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Age and Lymph Nodes Examination May Be Related to the Outcome of Ovarian Clear Cell Carcinoma: A SEER Analysis

Menghan Zhu
Obstetrics and Gynecology Hospital of Fudan University https://orcid.org/0000-0003-0951-4502
Nan Jia
Obstetrics and Gynecology Hospital of Fudan University
Wei Jiang (jw52317@126.com)
Fudan University https://orcid.org/0000-0003-0596-7811

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Abstract

Aim

To analyze and compare the demographics, treatment, and survival rates in patients with ovarian clear cell carcinoma (OCCC).

Methods

We conducted a population-based retrospective study examining the Surveillance, Epidemiology, and End Results Program from 1998 to 2016. Data of 4344 women with OCCC were compared, and survival was analyzed using the Kaplan–Meier method. Factors predictive of outcome were compared using the Cox proportional hazards model.

Results

There was no significant difference in cause specific survival (CSS) regardless of chemotherapy in stage I and stage II OCCC. In women with stage III/IV OCCC, there was an increased mortality in women without chemotherapy (5-year CSS 29.80% vs. 24.90%, p<0.001). Among stage I women younger than 60 years old, the 5-year CSS of those underwent chemotherapy was worse than that of non-chemotherapy (86.4% vs. 97.50%, p=0.002). Among these patients, omitting chemotherapy had improved CSS (HR 0.539; 95% CI 0.386-0.753), and omitting lymph nodes examination had decreased CSS (HR 1.666; 95% CI 1.230-2.256). In stage III/IV women who were 60 years or older, the 5-year CSS of those underwent chemotherapy was better than that of non-chemotherapy (32.60% vs. 24.30%, p<0.001). Among these patients, omitting chemotherapy (HR 1.769; 95% CI 1.385-2.258) and omitting lymph nodes examination (HR 1.709; 95% CI 1.371-2.130) had lower CSS.

Conclusion

Chemotherapy has different effects in patients with OCCC at different stages and ages. Age and lymph nodes examination may be factors that affect the outcome of patients with OCCC.

Introduction

Ovarian cancer is the most lethal gynecological neoplasm in the world[1]. More than 90% of malignant ovarian tumors are of epithelial origin, designated epithelial ovarian cancer (EOC)[2]. Over the past few decades, there have been many novel advances in the treatment of ovarian cancer, including chemotherapy, immunotherapy, and targeted therapy. These treatments have substantially improved median survival; however, overall cure rates remain relatively unchanged [3]. Several factors are associated with ovarian cancer survival, including race, use of oral contraceptives, tubal ligation, menopausal hormone use, stage, size of residual tumor after debulking surgery, and histotype[4-8]. Ovarian clear cell carcinomas (OCCC) comprise approximately 5–25% of all ovarian cancers[9]. OCCCs

have distinctly different clinical behavior from the more common papillary serous ovarian carcinomas. Low-stage OCCC have a relatively good prognosis, however, high-stage OCCC have a poorer prognosis than stage-matched high-grade serous ovarian carcinomas. OCCC in advanced stage has poor prognosis due to its inherent resistance to standard carboplatin paclitaxel chemotherapy [10, 11].

Adjuvant chemotherapy in early-stage OCCC is commonly used and conflicting data have been reported [9, 12]. Whether early ovarian clear cell carcinoma needs chemotherapy is still controversial. We retrospectively analyzed the data of patients with OCCC obtained from the National Cancer Institute's Surveillance, epidemiology, and End Results (SEER) program. The aim of this study is to investigate the impact of chemotherapy on survival among OCCC patients in different stages and different ages.

Materials And Methods

Data source

This is a population-based retrospective observational study examining data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. The SEER database is a public, de-identified database of cancer statistics. It has a more than a four-decade history of operation, and currently covers approximately 35% of the U.S. population. In this study, all data were extracted from the SEER database, and all patients were anonymous. Informed consents were not available.

Study eligibility

Women with OCCC who were diagnosed from 1998 to 2016 were eligible for the analysis. Women who were not diagnosed by positive histology were excluded, including diagnosed by death certificate, diagnosed at the time of autopsy and diagnosed by cytology without surgery. And women with a previous diagnosis of cancer were excluded from the study. Patients diagnosed outside of the study period were excluded from the study. The SEER Public Use Data include SEER incidence and population data grouped by age, race, year of diagnosis, and marital status in addition to providing information regarding stage of disease; tumor size, lymph node status; treatment with surgery and chemotherapy; and cause specific survival for each registered patient.

Data extraction

SEER*Stat 8.3.8. (IMS Inc., Calverton, MD, USA) was used for the data abstraction. The histology code was 8310/3.Age at diagnosis was categorized as <60, ≥60. Marital status was categorized as: married, unmarried and unknown. Race was categorized as: white, black, Asian, and unknown. Tumor stage according to FIGO staging was categorize as: stage I, stage II, and stage III/IV. Tumor size in diameter was categorized as: <10cm, ≥10cm. Performance of lymphadenectomy, surgery, and chemotherapy was noted for each subject. Years of diagnosis were classified into 1998-2003, 2004-2010, and 2011–2016. The outcome variables included vital status and the time-to-event from the date of diagnosis until death, censoring, or last follow-up, as verified by the SEER program vital status determination.

Statistical Analysis

Median age of each group was calculated by independent samples t-test, and the rest variables were evaluated by Pearson chi-squared test, Fisher exact test. We used the Kaplan–Meier method to estimate survival curves in order to compare observed survival between women with different age and different stage OCCC. Survival curves were constructed to show cause specific survival within the first five years of diagnosis for each tumor stage, although the hazard ratios (HR) and resulting P values were calculated using all available data through last date of follow-up at the end of 2017, not only the first five years after diagnosis.. Log-rank test with 95% confidence intervals (CIs) were applied to evaluate the outcomes. Cox proportional hazard model with 95% CIs was used to identify the predictors for cause specific survival (CSS).We considered $p < 0.05$ as statistically significant. All analyses were performed using the SPSS Statics software, version 20.0 (IBM Corporation, NY, USA).

Results

Patient selection

As shown in Figure 1, 4943 OCCC patients diagnosed from 1998 to 2016 were extracted from the SEER database. 559 patients were excluded from the final analysis: 39 cases were not diagnosed based on positive histology, 513 cases because of history of previous malignancy, and 47 cases because of disease stage were unknown. The final study group therefore consisted of 4344 women with OCCC, 2446 (56.31%) women were stage I, 550(12.66%) women were stage II, and 1348 (31.03%) women were stage III or stage IV. The demographic and clinical characteristics of the study population were shown in Table 1.

For patients with stage I disease, the 5-year CSS of patient with and without chemotherapy was 86.40% and 89.70% respectively (P = 0.104). Among patients with stage II disease, the 5-year CSS of patient with and without chemotherapy was 67.40% and 71.80% respectively (P = 0.345). In patients with stage III/IV disease, the 5-year CSS of patient with and without chemotherapy was 29.80% and 24.90% respectively (P<0.001). Five-year CSS for each stage with and without chemotherapy is shown in Table 2. Figure 2 displays Kaplan–Meier analyses of CSS for OCCC patients with and without chemotherapy across all stages.

To further analyze the relationship between age and chemotherapy outcome, we compared the survival time of patients age <60 and those age ≥60 with stage I and advanced stage III/IV. The demographic and clinical characteristics of stage I patients were shown in Table 3. It can be seen that the proportion of patients age <60 receiving chemotherapy was higher than that of age ≥60 in stage I (71.7% vs. 64.6%, p<0.001). The proportion of tumor size ≥10 cm in patients age ≥60 was higher than that in patients age <60 (55.0% vs. 45.3%, p<0.001). The demographic and clinical characteristics of stage III or IV patients were shown in Table 4.The proportion of patients age <60 receiving chemotherapy was higher than that of age ≥60 in stage III /IV (82.7% vs. 77.1%, p=0.012). The proportion of tumor size ≥10 cm in patients age ≥60 was lower than that in patients age <60 (43.4% vs. 51.7%, p=0.004).

For patients age <60 with stage I OCCC, the 5-year CSS of patient with and without chemotherapy was 86.40% and 97.50% respectively (P = 0.002). There was no benefit from chemotherapy in patients with stage I OCCC who were 60 years or older, and the 5-year CSS of these patients with and without chemotherapy was 86.40% and 84.60% respectively (P >0.05). Among patients age ≥60 with stage III/ IV disease, the 5-year CSS of patient with and without chemotherapy was 32.60% and 24.30% respectively (P<0.001). Meanwhile, there was no significant difference in the cause specific survival of women age <60 with or without chemotherapy, and the 5-year CSS of these patients with and without chemotherapy was 28.10% vs. 26.40% respectively (P >0.05). Five-year CSS for each group with and without chemotherapy is shown in Table 5. Figure 3 displays Kaplan–Meier analyses of CSS for each group with and without chemotherapy.

We further analyzed the factors related to the prognosis of patients age<60 in stage I OCCC. The Cox proportional hazards model identified an independent association of tumor diameter ≥10cm, absence of lymph node dissection and chemotherapy with cause specific mortality (Table 6). Among patients age<60 in stage I, tumor diameter ≥10cm had decreased CSS compared to tumor diameter <10cm (HR 1.968; 95% CI 1.408-2.750). Omitting lymph nodes examination had decreased CSS compared to receiving lymph nodes examination (HR 1.666; 95% CI 1.230-2.256). Omitting chemotherapy had improved cause specfic survival compared to receiving chemotherapy (HR 0.539; 95% CI 0.386-0.753). Meanwhile, we analyzed the factors related to the prognosis of patients age ≥60 with stage III/IV OCCC. The Cox proportional hazards model identified an independent association of absence of lymph node dissection and omitting chemotherapy with cause specific mortality (Table 7). Among patients age≥60 with stage III/IV, omitting lymph nodes examination had decreased CSS compared to receiving lymph nodes examination (HR 1.709; 95% CI 1.371-2.130). Omitting chemotherapy had lower cause specfic survival compared to receiving chemotherapy (HR 1.769; 95% CI 1.385-2.258).

Discussion

Ovarian cancer is a heterogeneous group of tumors. It is a distinct subtype of epithelial ovarian cancer that demonstrates a different clinical behavior from other histologic subtypes and is frequently associated with endometriosis[13].Ovarian clear cell carcinoma is considered to be relative resistant to chemotherapy. The reported response rates to chemotherapy range from 22% to 56% in patients with OCCC [14].

It remains controversial whether patients with OCCC may truly benefit from adjuvant chemotherapy, especially in patients with early-stage OCCC. Some studies suggested that chemotherapy has a role in improving disease-free survival. Shimizu D et al.[15] demonstrated that patients with stage I OCCC who received adjuvant chemotherapy had better disease-free survival than patients who did not. Bogani G et al.[16] observed that the administration of chemotherapy associate with an improvement in term of 5-year overall survival in patient with stage IC OCCC. Other investigations suggested that the administration of chemotherapy is not useful in OCCC. Lee H Y et al. [10] reported that in stage IA or IB patients, adjuvant

chemotherapy was not related to longer relapse free survival. Takano M et al.[17] suggested that adjuvant chemotherapy had little impact on the survival of stage I OCCC patients.

At present, various clinical guidelines have different recommendations for the treatment of early-stage ovarian clear cell carcinoma. The National Comprehensive Cancer Network (NCCN) demonstrate that adjuvant chemotherapy is optional to women with stage IA, but recommended to women with stage IB/IC, since ovarian clear cell carcinoma is regarded as grade 3 tumor, and has high-risk characteristic for relapse[18] [19]. The European Society of Medical Oncology (ESMO) practice guidelines recommend the benefit of adjuvant chemotherapy is uncertain for patients with early-stage ovarian clear cell carcinoma and should be discussed on an individual patient basis[2]. The Gynecologic Cancer Intergroup (CGIC) suggests that observation could be acceptable for those with surgical stage IA disease given the observed excellent survival rates[7].

In this study, we used a large sample of the SEER database to analyze the characteristics, prognosis, and factors related to the prognostic outcome of patients with ovarian clear cell carcinoma. We found that the administration of chemotherapy has not impact on stage I OCCC in term of 5-year cause specific survival. Moreover, after further stratification by age, we found that in stage I OCCC patients younger than 60 years old, the cause specific survival of those receiving chemotherapy was significantly lower than those omitting chemotherapy. Meanwhile, whether adopt chemotherapy or not has no significant difference on cause specific survival in advanced OCCC. This may be related to the natural instinct of chemotherapy resistance of OCCC. After stratification by age, we found that in patients age≥60 with advanced stage OCCC, omitting chemotherapy had lower cause specfic survival compared to receiving chemotherapy. It is the first time that age has been found to be related to the prognosis of chemotherapy in ovarian clear cell carcinoma.

According to the current retrospective literature, the necessity of systemic lymph node dissection in patients with OCCC is still controversial. Suzuk et al.[20] demonstrated that significant differences were observed in progression-free survival and overall survival between patients optimally and nonoptimally staged with stages IA/IC1 OCCC, but no significant difference was found in those with stages IC2/IC3. Surgical staging category was the only independent prognostic factor for recurrence-free survival in stages IA/IC1 OCCC. Yamazaki et al.[21] illustrated that pelvic lymph node dissection and para-aortic lymph node dissection were significantly and independently related to longer disease-specific survival. The study from Hirose et al. [22] showed the tendency that patients who received systematic lymph node dissection occurred fewer lymphogenous recurrences. In a multicenter retrospective study, Takano et al. [23] found that completion of surgical staging procedures was not a prognostic factor for overall survival in OCCC.

The NCCN treatment guidelines recommend investigation of retroperitoneal lymph nodes in early-stage ovarian cancer, and dissection of clinically negative nodes is not required for patients with stage≥IIB ovarian cancer[19]. The Japan Society of Gynecologic Oncology (JSGO) guidelines demonstrate that for

patients with stage I–IIA ovarian cancer, pelvic/para-aortic lymph node dissection (biopsy) is recommended in addition to bilateral salpingo-oophorectomy + total hysterectomy + omentectomy + peritoneal cytology + biopsies from sites in the abdominal cavity. For patients thought to have stage IIB or higher ovarian cancer, pelvic or para-aortic lymph node dissection is suggested to be not performed if no lymph node metastasis is clinically detected on imaging or by intraoperative palpation and visual inspection. When lymph node metastasis is clinically detected on diagnostic imaging or by intraoperative palpation and visual inspection, pelvic or para-aortic lymph node dissection or removal of swollen lymph nodes is recommended if complete resection can be achieved[24]. However, Magazzino et al [25] retrospectively assessed an Italian cohort of patients with clear cell ovarian cancer observed in the years 1991-2007 in 20 Italian centers, and found that disease-free survival was longer in patients undergoing lymphadenectomy at surgery, both in early stages and in stage III and IV diseases. The impact of lymphadenectomy was also evident on overall survival in patients with advanced-stage disease.In this study, we found that among patients age<60 in stage I and patients age≥60 with stage III/IV, omitting lymph nodes examination had decreased CSS compared to receiving lymph nodes examination. Therefore, the therapeutic significance of lymph node dissection for OCCC patients needs to be further clarified.

Conclusion

The present investigation reviewed the current evidence on the role of adjuvant chemotherapy in OCCC. We found that chemotherapy has different effects in patients with OCCC at different stages and ages. Lymph nodes examination and age may be related to the outcome of ovarian clear cell carcinoma. One weakness of our study is its retrospective nature and the lack of preoperative assessment. Further studies are needed to clarify the role of chemotherapy in ovarian clear cell carcinoma.

Declarations

Ethics approval and consent to participate

In this study, all data were extracted from the SEER database, and all patients were anonymous. Ethics approval was waived. Informed consents were not available.

Consent for publication

In this study, all data were extracted from the SEER database, and all patients were anonymous. Consent for publications were not available.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. They could be achieved upon reasonable request to the authors.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Author contributions

Menghan Zhu collected the data, did the data analysis and wrote the manuscript. Nan Jia reviewed the data and revised the manuscript. Wei Jiang designed the study, reviewed the data and revised the manuscript.

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Tables

Table 1 Demographic and clinical characteristics of the study population: SEER Program, 1998-2016.

characteristics	N(%)(Total N = 4344)
Age at diagnosis(year)	
<60	2810(64.7%)
≥60	1534(35.3%)
Mean(SD)	56.05(11.37)
Median（IQR）	55(17-85)
Date range	
1998-2003	1048(24.1%)
2004-2010	1666(38.4%)
2011-2016	1630(37.5%)
Race	
White	3367(77.5%)
Black	176(4.1%)
Asian	786(18.1%)
Unknown	15(0.3%)
Marital status at diagnosis	
Married	2389(55.0%)
Unmarried	1800(41.4%)
Unknown	155(3.6%)
Stage	
I	2446(56.3%)
II	550(12.7%)
III+IV	1348(31.1%)
Tumor size (diameter)	
<10cm	1361(33.3%)
≥10cm	2141(49.3%)
Unknown	842(19.4%)
Lymph nodes examined	
Examined	3137(72.2%)

None examined	1189(27.4%)
Unknown whether examined	18(0.4%)
Lymph nodes status [a]	
Negative	2643(84.3%)
Postive	490(15.6%)
Unknown	4(0.1%)
Chemotherapy	
Yes	3203(73.7%)
No/Unknown	1141(26.3%)
a Using population that had known lymph node dissection	

Table 2 Five-year cause specific survival of OCCC by stage

Stage		Chemotherapy		p
		Yes	No/Unknown	
I	N	1698	748	
	5-year CSS	86.40%	89.70%	0.104
II	N	421	129	
	5-year CSS	67.40%	71.80%	0.345
III+IV	N	1084	264	
	5-year CSS	29.80%	24.90%	<0.001

Table 3 Demographic and clinical characteristics of stage I patients

characteristics	Age <60	Age ≥60	p
	N(%)(Total N = 1661)	N(%)(Total N = 785)	
Age at diagnosis(year)	49.35±6.95	67.88±6.96	<0.001
Date range			
1998-2003	428(25.8%)	157(20.0%)	<0.001
2004-2010	643(38.7%)	290(36.9%)	
2011-2016	590(35.5%)	338(43.1%)	
Marital status at diagnosis			
Married	950(57.2%)	411(52.4%)	0.078
Unmarried	646(38.9%)	339(43.2%)	
Unknown	65(3.9%)	35(4.4%)	
Tumor size (diameter)			
<10cm	618(37.2%)	239(30.5%)	<0.001
≥10cm	752(45.3%)	432(55.0%)	
Unknown	291(17.5%)	114(14.5%)	
Lymph nodes examined			
Examined	1332(80.2%)	590(75.2%)	0.008
None examined	327(19.7%)	192(24.5%)	
Unknown	2(0.1%)	3(0.3%)	
Chemotherapy			
Yes	1191(71.7%)	507(64.6%)	<0.001
No/Unknown	470(28.3%)	278(35.4%)	

Table 4 Demographic and clinical characteristics of stage III/IV patients

characteristics	Age <60	Age ≥60	p
	N(%)(Total N = 807)	N(%)(Total N = 541)	
Age at diagnosis(year)	49.45±7.02	68.51±7.15	<0.001
Date range			
1998-2003	214(26.5%)	140(25.9%)	0.873
2004-2010	334(41.4%)	220(40.7%)	
2011-2016	259(32.1%)	181(33.4%)	
Marital status at diagnosis			
Married	452(56.0%)	279(51.5%)	0.269
Unmarried	332(41.1%)	246(45.5%)	
Unknown	23(2.9%)	16(3.0%)	
Tumor size (diameter)			
<10cm	201(24.9%)	141(26.1%)	0.004
≥10cm	417(51.7%)	235(43.4%)	
Unknown	189(23.4%)	165(30.5%)	
Lymph nodes examined			
Examined	522(64.7%)	277(51.2%)	<0.001
None examined	276(34.2%)	261(48.2%)	
Unknown	9(1.1%)	3(0.6%)	
Chemotherapy			
Yes	667(82.7%)	417(77.1%)	0.012
No/Unknown	140(17.3%)	124(22.9%)	

Table 5 Five-year cause specific survival of OCCC by stage, age and chemotherapy

		Age <60		p	Age ≥60		p
Stage		Chemo+	Chemo-		Chemo+	Chemo-	
I	N	1191	470		507	278	
	5-year CSS	86.40%	97.50%	0.002	86.40%	84.60%	0.203
III+IV	N	667	140		417	124	
	5-year CSS	28.10%	26.40%	0.18	32.60%	24.30%	<0.001

Table 6 Effect of various factors on cause specific survival in patients age<60 with stage I OCCC, SEER Program, 1998-2016.

Variable	N(%)(Total N =1661)	Univariate analysis	Multivariate analysis	
		p[a]	HR (95% CI)	p[b]
Date range				
1998-2003	428(25.8%)	0.958	/	/
2004-2010	643(38.7%)			
2011-2016	590(35.5%)			
Marital status at diagnosis				
Married	950(57.2%)	0.046	reference	
Unmarried	646(38.9%)		1.336(1.019-1.753)	0.036
Unknown	65(3.9%)		0.644(0.263-1.579)	0.336
Tumor size				
<10	618(37.2%)	<0.001	reference	
≥10	752(45.3%)		1.968(1.408-2.750)	<0.001
Unknown	291(17.5%)		1.986(1.352-2.918)	<0.001
Lymph nodes examined				
Examined	1332(80.2%)	0.003	reference	
None examined	327(19.7%)		1.666(1.230-2.256)	0.001
Unknown	2(0.1%)		7.647(1.046-55.886)	0.045
Chemotherapy				
Yes	1191(71.7%)	0.002	reference	
No/Unknown	470(28.3%)		0.539(0.386-0.753)	<0.001

p[a]: P value for comparisons between groups by log-rank test.

p[b]: P value for comparisons between groups by multivariable Cox regression analysis adjusting for covariates.

Table 7 Effect of various factors on cause specific survival in patients age ≥60 with stage III/IV OCCC, SEER Program, 1998-2016.

Variable	N(%)(Total N =541)	Univariate analysis	Multivariate analysis	
		p[a]	HR (95% CI)	p[b]
Date range				
1998-2003	140(25.9%)	0.173	/	/
2004-2010	220(40.7%)			
2011-2016	181(33.4%)			
Marital status at diagnosis				
Married	279(51.5%)	0.654	/	/
Unmarried	246(45.5%)			
Unknown	16(3.0%)			
Tumor size				
<10	141(26.1%)	<0.001	reference	
≥10	235(43.4%)		0.758(0.576-0.997)	0.048
Unknown	165(30.5%)		1.310(0.999-1.717)	0.051
Lymph nodes examined				
Examined	277(51.2%)	<0.001	reference	
None examined	261(48.2%)		1.709(1.371-2.130)	<0.001
Unknown	3(0.6%)		3.703(1.159-11.827)	0.027
Chemotherapy				
Yes	417(77.1%)	<0.001	reference	
No/Unknown	124(22.9%)		1.769(1.385-2.258)	<0.001

p[a]: P value for comparisons between groups by log-rank test.

p[b]: P value for comparisons between groups by multivariable Cox regression analysis adjusting for covariates.

Figures

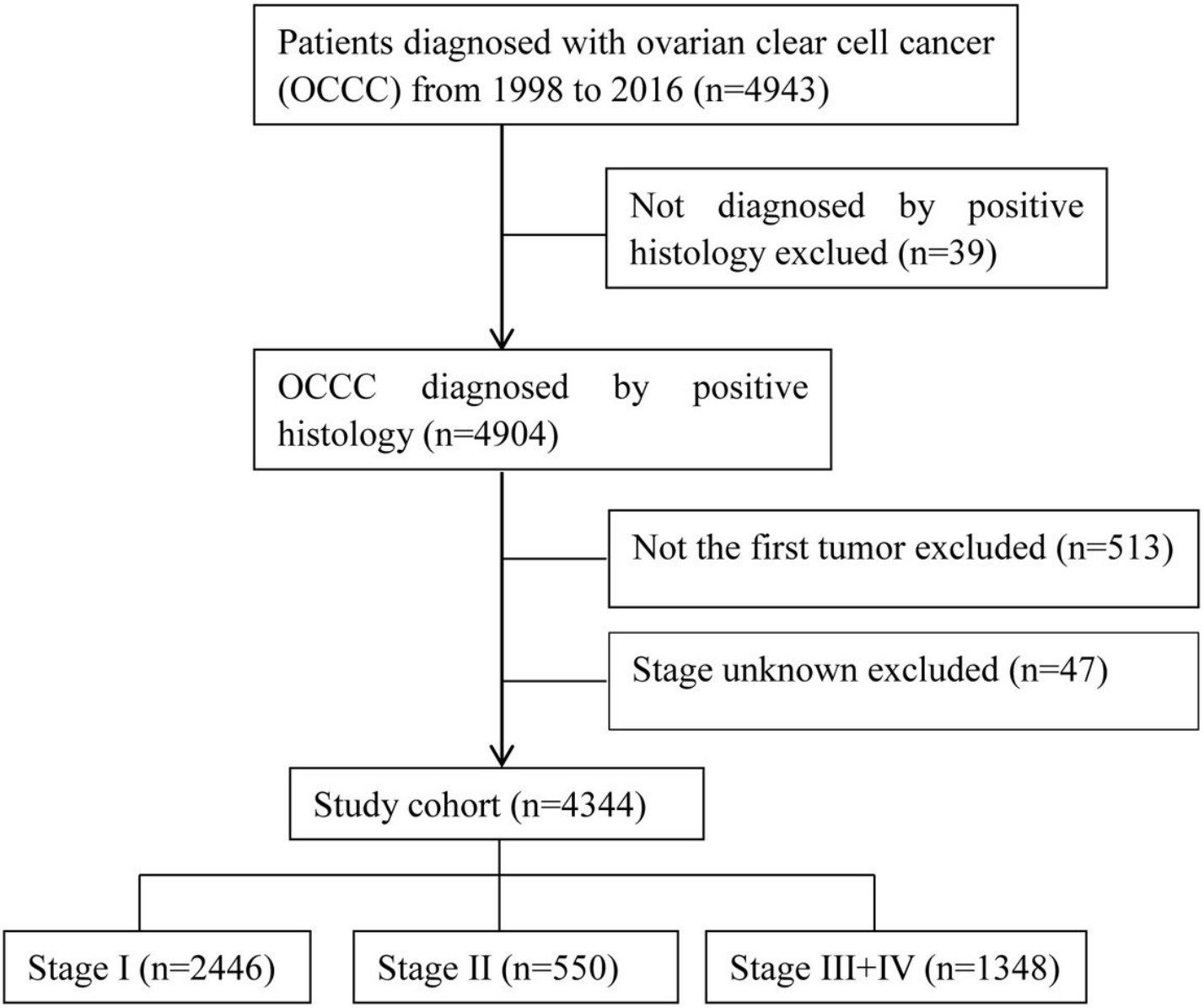

Figure 1 Patient selection flowchart

Figure 1

Patient selection flowchart

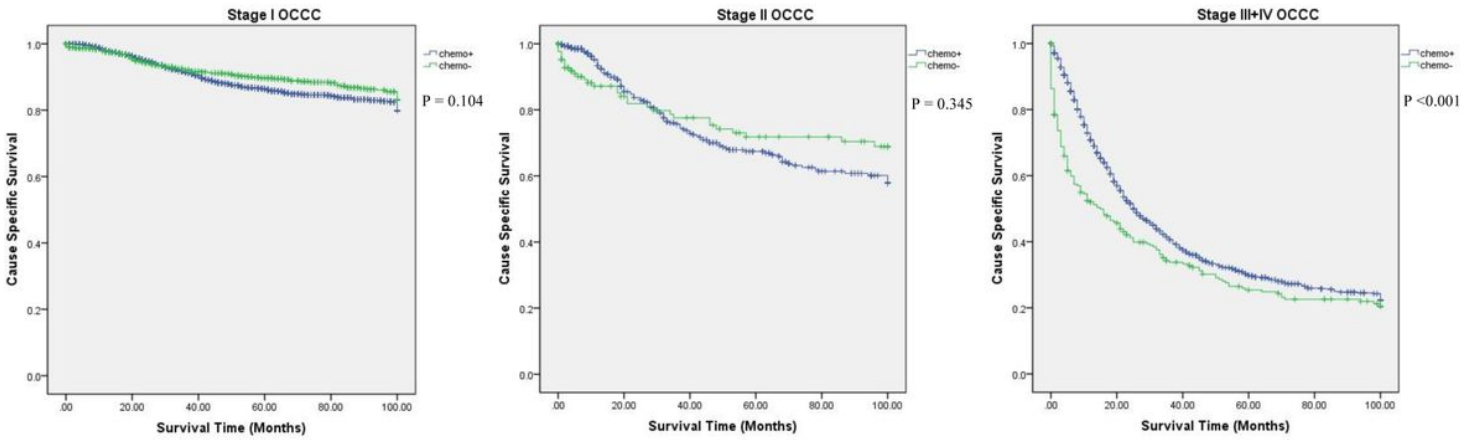

Figure 2 Kaplan–Meier survival curves for CSS for each group of OCCC stratified by stage.

Figure 2

Kaplan–Meier survival curves for CSS for each group of OCCC stratified by stage.

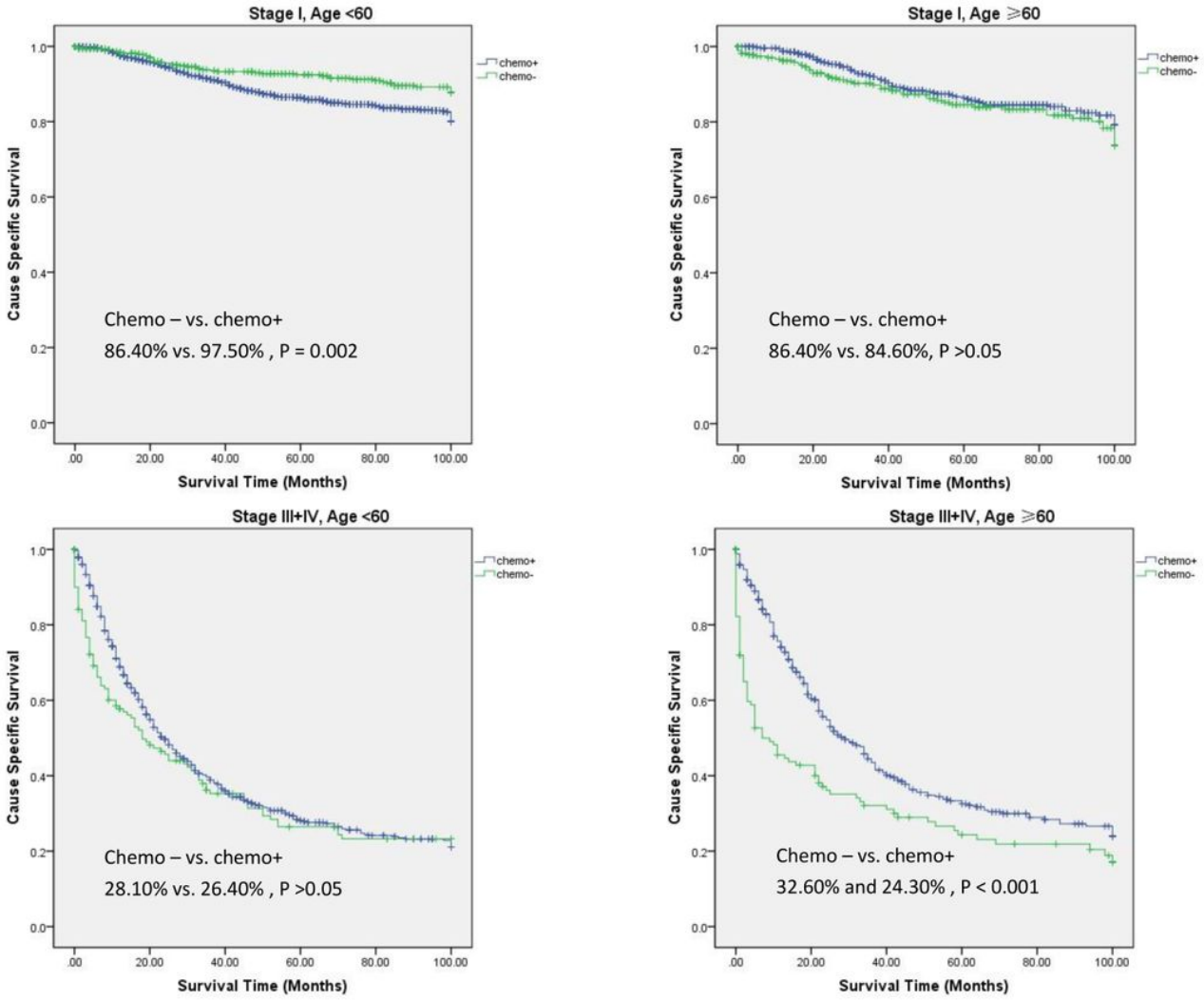

Figure 3 Kaplan–Meier survival curves for CSS for each group of OCCC stratified by stage and age.

Figure 3

Kaplan–Meier survival curves for CSS for each group of OCCC stratified by stage and age.