Comparison of outcomes in epithelial ovarian cancer, fallopian tube cancer and primary peritoneal serous carcinoma between a multidisciplinary and a single-speciality centre

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ABSTRACT

Introduction: Epithelial ovarian cancer (EOC) is the fourth most common malignancy among Malaysian women. This study aims to evaluate the outcomes of EOC, fallopian tube cancer and primary peritoneal serous carcinoma (PPSC) between a centre managed by both clinical oncologists and gynaecologic oncologists, Institut Kanser Negara (IKN) and a centre managed solely by gynaecologic oncologists, Hospital Ampang (HA).

Materials and Methods: This retrospective cohort study involved data review of all the newly diagnosed patients with EOC, fallopian tube cancer and PPSC who received treatment in IKN and HA from January 2015 to December 2019, with follow-up continuing until December 2022. The primary outcome is overall survival (OS) and the secondary outcome is progression free survival (PFS) rates; estimated using the Kaplan-Meier method and compared using the log-rank test. Another secondary outcome is to determine the prognostic factors affecting the OS of patients from these two cohorts using Cox regression analysis.

Results: A total of 256 patients from both centres were recruited (106 and 150 patients from IKN and HA respectively) and at the time of diagnosis, more than half of the patients were diagnosed with advanced stage disease (67.5% and 62% from IKN and HA respectively). The median OS for patients with EOC was significantly longer for HA compared to IKN (69 months vs 39 months, p < 0.042). There was no significant difference in the median PFS for both centres. Furthermore, when the comparison was made based on the disease staging, there was no difference in the median OS and median PFS. Multivariate analysis identified that patients aged between 41 and 60 years (Hazard ratio [HR]: 2.83; 95% CI: 1.11, 7.25, p = 0.030), patients with medical illness (HR 1.51; 95% CI: 1.04, 2.21, p = 0.033), patients with advanced-stage disease (HR: 3.63; 95% CI: 2.20, 6.00, p < 0.001) and patients with ECOG ≥ 1 (HR: 2.00; 95%CI: 1.38, 2.91, p < 0.001) as independent risk factors for adverse outcome. Meanwhile, optimal surgery is found to be a protective factor (HR 0.60; 95% CI: 0.41, 0.89, p = 0.011). Patients with optimal surgery had reduced the risk of adverse outcome.

Conclusion: Our findings confirmed that the median OS was significantly longer for patients with EOC in HA compared to IKN. However, there was no significant difference in the median OS based on the disease staging; therefore, we could not establish the non-inferiority outcome between the two centres. Furthermore, there was no significant difference in median PFS for both centres. This could be due to small sample size to be able to detect any difference. In addition, it could also be contributed by the different treatment options available and unequal volume of patients treated in both centres. Thus, further study with larger sample size and longer time period is needed to provide better guidance and treatments for the patients.

KEYWORDS:
Epithelial ovarian cancer, fallopian tube cancer, primary peritoneal serous carcinoma, clinical oncologist, gynaecologic oncologist

INTRODUCTION

Epithelial cancers of the ovary and fallopian tube, as well as primary peritoneal serous carcinoma (PPSC) have been shown to share similar clinical characteristics and behaviour. Therefore, they are frequently combined together and defined as epithelial ovarian cancer (EOC) in clinical trials and clinical practice.[1]

According to Malaysia national cancer registry, ovarian cancer is ranked as the fourth most common cancer among women in Malaysia, accounting for 5.6% of all female cancer cases; and among these patients, more than half (56.3%) were detected at an advanced stage (III and IV).[2] However, the registry report does not provide any information on the survival outcome of these patients. From the literature review, there is no published data or information available regarding the treatment outcome for patients with EOC in Malaysia. Currently in Malaysia, patients with EOC are being treated either by both clinical oncologists and gynaecologic oncologists or solely by gynaecologic oncologists, based on the services available at the respective centres (both in government and private centres).

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At the present moment, oncology services in government hospitals are mainly based in a number of state hospitals and university hospitals whilst gynaecologic oncology services are more widely available in all states and most major hospitals (including university hospitals).

This study is designed to evaluate the outcomes of EOC, fallopian tube cancer and PPSC between a centre managed by both clinical oncologists and gynaecologic oncologists, Institut Kanser Negara (IKN) versus a centre managed solely by gynaecologic oncologists, Hospital Ampang (HA).

The primary endpoint of this study is to compare the overall survival (OS) between the two centres (OS is calculated from the date of treatment initiation by the clinicians to the time of death from any cause). The secondary endpoints are to compare the progression-free survival (PFS) as calculated from date of treatment initiation by the clinicians to the time clinically defined disease progression or death from any cause, whichever occurred first; and to determine the prognostic factors affecting the OS of patients with EOC from these two cohorts.

The hypothesis of this study is that there is no difference in the outcome of EOC patients treated in both centres despite having different management structures. If the hypothesis is supported by the study findings, it could potentially streamline the patient care by allowing flexibility in choosing treatment centres based on factors such as accessibility or patient preference without compromising the clinical outcomes.

MATERIALS AND METHODS

Approval from the Medical Research and Ethics Committee (MREC) was obtained prior to the commencement of this study (NMRR ID-22-02823-XFS).

Study Design and Participants

This retrospective cohort study involved data review of all the newly diagnosed patients with EOC, fallopian tube cancer and PPSC who received treatment in IKN and HA from January 2015 to December 2019, with follow-up continuing until December 2022.

The eligible patients were aged 18 and older with newly diagnosed (histologically confirmed) EOC, fallopian tube cancer and PPSC that underwent surgical procedures, received chemotherapy and continued follow up in IKN and HA from the aforementioned dates. Exclusion criteria encompassed patients with borderline ovarian tumour, non-epithelial ovarian cancer, synchronous tumour or more than one primary cancer and those who did not complete the initial treatment (surgery with or without chemotherapy) at the respective centres.

Statistical Analyses

Continuous variables are expressed as mean ± standard deviations or as medians ± interquartile ranges (IQR) following normality testing, whereas categorical variables are presented as frequencies and percentages. Data were analysed using IBM SPSS statistics version 26. Survival was estimated using the Kaplan-Meier method and was compared using the log-rank test (for both OS and PFS). Statistical significance was set at two-sided $p < 0.05$. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The independent effects of the clinical prognostic factors on overall survival were analysed in multivariate Cox regression analysis.

RESULTS

Patient Demographics

Patient demographic characteristics are described in Table I. A total of 404 patient data records were reviewed (186 and 218 patients from IKN and HA, respectively) and 256 patients met the selection criteria (106 and 150 patients from IKN and HA, respectively) aged 21 to 84 years (mean 54.2 ± 11.7). The performance status was classified based on the Eastern Cooperative Oncology Group (ECOG) score, and the majority of the patients had ECOG 0 (59.4% from IKN and 72.7% from HA). One patient had ECOG score 2 from HA and for IKN, one patient had ECOG score 2 and one patient had ECOG score 3. Among all the patients, 53.8% from IKN and 47.3% from HA were recorded to have medical illness.

EOC is further subclassified into high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), endometrioid, clear cell, mucinous, mixed carcinoma, undifferentiated and dedifferentiated carcinoma. HGSC comprises the highest number of histological subtypes in both centres (43.4% and 54% from IKN and HA respectively). For HGSC, the ovary was the most common site of origin. All patients were staged based on 2014 FIGO staging classification and at the time of diagnosis, more than half of the patients were diagnosed with advanced stage disease (67.5% and 62% from IKN and HA, respectively). The median follow-up period was 39 months (IQR 46.5) for IKN and 46 months (IQR 40.5) for HA. Patients' status at last follow-up is also included in Table I. For patients who have defaulted, their status (alive or dead) was confirmed via phone or through National Registration Department.

The surgery type and treatment regime received by patients are depicted in Table II. All patients had undergone some form of surgery, the majority of them having had a total abdominal hysterectomy with bilateral salphingo-opherectomy (TAHBSO), omentectomy with or without pelvic and/or para-aortic lymphadenectomy (PL/PAL) and also with or without tumour debulking (88.7% and 87.4% from IKN and HA, respectively). A small number of patients opted for fertility sparing surgery i.e., unilateral salphingo-opherectomy and omentectomy, with or without PL/PAL (8.5% and 9.3% from IKN and HA, respectively). About 72.6% patients from IKN and 80% patients from HA had optimal surgery (defined as residual disease of less than 1 cm).

More than 80.0% patients from both centres received first line chemotherapy either as neoadjuvant or adjuvant treatment. For patients with early-stage disease, 74.4% patients from IKN and 75.4% patients from HA, received adjuvant chemotherapy. For patients with advanced disease, 32.8% patients from IKN and 57.0% patients from HA received neoadjuvant chemotherapy prior to surgical treatment, while

Table I: Demographic, clinicopathologic, and patients' outcome characteristics for the entire patient cohorts and separately for Institut Kanser Negara versus Hospital Ampang

Characteristics	All patients, (n = 256) n (%)	IKN (n = 106) n (%)	HA (n = 256) n (%)	p-value
Age, mean (SD)	54.2 (11.7)	52.9 (11.1)	55.1 (12.0)	0.130[a]
ECOG score				
0	172 (67.2)	63 (59.4)	109 (72.7)	0.026
≥ 1	84 (32.8)	43 (40.6)	41 (27.3)	
Medical illness				
Yes	128 (50.0)	57 (53.8)	71 (47.3)	0.310
No	128 (50.0)	49 (46.2)	79 (52.7)	
Histology				
HGSC	127 (49.6)	46 (43.4)	81 (54.0)	0.076[b]
LGSC	6 (2.3)	4 (3.8)	2 (1.3)	
Endometrioid	33 (12.9)	12 (11.3)	21 (14.0)	
Clear cell	59 (23.0)	27 (25.5)	32 (21.3)	
Mucinous	25 (9.)	12 (11.3)	13 (8.7)	
Mixed carcinoma	4 (1.6)	4 (3.8)	0 (0.0)	
Undifferentiated	1 (0.4)	1 (0.9)	0 (0.0)	
Dedifferentiated	1 (0.4)	0 (0.0)	1 (0.7)	
HGSC -organ**, n = 127		n = 46	n = 81	
Ovary	98 (77.2)	35 (76.0)	63 (77.8)	0.005
Fallopian tube	15 (11.8)	8 (17.5)	7 (8.6)	
PPSC	14 (11.0)	3 (6.5)	11 (13.6)	
FIGO staging				
Early				0.485
Stage 1A	16 (6.3)	6 (5.7)	10 (6.7)	
Stage 1C	58 (22.7)	25 (23.6)	33 (22.0)	
Stage 2	21 (8.2)	7 (6.6)	14 (9.3)	
Advanced				
Stage 3	126 (49.2)	49 (46.2)	77 (51.3)	
Stage 4	35 (13.7)	19 (17.9)	16 (10.7)	
Status at last follow-up				
Died	130 (50.8)	61 (57.5)	69 (46.0)	0.132[b]
Alive	95 (37.1)	37 (34.9)	58 (38.7)	
Defaulted	28 (10.9)	8 (7.5)	20 (13.3)	
Unknown	3 (1.2)	0 (0.0)	3 (2.0)	
Follow up time (months)				
Overall, mean (SD)	42.1 (24.7)			
Median (interquartile range)		39.0 (46.5)	46.0 (40.5)	0.100[c]

Values are presented as number (percentage) unless otherwise indicated; SD: standard deviation; n: patient number; HA: Hospital Ampang, IKN: InstitutKanser Negara, ECOG: Eastern Cooperative Oncology Group, HGSC: High grade serous carcinoma, LGSC: Low grade serous carcinoma, PPSC: Primary peritoneal serous carcinoma; aIndependent t-test; b Fisher's exact test; otherwise by Pearson Chi-square test; cMann-Whitney test; **Denominator is the total no of patients in the subgroup; Bold P-values indicate statistically significant.

the remaining patients with advanced disease received adjuvant chemotherapy after primary surgery were 50.8% and 38.7% from IKN and HA, respectively. The majority of patients received platinum-based doublet (i.e., carboplatin and paclitaxel) as the first line chemotherapy. After primary surgery, the average time for patients to receive the first dose of adjuvant chemotherapy was 5 weeks and 8 weeks for HA and IKN, respectively.

About 68.9% and 61.3% patients had recurrent disease or disease progression from IKN and HA, respectively. The treatment following the events for these patients were determined by the assessment and discretion of the attending doctors, after which the majority of the patients received chemotherapy (61.6% and 78.2% from IKN and HA, respectively). The type and course of chemotherapy received by patients were determined by multiple factors, which include the duration from the previous line of chemotherapy (platinum sensitivity), side effects from previous chemotherapy exposure, clinical symptoms and performance status. The drugs used include single agent regime such as carboplatin, gemcitabine, pegylated liposomal doxorubicin (Caelyx) or double agents regime such as carboplatin/paclitaxel, carboplatin/gemcitabine, carboplatin/Caelyx and cisplatin/paclitaxel. Other treatment modalities offered to a small number of patients with recurrent or progressive disease include secondary surgery, poly ADP-ribose polymerase inhibitors (PARP-i), radiotherapy (for metastatic extra abdominal disease such as the brain, spine, thorax etc) and transarterial chemoembolisation (TACE). Another additional treatment received patients with advanced disease in HA (10%) was bevacizumab (BEV) which was used in combination with chemotherapy and continued as maintenance therapy in the first line setting or recurrent disease.

Survival Outcomes

The Kaplan-Meier curves depicting median OS and median PFS between IKN and HA are illustrated in Figure 1. The comparison was made between all patients, early stage and

Table II: Surgery and treatment regime for Institut Kanser Negara versus Hospital Ampang

Characteristics		IKN (n = 106) n (%)	HA (n = 150) n (%)	p-value
Surgery type				
TAHBSO, Omentectomy +/- PL/PAL, tumour debulking		94 (88.7)	131 (87.4)	0.864
SO, omentectomy +/- PL/PAL		9 (8.5)	14 (9.3)	
Completion surgery, omentectomy +/- PL/PAL		2 (1.9)	5 (3.3)	
Laparotomy and biopsy		1 (0.9)	0 (0.0)	
Surgery outcome				
Optimal		77 (72.6)	120 (80.0)	0.168
Suboptimal		29 (27.4)	30 (20.0)	
Chemotherapy regime				
Early stage **, n = 95		n = 38	n = 57	
Adjuvant	NA	6 (15.4)	9 (15.8)	0.954b
	Yes	29 (74.4)	43 (75.4)	
	Refused	4 (10.3)	5 (8.8)	
Advanced stage		n = 68	n = 93	
Neoadjuvant**, n = 77		25 (36.8)	52 (55.9)	0.006
Adjuvant**, n = 84				
	Yes	34 (50.0)	36 (38.7)	
	Refused	7 (10.3)	4 (4.3)	
	Other****	2 (2.9)	1 (1.1)	
Type of chemotherapy**, n = 217		n = 86	n = 131	
Carboplatin		19 (22.1)	18 (13.7)	0.110
Carboplatin + Paclitaxel		67 (77.9)	113 (86.3)	
Recurrent/disease progression**		n = 73	n = 92	
2nd line***		45 (61.6)	72 (78.3)	Nilc
3rd line***		24 (32.9)	27 (29.3)	
4th line or higher***		11 (15.1)	14 (15.2)	
Secondary surgery***		1 (1.4)	14 (15.2)	
Yes**		n =1	n = 14	
Optimal		1 (100.0)	11 (78.6)	> 0.950b
Suboptimal		0 (0.0)	3 (21.4)	
Other treatment				
PARP-I, n = 9		0 (0.0)	9 (6.0)	Nilc
Radiotherapy, n = 8		3 (2.8)	5 (3.3)	
TACE, n = 1		1(0.9)	0 (0.0)	
BEV, n = 15		0 (0.0)	15 (10.0)	

HA: Hospital Ampang, IKN: Institut Kanser Negara ; TAHBSO: Total abdominal hysterectomy bilateral salpingo-oophorectomy, SO: salpingo-oophorectomy, PL: pelvic lymphadenectomy; PAL: para-aortic lymphadenectomy, NA: Not applicable, PARP-i: PARP inhibitor, BEV: Bevacizumab, TACE: Transarterialchemoembolisation; n: patient number; a Independent t-test; b Fisher's exact test; otherwise by Pearson Chi-square test;cNot comparing for the differences; **Denominator is the total no of patients in the subgroup; ***Total number is different as the same patient might go for subsequent line of therapy; Patient number and percentages based on total number of cases for recurrent disease in both centres; ****Patients died before the initiation of chemotherapy; Bold P-values indicate statistically significant.

advanced stage diseases from each centre. The median OS for all patients was significantly longer for HA compared to IKN (69 months vs 39 months, $p < 0.042$) (Figure 1(A) and Table III). However, when the comparison was made according to the stage of disease, there was no significant difference of median OS between these two centres (Figure 1 (B, C) and Table III). For the median PFS, there were no significant difference between IKN and HA for all patients and for disease staging as presented in Figure 1(D-F) and Table III.

Prognostic Factors

Table IV depicted the prognostic factors for OS of all patients with EOC from the two cohorts using univariate and multivariate Cox regression analyses. During the multivariate analysis, all except, neoadjuvant chemotherapy variables, were significant in predicting the OS in this study. Patients aged between 41 and 60 years old had 2.8 times higher risk of dying compared to age ≤ 40 years old (HR: 2.83; 95% CI: 1.11, 7.25, $p = 0.030$), patients with medical illness had 51% higher risk of dying compared to those without medical illness (HR 1.51; 95% CI: 1.04, 2.21, $p = 0.033$), patients with advanced-stage disease had 3.6 times higher risk of dying compared to those with early-stage disease (HR: 3.63; 95% CI: 2.20, 6.00, $p < 0.001$) and patients with ECOG ≥ 1 had 2 times higher risk of dying compare to those with ECOG = 0 (HR: 2.00; 95% CI: 1.38, 2.91, $p < 0.001$). Meanwhile, optimal surgery is found to be a protective factor as patients with optimal surgery had reduced risk of dying by 40% compared to those with suboptimal surgery (HR 0.60; 95% CI: 0.41, 0.89, $p = 0.011$)

DISCUSSION

Hospital Ampang and IKN are both government hospitals which are located in urban areas and the services offered are largely subsidised. The gynaecologic oncology service was

Table IV: Prognostic factors for overall survival of ovarian cancer (EOC), fallopian tube cancer, and primary peritoneal serous carcinoma (PPSC) by univariate and multivariate Cox regression analyses

Variables	Univariate		Multivariate	
	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age group				
≤ 40 years	1 (Reference)		1 (Reference)	
41 – 60 years	3.80 (1.54, 9.41)	0.004	2.83 (1.11, 7.25)	0.030
≥ 61 years	5.97 (2.38, 15.00)	< 0.001	2.60 (0.97, 6.95)	0.056
Medical illness				
No	1 (Reference)		1 (Reference)	
Yes	2.15 (1.51, 3.06)	< 0.001	1.51 (1.04, 2.21)	0.033
Optimal surgery*				
No	1 (Reference)			
Yes	0.319 (0.22, 0.46)	< 0.001	0.60 (0.41, 0.89)	0.011
Neoadjuvant chemotherapy				
No	1 (Reference)			
Yes	2.09 (1.47, 2.96)	< 0.001	NS	NS
Figo staging				
Early disease	1 (Reference)		1 (Reference)	
Advanced disease	5.09 (3.12, 8.30)	< 0.001	3.63 (2.20, 6.00)	< 0.001
ECOG				
0	1 (Reference)		1 (Reference)	
≥ 1	2.91 (2.05, 4.11)	< 0.001	2.00 (1.38, 2.91)	< 0.001

HR: Hazard ratio; CI: Confidence interval; Backward stepwise was applied; Two-way interaction and multicollinearity problem were checked and not detected. Proportional hazard assumptions were fulfilled (hazard function plot and hazard function plots were checked); Bold P-values indicate statistically significant; NS: Not selected during multivariable variable selection; *protective factor.

Table III: Comparison of median overall survival and progression free survival time between IKN and HA

Characteristics	Median overall survival time (95% CI)		Log-rank statistics (df)	p-value	Median progression free survival time (df)		Log-Rank statistics	p-value
	IKN	HA			IKN	HA		
All patients, n = 256	39.00 (21.58, 56.42)	69.00 (52.67, 85.33)	4.13 (1)	0.042	22.00 (8.50, 35.50)	Nil (Nil, Nil)	3.79 (1)	0.052
Early disease, n = 95	Nil (Nil, Nil)	Nil (Nil, Nil)	1.36 (1)	0.244	Nil (Nil, Nil)	Nil (Nil, Nil)	1.89 (1)	0.241
Advanced disease, n = 161	27.00 (18.92, 35.08)	32.00 (19.25, 44.76)	2.85 (1)	0.092	12.00 (10.79, 13.21)	18.00 (14.88, 21.12)	2.97 (1)	0.085

CI: Confidence interval; Nil: Median survival time not reach; Bold p-values indicate statistically significant.

established in Hospital Ampang in the year of 2009 while for IKN, the service only started in 2015. This explains the difference in the number of patients between the two centres as IKN only started to receive more referrals from other health centres in the later years of this study. Even though IKN was a new centre at that point of time, the departments were established and led by experienced clinical consultants. This would reduce the risk of comparative bias between the two centres.

In addition to that, patients who have had surgeries in other health centres and referred directly to the clinical oncologists were also excluded from this study as it was difficult to ascertain whether or not a complete surgical staging had been performed by trained gynaecologic oncologists. This is a paramount factor in subsequent staging and management as even in apparent stage I EOC, comprehensive surgical staging is found to upstage one third of the patients; and one third of these upstaged patients had altered treatment plans.[3] The outcomes for patients with early stage EOC have also been shown to improve if the surgery is performed by gynaecologic oncologists.[4] By having only patients that were operated from these two centres as one of the inclusion criteria of this study, the homogeneity of the subjects could be preserved.

Similar to published data, the majority of the patients in these two centres had advanced disease at diagnosis.[5] The disease was surgically staged based on 2014 FIGO staging and the operative findings determined the precise histologic diagnosis and therefore the prognosis.[6] In terms of the histological subtype, high grade serous carcinoma (HGSC) is the most common subtype encountered in this study, followed by clear cell, endometrioid, mucinous, low grade serous carcinoma and others. The distribution is also in line with other published data.[6,7] Almost all patients in this cohort had good performance score prior to surgery, except for one patient from IKN who had ECOG 3 which was due to her underlying physical disability.

Patients with medical illness as comorbidities are found to have higher risk of poor outcomes. In this study, the medical illness encompasses mostly non-communicable diseases such as hypertension, diabetes, dyslipidaemia, chronic kidney

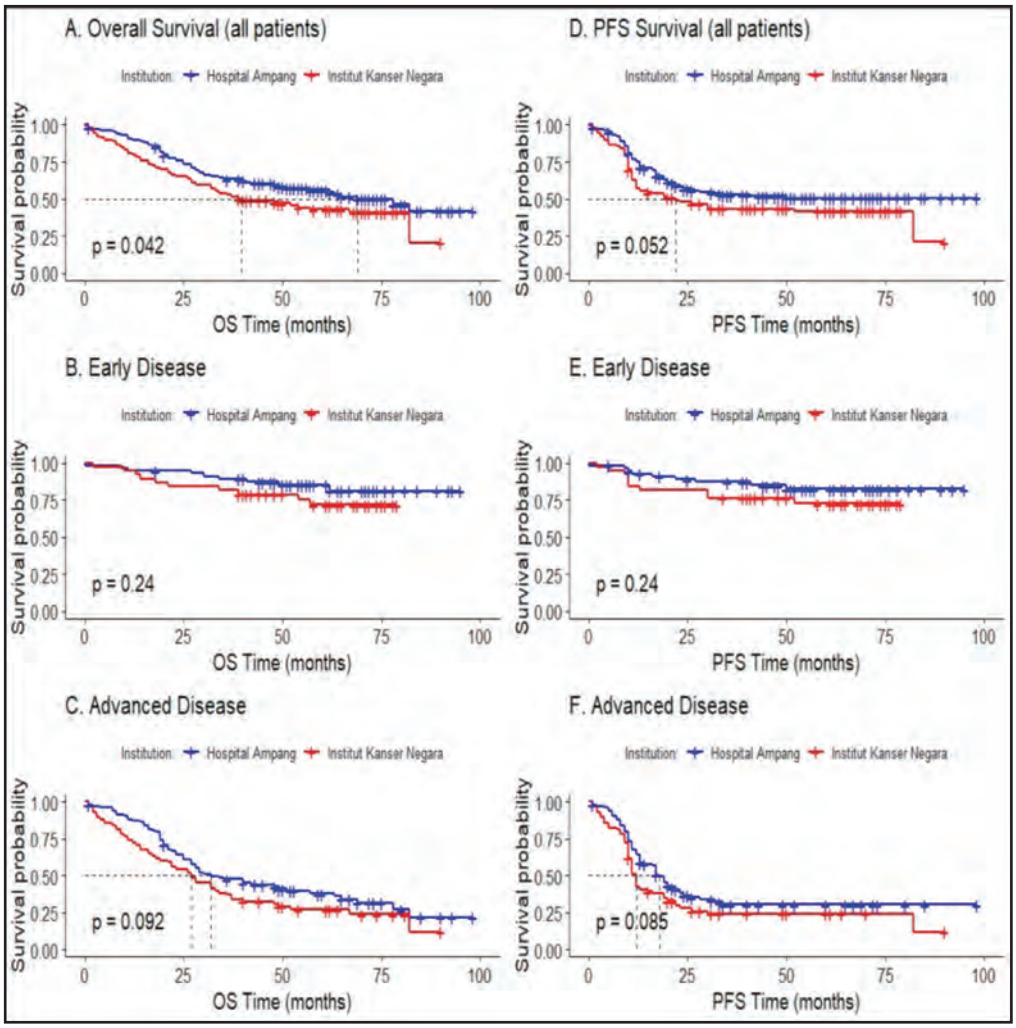

Fig. 1: Kaplan Meier curves for OS (A-C) and PFS (D-F) based on two institutions. (A) Probability of OS according to the institutions (all patients), (B) Probability of OS according to the early-stage disease patients, (C) Probability of OS according to the of advanced stage disease patients, (D) Probability of PFS according to the institutions (all patients), (E) Probability of PFS according to the early-stage disease patients, and (F) Probability of PFS according to the advanced stage disease patients.

disease, heart disease, bronchial asthma, autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis), cerebrovascular disease etc. A few patients had communicable disease such as active tuberculosis, HIV and hepatitis carrier status. The individual's medical illness and overall comorbidity burden has an impact on the cancer outcome.[8] This is in line with the study finding in which patients with medical illness had 51.0% higher risk of dying compared to those without medical illness (Table IV).

A complete cytoreduction surgery by gynaecologic oncologists has been established to be one of the paramount treatments in EOC.[9,10] For apparent early stage ovarian cancer, primary surgery with systematic pelvic and para-aortic lymphadenectomy is advocated.[11,12] Meanwhile, in the case of advanced EOC, the cytoreduction surgery can be performed as primary surgery followed by adjuvant chemotherapy or as interval debulking surgery (IDS) in between chemotherapy. Trials have shown similar outcomes with respect to OS and PFS for both groups, but with better perioperative outcomes for the patients who received neoadjuvant chemotherapy and IDS.[13,14] With regards to systematic pelvic and paraaortic lymphadenectomy in patients with advanced EOC, studies have demonstrated that routine systemic pelvic and para aortic lymphadenectomy does not improve overall survival and results in increased perioperative morbidity.[15,16] In this study, majority of patients from both centres had undergone cytoreductive surgery with comparable optimal outcome (p = 0.168). With regard to patients with advanced disease, more patients in Hospital Ampang received neoadjuvant chemotherapy prior to surgery compared to IKN (p = 0.006) (Table II). However this did not change the median OS and PFS of the two groups, which concurs with the available evidence.

Chemotherapy has also been established as an integral part in the treatment of EOC. However, this is an exception for those with EOC confined to the ovary (stage IA and IB) and/or well differentiated (grade 1) tumours as the survival of this group is at least 90% following surgery alone.[17,18] For

high-risk early stage disease, defined as Stage IC or stage II, clear cell histology, and high grade tumour (grade 3), systemic reviews have shown the benefits of adjuvant chemotherapy in terms of PFS and OS.[19,20] The preferred choice of chemotherapy is a platinum-based doublet (i.e., carboplatin and paclitaxel) and this is based upon its efficacy in the adjuvant therapy of women with advanced stage EOC.[21,22]

The use of platinum-based doublet (carboplatin and paclitaxel) in adjuvant setting for advanced stage EOC has been shown to improve the OS and PFS.[23,24] Based on Table II, all patients that required chemotherapy received at least a platinum-based drug (carboplatin) and the majority of them received a platinum-based doublet drugs. The difference in the average time taken for patients to receive adjuvant chemotherapy following surgery between the two centres did not appear to affect the comparison median OS and PFS of patients with early and advance disease EOC (Figure 1). The addition of BEV, a vascular endothelial growth factor inhibitor as part of the front-line treatment for advanced EOC was evaluated in two trials (GOG 218 and ICON 7). Their post hoc subgroup analysis indicated statistically significant OS benefit in patients with stage IV disease in GOG 218 and in patients at high risk of progression in the ICON 7 trial.[25,26] Despite the combination of optimal surgery and the use of standard first line chemotherapy, approximately 70% of patients will relapse within 3 years.[27,28] The subsequent platinum-based treatments would lead to disease control for shorter periods.[29,30] The treatment approach for relapsed disease would be based on the multiple factors which include the performance status, clinical symptoms, site of metastasis and response towards platinum (the time elapsed between the completion of treatment and the detection of relapse; platinum sensitive are those who relapsed 6 months or longer after initial treatment while platinum resistance are those who relapsed in less than 6 months).

Patients with platinum-sensitive recurrent EOC could be offered secondary cytoreduction (if complete gross resection is predicted to be achievable) plus chemotherapy with the aim to prolong survival.[31] However this option is limited to selected group of patients especially to those with isolated nodal disease or isolated peritoneal disease. Patients with peritoneal carcinomatosis are mostly treated with chemotherapy with or without BEV. In most cases, combination therapy is preferred to single agent chemotherapy as it is associated with superior objective response and PFS.[32,33] There are a few combination options which include carboplatin plus paclitaxel, carboplatin plus gemcitabine and carboplatin plus pegylated liposomal doxorubicin.[34-36] However there is no ideal combination therapy and the use of single agent chemotherapy might be preferred for medically frail patients or those who had hypersensitivity reaction or persistent toxicities from previous treatment.

The use of PARP-i as maintenance therapy after platinum-based therapy in the first line and recurrent setting for patients with BRCA mutations and homologous recombinant deficiency (HRD) has been well established to improve OS and PFS.[37-40] At the time of this writing, Olaparib is the only PARP-i available in Malaysia but because of its high price, the medication is not subsidised. Due to this, the use of PARP-i is very limited in government hospital setting and the uptake for BRCA and HRD testing is still low as it is also not subsidised. The comparison between the two centres showed that both centres are able to provide surgery and chemotherapy as per recommendations; however, both centres are not able to provide routine maintenance therapy of advanced ovarian cancer such as BEV and PARP-i due to cost and availability of these drugs in the government settings.

We noted that when we stratified based on disease staging, there was no significant difference in the median OS and PFS. The discrepancy between median OS for all patients and median OS based on the disease stage could be contributed by the additional treatment received by patients in HA i.e., more patients underwent secondary surgery (15.2% vs 1.4%) and more patients received BEV (10.0% vs 0.0%) and poly (ADP-ribose) polymerase inhibitors (PARP-i) (6.0% vs 0.0%). Another contributing factor would be small sample size and unequal number of patients between the two centres which could have also contributed to the different outcomes of this study. Suggestions for future studies include a longer study period to obtain a larger sample size and the recruitment of patients could be started in the later years when the gynaecologic oncology service in IKN has been well established. Moreover, further study could be conducted looking into patients' preferences and outcomes in terms of quality of life between these two centres.

CONCLUSION

Our findings confirmed that the median overall survival (OS) was significantly longer for patients with epithelial ovarian cancer (EOC) in Hospital Ampang (HA) compared to Institut Kanser Negara (IKN). However, there was no significant difference in the median OS based on the disease staging; therefore, we could not establish the non-inferiority outcome between the two centres. Furthermore, there was no significant difference in median PFS for both centres. This could be due to small sample size to be able to detect any difference. In addition, it could also be contributed by the different treatment options available and unequal volume of patients treated in both centres. Thus, further study with larger sample size and longer time period is needed to provide better guidance and treatments for the patients. As the majority of patients present in advanced stage of disease, the use of PARP-i as maintenance in those with BRCA mutations and HRD could prove to be beneficial in the improvement of the OS and PFS of EOC patients in Malaysia; thus, strategies to ensure the availability of genetic testing and the medications should be implemented in the public hospital settings.

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CONFLICT OF INTEREST
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