12 (18)	21 (29)	
Unilateral mass	51 (76)	50 (67)	
Size <10cm	21 (31)	24 (33)	
Size >10cm	45 (67)	47 (63)	
Ascites	11 (16)	27 (37)	
Extraperitoneal spread			0.12
Pleural effusion	4 (2)	11 (14)	
Liver	5 (8)	4 (7)	
Multiple	1 (2)	2 (4)	
Lymph node	1 (2)	3 (3)	

Adjuvant chemotherapy was given to 52 (78%) patients in the young aged group with 61% being given several types of combination chemotherapy drugs: 29% were given cisplatinum, adriamycin and cyclophosphamide (the most common combination regime used) and 17% were given single agent platinum based chemotherapy (either carboplatin or cisplatinum). Sixty four (88%) menopausal patients were given chemotherapy, 59% were given different combination chemotherapy drugs, 45% were given cisplatinum, adriamycin

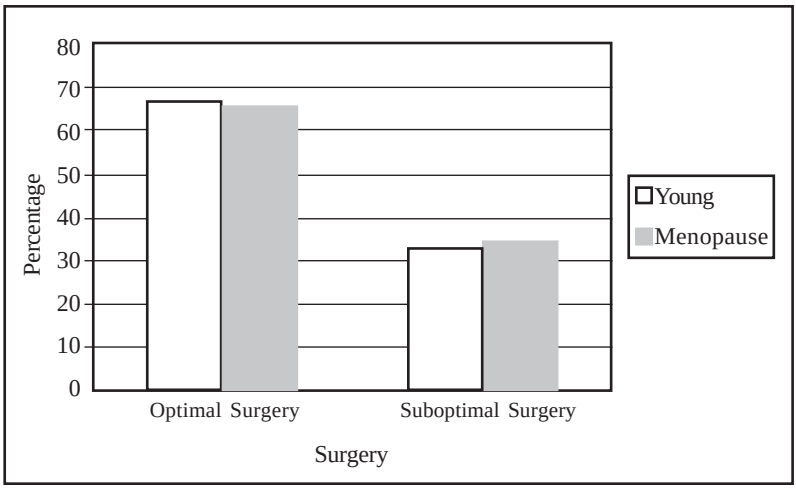

Figure 1. Young aged and menopausal women who underwent tumour debulking surgery

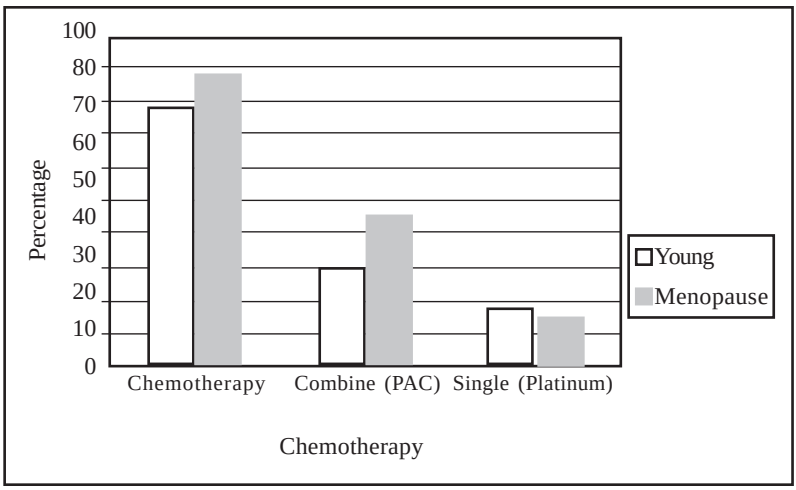

Figure 2. Young aged and menopausal women given chemotherapy

and cyclophosphamide(the most common combination regime used), 14% single platinum based agent and 8% were given chorambucil only. Chemotherapy drugs were given when disease had exceeded stage 1c.

Survival Rate and Prognostic Factors

The overall 5-year survival rate was 54% in the young and 41% in menopausal women. The 5-year survival rates were 71, 50, 40% for patients with stages I, II and III respectively in young women and the median survival period for stage IV young women was 6 months. The 5-year survival rates were 69, 47, 44% for patients with stages I, II and III respectively in post-menopausal women and median survival for stage IV disease in these women was 1 year.

Table 2 shows 5-year survival rates according to prognostic indicators after univariate analysis. Age was not a significant prognostic indicator by univariate analysis for both young and menopausal women, (*p* value=0.3). The 5-year survival was 54% in those below 40 years and 41% in menopausal women.

FIGO stage was a significant prognostic indicator by univariate analysis for both young and menopausal women (*p* value< 0.05) but in this study, there was no difference in 5-year survival rates according to the stage of the disease when comparing these two groups of women.

Peritoneal fluid cytology was a significant prognostic indicator in young aged women (*p* value <0.05) but it was not a significant indicator in menopausal women. It was also not a significant indicator when both groups were compared.

The extent of surgery was a significant indicator for both young and menopausal women ($p<0.05$) but it was not a prognostic indicator when comparing the two groups of women in this study.

The residual disease and adjuvant chemotherapy were significant prognostic factors for menopausal women if the patients with borderline malignancy were excluded (*p* value< 0.05); but it was not significant for the young group.

Survival probability curves of the young aged and menopausal women are shown in Figure 3. Overall survival for both groups of women was not statistically different (p=0.13) but after 10 years the difference became statistically significant (p<0.001).

The survival probability curves according to the stage of the disease in the young group and menopausal women are shown in Figures 4 and 5 respectively. There was a significant difference in survival probability according to the stage of disease in both young and menopausal women but when comparing both, the survival probability according to stage of the disease was not statistically significant in this study.

There was no statistical significance in survival probability when young and menopausal women were compared according to histology type. Table 2 shows the survival probability according to the optimal debulking surgery in young and menopausal women.

There was a significant difference in survival probability according to optimal debulking surgery in both young and menopausal women. However, in this study when comparing the two groups, the overall survival probability was not statistically significant (*p* value=0.3)

Table 2. Five-year survival rates according to prognostic indicators by univariate analysis

Prognostic indicators	5-year survival rate (%)			
	Young	*P*-value	Menopause	*P*-value
Age		0.3		
40 years and below	54			
41-50 years			42	
Above 50 years			41	
FIGO Stage		0.003		0.003
Stage I	71		69	
Stage II	50		47	
Stage III	40		44	
Stage IV	0		1	
Peritoneal fluid cytology		0.029		0.16
Positive	36		38	
Negative	73		57	
Histologic type		0.13		0.6
Serous	47		50	
Mucinous	50		36	
Endometriod	100		50	
Clear Cell	50		38	
Extent of surgery		0.01		0.01
Optimal	60		51	
Suboptimal/Non-optimal	40		20	
Residual tumour		0.159		0.05
Negative	60		52	
<1cm	33		33	
>1cm	38		19	
Chemotherapy		0.9		0.05
Yes	54		45	
No	53		11	

within 10 years but became statistically significant only after a 10-year period ($p < 0.01$) as shown in Figure 6.

The survival probability according to the type of chemotherapy given in young and menopausal women was not statistically significant. A multivariate analysis was performed to evaluate all factors that were significant in the univariate analysis.

In the final multivariate Cox proportional hazard model analysis, optimal tumour debulking surgery was a significant (0.25; 95% CI (0.1-0.3) p <0.01) independent prognostic factor in both young and menopausal women.

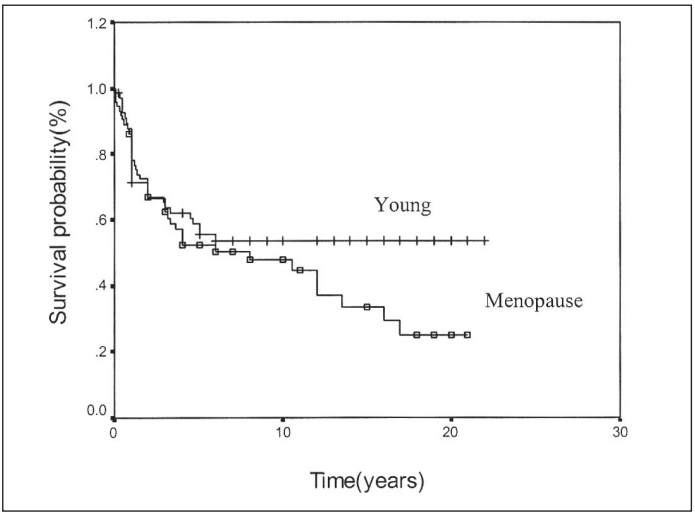

Figure 3. Survival probability in epithelial ovarian malignancy in young and menopausal women

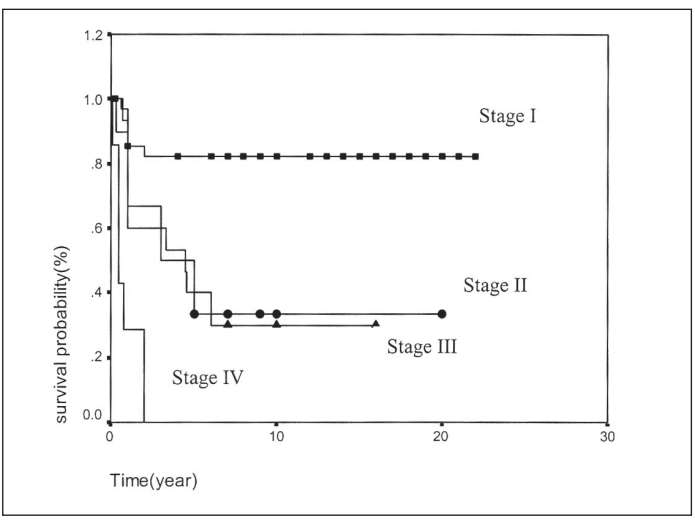

Figure 4. Survival probability according to stage of disease in young aged women

DISCUSSION

Epithelial ovarian malignancy had been extensively studied in developed countries from the epidemiological point of view, clinical presentation, histopathological examination and prognostic factors related to 5-year survival rates. [8,9,10] Similar to many other studies[10,11,12], this study also showed that ovarian malignancy was a disease of perimenopausal and

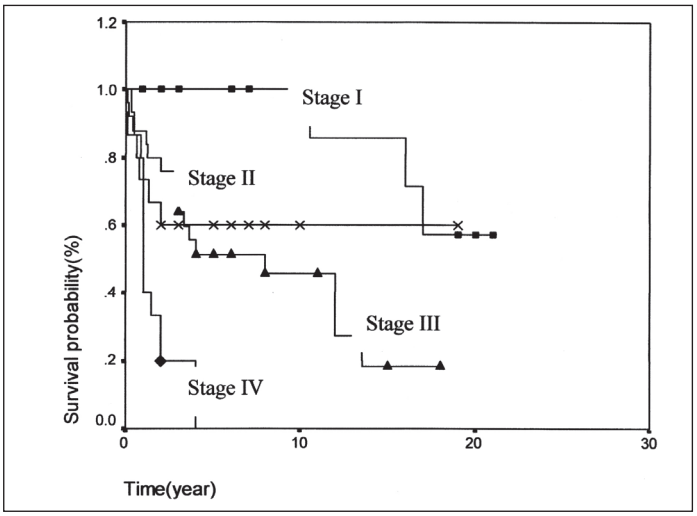

Figure 5. Survival probability according to stage of disease in menopausal women

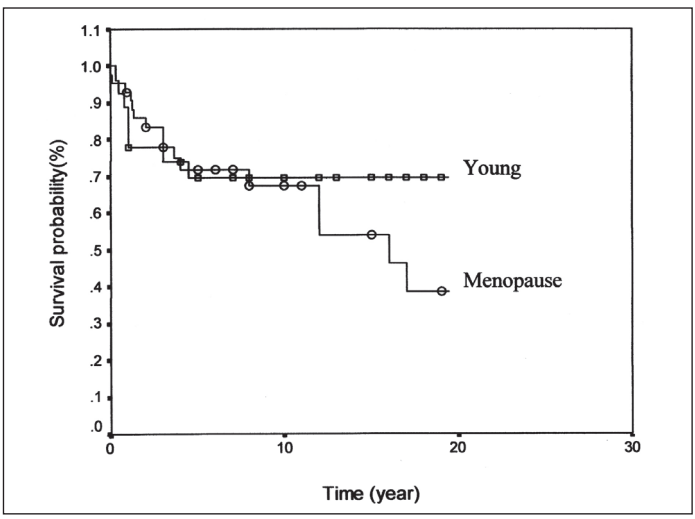

Figure 6. Survival probability of the young aged group and menopausal women according to optimal surgery

menopausal women (70% of identified cases belonged to this group). The epithelial ovarian malignancies rarely occurred before puberty and were uncommon prior to age 40.[13] Jensen & Norris, reporting on 353 cases of benign and malignant ovarian neoplasms' in females under age 20, found no epithelial malignancies among 54 neoplasms in the 0-9 years age group, 1 among 82 neoplasms in the 10 to 14 years age group, and only 7 among 217

neoplasms in the 15 to 19 year group. Five of the eight malignant epithelial ovarian tumours were classified as cystadenomas of low malignant potential (borderline malignant tumours).[14]

In this study, 40/141 patients (28%) were less than 40 years old at diagnosis, making epithelial ovarian carcinoma not uncommon in young patients in our society. The initial presentation at diagnosis was similar in the young and menopausal patients. Most of them presented with abdominal distension (78% in young and 66% in menopausal) and with palpable masses per abdomen (58% in the young and 56% in those menopausal). Only 6% were asymptomatic (3 patients in young aged group and 5 patients in menopausal group). Buka & MacFarlane reported that 66% of 223 cases had palpable ovarian masses, 18% had masses with ascites, 9% had ascites without a palpable mass and 18% had pelvic nodules.[15]

In this study most young aged patients presented at an early stage of the disease (52%) but the menopausal patients presented at an advanced stage (54%). This was probably due to the asymptomatic nature of the disease in its early stage in menopausal women. Several investigators documented that younger women with ovarian carcinoma had a better prognosis than older women. Smedley & Sikora, in reviewing of 2305 ovarian cancer patients in the United Kingdom, found that the 5-year survival rate for women aged 15 to 35 years was approximately 60%, versus 30% for older women.[16] In this study, the 5-year survival rate for young women was 54% and 41% in menopausal women. The age of patients was not a significant prognostic factor and optimal debulking surgery was an independent prognostic factor in both young and menopausal patients in this study.

FIGO stage was a prognostic indicator recognised by most authors, occasionally independent from the results of surgery and the type of chemotherapy.[17,18] In this study it was a significant prognostic factor by univariate analysis but not by multivariate analysis.

Most studies reported a low prognostic value for histologic type, probably due to a bias in analysing small samples such as the case of this study. However; serous and undifferentiated carcinoma tend classically to decrease survival. [5,6] In this study, the 5-year survival rates for serous cystadenocarcinoma were 50% and 47% in menopausal women and young aged group respectively. The prognostic significance of grade was demonstrated by several clinical studies in the 1980s.[5,6] However, grading has not been accepted enthusiastically by pathologists, because no standard is easily reproducible, and objective classification exist. Furthermore, after adjusting for FIGO stage and histologic type, the grade did not appear to be an independent factor in some recent multivariate analyses.[18,19] In University Malaya Medical Centre, grading was not defined in most of the histopathological examination. In this study, 69% of the histopathological examinations, were without any grading resulting in histologic grade details being not analysed as a prognostic indicator. Patients with borderline malignancy had a 100% five-year survival rate in young aged group and 75% in menopausal women.

The role of debulking surgery in the management of stage III epithelial ovarian cancer has been well established.[20,21,22] In this study, the extent of surgery was a significant prognostic factor in both menopausal and young aged patients. Residual disease at the end of surgery and adjuvant chemotherapy were significant prognostic factors in menopausal women but not in the young as most of the young patients presented at an early stage of the disease. A re-laparotomy for tumour debulking in the advanced stage of disease or in patients who had suboptimal surgery due to improper staging improved the 5-year survival

rate in both young and menopausal women. A meta-analysis of prognostic factors has been conducted to identify the different variables cited in prospective and randomised studies.[10]

In this study, 77.6% of young and 87.6% of menopausal patients had received chemotherapy. Patients who were not treated by adjuvant chemotherapy belonged either to a very bad prognostic group with short-term death or to a very good prognosis such as stage Ia or borderline malignancy tumour where adjuvant treatment was not indicated.

Chemotherapy including cisplatin as initial treatment with a residual tumour mass of less than 2 cm prior to therapy was found to be the only factors of prognostic relevance in the multivariate model.[10] However, the impact of maximum cytoreductive surgery in comparison with platinum-based combination chemotherapy has become controversial. In a meta-analysis of 58 suitable studies encompassing 6962 patients, maximum cytoreductive surgery was associated with only a small improvement in median survival time (+4.1%,95% CI (-0.6 to 9.1%), P=0.089), while platinum-containing chemotherapy improved median survival time substantially (+53%, 95% CI (35 to 73%), P<0.001). [23] Progress in chemotherapy has certainly contributed to the increased survival rate observed during the past 20 years, an improvement of 20% between 1978 and 1989 in women under 65.[24,25]

The limitation of this study was the inability to get all the information of patients in the earlier phase as their original case notes/records had already been destroyed. The clinical summary given in the histopathological examination request forms was inadequate. It would have been useful if the peri-menopausal women were also evaluated for comparison as the majority of epithelial ovarian malignancy occured in this age group. However, in this study, this group was not evaluated due to difficulty in retrieving clinical information. A prospective study should be continued for the next few years in the gynaecology oncology centre to obtain clinical and management details without missing relevant data.

CONCLUSION

There are limited reports in the literature comparing the outcomes of younger and menopausal women with epithelial ovarian malignancy treated by any gynaecology oncologist from a single academic institution. Our results showed that the proportion of epithelial ovarian malignancies in young aged women was 30% from the total identified number of patients (141 identifiable cases) treated for epithelial ovarian malignancy. The symptoms and signs at presentation were similar in menopausal women but the young aged women presented at an early stage of disease. Although different types of carcinoma occurred in the young aged and menopausal women, the stage of the disease at presentation and optimal debulking surgery were two important prognostic factors (not the patient's age at diagnosis) to ensure better survival rate of the patients.

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