Do Chinese older adults with epithelial ovarian cancer survive a poorer prognosis?

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Research Article

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Abstract

Background: The risk of suffering epithelial ovarian cancer (EOC) for women increasing with age evidently, while the prognosis of older EOC patients remain unclear. Against the backdrop of the accelerate aging process in China, this paper investigates whether the older EOC patients have a lower overall survival probability than the younger patients based on the sample of ethnic Chinese population.

Methods: A total of 323 ethnic Chinese patients diagnosed as epithelial ovarian cancer were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. We compared the overall survival probability between the younger group (<65 years) and the older patients group (≥ 65 years). Survival curves were drawn using the Kaplan-Meier method, comparisons among different subgroups were evaluated using log-rank tests, and independent prognostic factors were identified by univariate and multivariate Cox regression analyses.

Results: 61 patients were (18.9 %) in the older patients group and 262 (81.1%) in the younger group. The distribution patterns between two groups were significantly different with regard to marital status, histologic type and FIGO stage. The median overall survival (OS) was significantly longer in the younger group than the older patients group (not reached vs median 50 months, $p < 0.05$). Univariate Cox regression analysis showed that age, as well as primary tumor laterality, tumor histological grading, histology, FIGO stage, surgical range and the number of lymph nodes dissected were significantly associated with OS. However, the multivariate analysis demonstrated that the age no longer had an independent impact on overall survival once other confounding variables were controlled (HR: 1.334, $P = 0.226$). Only primary tumor laterality, histology, and FIGO stage, were independent risk factors (HR: 1.885, $P = 0.008$; HR: 2.003, $P = 0.035$; HR: 4.006, $P = 0.008$ and HR: 5.272, $P < 0.001$; HR: 1.885, $P = 0.008$). Moreover, the number of lymph nodes dissected more than 10 was a protective factor (HR: 0.397, $P = 0.008$).

Conclusion: Older EOC patients have a worse prognosis than the younger patients largely, but not directly and independently. FIGO stage still stands as the most potent risk factor for older patients' survival.

Background

In 2020, over 313,000 women were diagnosed with ovarian cancer and nearly 207,000 died from this disease worldwide(1). The risk of suffering ovarian cancer for women increasing with age evidently. Among ovarian cancer patients, only 10 to 15 percent of cases are diagnosed before menopause(2). Due to the aggressiveness of ovarian cancer and the lack of specific symptoms for early detection, fewer than one-half of women survive beyond 5 years after diagnosis(3).

Surgical staging or cytoreduction followed by adjuvant chemotherapy is the standard treatment for most patients with epithelial ovarian cancer (EOC). With increasing age, more and more people are getting comorbid conditions, polypharmacy, cognitive impairment, depression, frailty, poor nutrition, and inadequate social support (4). Due to these potential risk factors, numerous older advanced ovarian

cancer patients might obtain less aggressive therapies and have poorer disease-specific survival, compared with the younger counterparts.

Previous studies have showed that age may affect the prognosis of different tumor types, such as breast cancer(5), colon cancer(6), lung cancer(7), as well as epithelial ovarian cancer. For instance, recent one study showed that the age at the time of diagnosis younger than 40 years was an independent protective prognostic factor for ovarian cancer patients both for overall survival (OS) and progression-free survival (PFS)(8). And in the Netherlands, the optimal treatment rates of ovarian cancer cases have improved from 1989 to 2009 with a corresponding rise in 5-year survival rates and treatment rates for women aged 75 and older(9). Therefore, the definition of the older patients and the inclusion criteria are different in each study, which might result in inconsistent conclusions regarding the prognostic value of age. Moreover, most of existing studies focus on the Whites or the Hispanics, the studies on other ethnic groups in particular the Chinese, are very limited.

Population aging has been the most noticeable demographic transition in the 21st century. Due to the extraordinarily rapid decline in fertility and mortality, China's population aging has been and will continue to occur at an accelerating pace. The proportion of people aged 65 and over in China almost doubled from 7% in 2000 to 13.5% in 2020 in China according to the latest national census, and is projected to reach 26.3% by 2050(10). How to alleviate disease burden and promote healthy aging thus becomes a priority in China. However, due to data restrictions, there is limited research on the survival probability of Chinese older women with ovarian cancer yet. Both ethnic Chinese in the US and Chinese women in China have a similar genetic background, which is closely associated with the occurrence of the cancer. Ethnicity is defined by specific physical, hereditary and cultural traditions or origins, not necessarily by birthplace, place of residence, or citizenship in SEER database. Thus, we aimed to investigate the differences in prognosis between the older and younger ethnic Chinese patients diagnosed with epithelial ovarian cancer, to offer new insights into the treatment of Chinese population.

Data And Methods

Data source

Medical records of patients with ovarian epithelial cancer were acquired from the Surveillance, Epidemiology, and End Results (SEER) database. The cancer patients in SEER were from 18 regional registries and covered approximately 34.6% of the total United States population⁽¹¹⁾. Patient identification, data accumulation and entry, and rigorous quality control for the SEER Program are managed by registered trained personnel(12). Data was obtained using SEER*Stat software version 8.3.9 (<https://seer.cancer.gov/seerstat/>).

Data Extraction

Patients with epithelial ovarian cancer from 2004 to 2016 were selected by the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) morphology codes “8310/3; 8380/3; 8441/3; 8442/3; 8460/3; 8461/3”; 8470/3”; 8471/3”; 8480/3” and the ethnicity “Chinese” (ethnicity code “04” in SEER) from ovarian cancer patients. Detailed flow chart for patient selection was shown in Fig. 1.

Measurement

In this study, patients aged 65 and above at diagnosis were coded as the older patients group while those younger than age 65 were coded as the younger group. Marital status was classified into three types, the currently married, the never married and the separated/ divorced/widowed (13). Tumor characteristics included tumor differentiation (Grade I (High differentiated), Grade II (Medium differentiated), Grade III (Low differentiated) or Grade IV (Undifferentiated)), FIGO stage (The FIGO stage was re-evaluated based on information from the database, which included TNM stage (American Joint Commission on Cancer [AJCC] 6th version and 7th version), tumor size, lymph node status and distant metastasis), tumor size (cm), ovarian tumor laterality (Unilateral versus Bilateral), performance of regional lymphadenectomy (no, adequate, and non-adequate; ≥ 10 excised lymph nodes was defined as adequate lymphadenectomy according to the GOG criteria(14)), chemotherapy use (No/Unknown versus Yes), radiotherapy(No/Unknown versus Yes), and types of surgery (No surgery/Uncomplete surgical staging group, Complete surgical staging group, and Cytoreductive surgery group). Overall Survival (OS) was our outcome index.

Statistical analysis

ANOVA analysis, t-test or chi-square test were used for statistical analysis for parametric data. The overall survival curve was plotted by Kaplan-Meier estimation. Additionally, univariate and multivariate Cox proportional hazard regression model were used to identify prognostic factors. All statistical analyses were performed with SPSS (version 24.0, SPSS, Chicago, IL, USA) and R software (version 4.0.4; <http://www.r-project.org/>).

Results

Clinicopathological characteristics and survival outcomes

A total of 323 ethnic Chinese patients diagnosed with epithelial ovarian cancer aged from 18 to 92 were included in the study, with an average age of (54.49 ± 12.31) years old. The 5-year OS rates were 62.5% for all patients (Fig. 2). Only 2 patients did not receive any surgical treatment and 23.5% of patients had ever used no/unknown chemotherapy, as shown in Table 1.

Table 1
Clinicopathological characteristics of the younger group and the older patients group

Age				
Variables	All patients n (%)	The younger(<65) n (%)	The older (≥ 65) n (%)	P
Total	323(100)	262(81.1)	61(18.9)	
Age	54.49 $\pm$ 12.31	49.96 $\pm$ 8.33	73.93 $\pm$ 6.07	0.033
Tumor_size	11.27 $\pm$ 11.34	12.15 $\pm$ 12.26	7.49 $\pm$ 4.35	0.037
Marital status				$<$ 0.001*
Currently married	208(64.4)	178(55.1)	30(49.2)	
Never married	60(18.6)	56(21.4)	4(6.6)	
SDW	55(17.0)	28(10.7)	27(44.3)	
Year of diagnosis				0.579
2004–2009	105(32.5)	87(33.2)	18(29.5)	
2010–2016	218(67.5)	175(66.8)	43(70.5)	
Laterality				0.856
Unilateral	215(66.6)	175(66.8)	40(65.6)	
Bilateral	108(33.4)	87(33.2)	21(34.4)	
Grade				0.132
I	39(12.1)	36(13.7)	3(4.9)	
II	57(17.6)	47(17.9)	10(16.4)	
III	134(41.5)	102(38.9)	32(52.5)	
IV	93(28.8)	77(29.4)	16(26.2)	
Histology				0.003*
HGSOC	164(50.8)	121(46.2)	43(70.5)	
LGSOC	4(1.2)	4(1.5)	0(0.0)	
CCOC	62(19.2)	59(22.5)	3(4.9)	

		Age		
	EC	64(19.8)	55(21.0)	9(14.8)
	MOC	29(9.0)	23(8.8)	6(9.8)
FIGO				0.001*
	Stage I	119(36.8)	107(40.8)	12(19.7)
	Stage II	33(10.2)	26(9.9)	7(11.5)
	Stage III	125(38.7)	100(38.2)	25(41.0)
	Stage IV	46(14.2)	29(11.1)	17(27.9)
Surgery				0.048*
	No surgery/Uncomplete surgical staging	2/102(32.2)	2/84(32.9)	18(29.5)
	Complete surgical staging	90(27.9)	80(30.5)	10(16.4)
	Cytoreductive surgery	129(39.9)	96(36.6)	33(54.1)
LN_dissected				0.232
	No or examined	87(26.9)	66(25.2)	21(34.4)
	1–10	91(28.2)	73(27.9)	18(29.5)
	≥ 11	145(44.9)	123(46.9)	22(36.1)
Chemotherapy				0.581
	No/Unknow	76(23.5)	60(22.9)	16(26.2)
	Yes	247(76.5)	202(77.1)	45(73.8)
Radiation				0.197
	None/Unknown	316(97.8)	255(97.3)	61(100.0)
	Beam radiation	7(2.2)	7(2.7)	0(0.0)
Cause of death				0.007*
	alive	139(43.0)	119(45.4)	20(32.8)
	dead due to cancer	171(52.9)	136(51.9)	35(57.4)
	dead due to other	8(2.5)	3(1.1)	5(8.2)
	missing/unknown	5(1.5)	4(1.5)	1(1.6)

There were 61 patients (18.9%) in the older patients group, and 262 (81.1%) in the younger group. The average age of the younger group was 49.96 years old, as compared with the mean age of 73.93 for the older patients group. The proportion of those who were separated, divorced or widowed in the older patients group was significantly higher than the younger group ($P < 0.001$), which meant older patients were faced with much more limited family support.

The average tumor size in the older patients group was significantly smaller than the younger patients ($P = 0.037$). The most common epithelial ovarian cancer histologic type was high-grade serous ovarian cancer (HGSOC), which accounted for 70.5% among the older patients group. In addition, ovarian clear cell cancer (CCOC, 22.5%), and endometrioid ovarian cancer (EC, 21.0%) were more common in younger group. Low-grade serous ovarian cancer (LGSOC) was the most infrequent histologic type, with only 4 patients in the younger group. Mucinous ovarian cancer (MOC) accounted for 8.8% and 9.8% in the younger and older patients group, respectively. The percentage of patients with advanced FIGO stage was significantly higher in the older patients group than the younger group. ($P = 0.001$).

As for cancer treatment, 54.1% of older patients underwent cytoreductive surgery as compared with 36.6% for younger patients. Five older patients (8.2%) died due to other diseases (including cerebrovascular diseases and diseases of heart) while only 1.1% younger patients died of them ($P = 0.007$).

It was not significantly different in the distribution of year of diagnosis, laterality, histological grading, chemotherapy, radiotherapy, and the number of lymph dissected between these two groups.

Comparison of overall survival between the older patients and younger patients

Kaplan-Meier curve of overall survival (OS) showed that the median survival of the older patients and younger patients were 50 months and not reached respectively. It further revealed that OS was significantly lower in the older patients group than the younger group (Fig. 3).

Prognostic Factors For The Patients

Univariate Cox regression analysis revealed that age, primary tumor laterality, tumor histological grading, histology, FIGO stage, surgical range and the number of lymph node dissected were significantly associated with OS. However, the multivariate analysis demonstrated that once other confounding factors were controlled, the older patients group no longer had significantly lower survival probability than the younger group (HR: 1.334, $P = 0.226$). Primary tumor laterality, histology, FIGO stage, (HR: 1.885, $P = 0.008$; HR: 2.003, $P = 0.035$; HR: 4.006, $P = 0.008$ and HR: 5.272, $P < 0.001$; HR: 1.885, $P = 0.008$) remained as important risk factors while the number of lymph node dissected more than 10 was a protective factor (HR: 0.397, $P = 0.008$). (Table 2)

Table 2
Univariate and multivariate Cox regression analysis for the overall survival of ethnic Chinese patients

		Univariate		Multivariable	
		HR (95% CI)	P	HR (95% CI)	P
Age					
	The younger	Reference		Reference	
	The older	2.023(1.312–3.119)	0.001	1.334(0.837–2.127)	0.226
Marital status					
	Currently married	Reference			
	Never married	0.722(0.413–1.264)	0.254		
	SDW	1.260(0.785–2.022)	0.339		
Year of diagnosis					
	2004–2009	Reference		Reference	
	2010–2016	1.466(0.961–2.237)	0.076	1.513(0.954–2.399)	0.079
Laterality					
	Unilateral	Reference		Reference	
	Bilateral	3.726(2.515–5.519)	< 0.001	1.885(1.183–3.003)	0.008
Grade					
	I	Reference		Reference	
	II	2.522(0.718–8.851)	0.149	0.880(0.224–3.459)	0.855
	III	5.739(1.795–18.347)	0.003	1.140(0.290–4.476)	0.851
	IV	6.277(1.929–20.423)	0.002	1.109(0.266–4.614)	0.887
Histology					
	HGSOC	Reference		Reference	
	LGSOC	0.000(0.000–2.319E + 173)	0.956	0.000(0.000–1.095E + 162)	0.956

		Univariate		Multivariable	
	CCOC	0.527(0.338–0.968)	0.038	2.003(1.051–3.815)	0.035
	EC	0.239(0.120–0.477)	< 0.001	0.763(0.3289–1.777)	0.531
	MOC	0.173(0.054–0.549)	0.003	1.141(0.290–4.487)	0.850
FIGO					
	I	Reference		Reference	
	II	1.972(0.749–5.190)	0.169	2.149(0.784–5.885)	0.137
	III	6.275(3.441–11.442)	< 0.001	4.006(1.833–9.021)	0.001
	IV	8.244(4.224–16.092)	< 0.001	5.272(2.159–12.873)	< 0.001
Surgery					
	No surgery/Uncomplete surgical staging	Reference		Reference	
	Complete surgical staging	0.897(0.509–1.580)	0.706	1.761(0.877–3.534)	0.111
	Cytoreductive surgery	2.535(1.605–4.003)	< 0.001	1.571(0.913–2.704)	0.103
LN_dissected					
	No or examined	Reference		Reference	
	1–10	0.497(0.308–0.802)	0.004	0.577(0.329–1.010)	0.054
	≥ 11	0.388(0.248–0.605)	< 0.001	0.397(0.235–0.672)	0.001
Chemotherapy					
	No/Unknow	Reference			
	Yes	0.676(0.416–1.101)	0.116		
Radiation					
	None/Unknown	Reference			

	Univariate	Multivariable
Beam radiation	0.565(0.139–2.291)	0.424

Discussion

With sustained low fertility and prolonged life expectancy, the proportion of the older population has increased worldwide. Therefore, how to alleviate disease burden and promote healthy aging thus becomes a priority for aging societies. For women, gynecological malignancies account for a large proportion of all tumors, with epithelial ovarian cancer coupled with the highest mortality(15). Previous studies have revealed that the risk of suffering from ovarian cancer might increase with age for European or American population(2). China stands out as one of the fastest aging societies due to compressed fertility and mortality transition. However, due to data restrictions, there is limited research on the survival probability of Chinese older women with ovarian cancer yet.

Due to the unavailability of data on Chinese ovarian cancer patients, we had to resort to ethnic Chinese ovarian cancer patients in the United State, given the fact that the ethnic Chinese share the similar genetic background to Chinese women and genetic mutation is closely associated with the occurrence of the cancer. Thus, we compared the overall survival probability between the older and the younger ethnic Chinese patients diagnosed with epithelial ovarian cancer from the SEER database to offer new evidences on Chinese population.

To the best of our knowledge, our study was the first to analyze the difference in prognosis between the younger and the older ethnic Chinese patients with EOC. Our study showed that EOC patients aged 65 and above had significantly worse prognosis and higher risk of death, compared with younger ones (OS: median 50 months vs not reached). However, multivariate Cox regression analysis indicated that age was not an independent risk factor once the confounding factors were controlled for. Only primary tumor laterality, histology, and FIGO stage, were independent risk factors and the number of lymph node dissected more than 10 was an independent protective factor.

The treatment strategy for the older ovarian cancer patients remains controversial nowadays, largely because the older patients might have more coexisting comorbid conditions and are less able to tolerate the side-effects of treatment. Therefore, the physicians might be less inclined to provide standardized treatment for older ovarian cancer therapy at the baseline. Older patients are more likely to suffer polypharmacy, cognitive impairment, depression, and to receive less social support, which in turn lead to intolerance of subsequent treatment. A recent study in the context of America also showed that older women aged ≥ 70 years old had significantly higher Cumulative Illness Rating Scale-Geriatric score, less completion of adjuvant chemotherapy, less intraperitoneal (IP) therapy, and less clinical trial participation, and thus they were less likely to have optimal cytoreductive surgery (CRS) with same surgical complexity(16).

In our study, we further compared the cause of death between older patients and younger patients. In the older patients group, four patients (8.2%) died of heart disease and one patient of cerebrovascular disease while the proportion in younger group was only 1.1%. Patients with comorbidity were more unlikely to tolerate treatment toxicity, and at the same time, treatments may also exacerbate existing comorbidity. Additionally, a large proportion of older patients in our study were separated, divorced or widowed. When considering systemic anti-cancer therapy, it is a big challenge that patients are in lack of familial support and comfort.

As a result, in view of the worse perioperative morbidity and mortality, older patients may have less opportunity to complete surgical cytoreduction than younger patients(17). They may also receive reduced dose adjuvant chemotherapy and with chemotherapy treatment delays.(18, 19). A previous study showed that if the older patients were able to tolerate procedure, they may have similar rates of response to initial chemotherapy, platinum sensitivity, and overall survival to younger counterparts⁽²⁰⁾. Our study confirmed this finding. After adjustment of FIGO stage, performance status and first-line treatment received, age was no longer an independent risk factor for OS(21).

In our study, few patients did not receive any surgical treatment. Noticeably, debulking surgery was performed in 54.1% in older patients group compared with 36.6% in the younger group. This discrepancy may be due to the age difference in patients' FIGO stage distribution. At the same time, there was no difference in the proportion of patients using chemotherapy and performance of regional lymphadenectomy between the two groups. Patients with adequate lymphadenectomy had longer overall survival time both in the younger and older patients group. Taken together, although the role of lymphadenectomy requires further investigation, age should not be the excuse to forgo systematic lymphadenectomy or other treatments.

On the other hand, EOC consists of a heterogeneous group of neoplasms with multiple histologic subtypes(22). The differences of tumor biology may also be associated with inherent platinum resistance(23). It is worth noting that clear cell cancer constitutes a larger percentage of ovarian cancers in East Asia ^[20]. Our study was concordant with previous ones(16, 24). In our study, there was also difference in histological subtypes between older patients and younger groups. The older patients were more likely to be diagnosed with an advanced disease as well as more invasive and aggressive histological subtype.

There are several limitations in this study, therefore our findings deserve more cautious interpretations. First, this retrospective analysis was based on the SEER database, and inherent bias in the study sample cannot be excluded. Second, because details on chemotherapy drugs and residual disease were not provided, we cannot comment on the ideal chemotherapy regimen and the quality of surgery. Moreover, as there is no data of Chinese patients with ovarian cancer available, this study used the sample of ethnic Chinese patients instead to shed light on the association between age and cancer prognosis. However, due to differences in economic and medical services between China and the U.S. Our findings among the ethnic Chinese patients may not be fully generalized to Chinese patients with ovarian cancer.

Conclusion

In conclusion, older EOC patients have a significantly lower overall survival probability than the younger patients among the ethnic Chinese population, largely because older patients are more likely to develop aggressive histological subtype and progress to an advanced stage. Once the other confounding factors are adjusted, the older was no longer an independent prognostic factor for EOC. FIGO stage still stands as the most potent risk factor for patients' survival. These results may be useful for patient counseling in China, trial stratification and more studies are warranted for further investigation. In order to improve cancer prognosis, government, community and health institutions should provide more cancer-related education to female older adults to increase their awareness of 'red flag' symptoms, so that older patients could be diagnosed at early stage.

Declarations

Ethical approval and consent to participate

No personal identifying information was used in the study. Hence, we did not require Institutional Review Board approval or informed consent from patients. Data extraction and usage has been approved by SEER Program. All methods were performed in accordance with the relevant guidelines and regulations

Consent for publication

All authors provided consent for publication

Availability of data and materials

The dataset supporting the conclusions of this article is available in the Surveillance, Epidemiology, and End Results (SEER) database. The URL of the database is <https://seer.cancer.gov/data>.

Competing interests

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Authors' contributions

LY is the guarantor of the manuscript. WH and LY contributed to conception and design of the study. WH, LQY, YB, and XL contributed to the acquisition and analysis of data. WH wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Figures

Figure 1

Flow chart

Figure 2

Survival curves of overall survival for all patients

Figure 3

Kaplan-Meier survival curves of overall survival between the younger and older