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Clinical-pathological Characteristics, Survival Outcomes, and Prognostic Factors of Stage I Ovarian Endometrioid Carcinoma: A SEER-based Study

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Abstract

Objective: To identify the factors that predict survival in patients with Stage I ovarian endometrioid carcinoma and to determine whether lymph node dissection treatment can improve survival rates. **Methods:** Clinical information for patients with Stage I ovarian endometrioid cancer from 2004 to 2015 was obtained from the Surveillance, Epidemiology, and End Results (SEER) database. Univariate and multivariate Cox analyses were used to identify independent prognostic factors, with patients categorized into subgroups based on lymph node dissection (defined as the removal of more than four lymph nodes). Kaplan-Meier curves were used to compare survival rates between the subgroups. **Results:** A total of 3,659 patients with Stage I ovarian endometrioid carcinoma were included, 1,247 (34.1%) underwent resection of fewer than four lymph nodes, while 2,412 (65.9%) underwent resection of four or more lymph nodes. The mean follow-up duration was 91.99 months. In the multivariate Cox analysis, lymphadenectomy, age, grade, tumor size, and chemotherapy were significant predictors of survival outcomes ($P < 0.05$). Patients who underwent resection of more than four lymph nodes and received adjuvant chemotherapy, along with those who were younger, had well-differentiated tumors, had smaller tumor sizes, and showed higher overall survival rates. **Conclusion:** Lymphadenectomy can improve the overall survival rate of patients with Stage I ovarian endometrioid carcinoma.

Keywords

Ovarian endometrioid carcinoma, SEER, lymph node dissection, prognosis

1. Introduction

Ovarian Endometrioid Carcinoma (OEC) is a malignant epithelial tumor originating from the ovaries, with histopathological characteristics similar to those of endometrial carcinoma originating from the uterine lining [1]. OEC is the second most common type of epithelial ovarian cancer, followed by serous ovarian carcinoma, accounting for approximately 10% of all epithelial ovarian malignancies [2], with an incidence rate of 31% in its early stages [3]. OEC is associated with endometriosis and Lynch syndrome, and the main treatment for early-stage OEC is

comprehensive staging surgery [4-7]. The ESMO-ESGO guidelines also recommend comprehensive peritoneal and retroperitoneal staging for all patients with apparent early-stage OEC, regardless of the histological type or grade of the cancer, as such staging could influence subsequent adjuvant therapy [8]. Nevertheless, previous studies have questioned the necessity of lymphadenectomy in patients with early-stage endometrioid ovarian cancer, as this specific subgroup does not appear to be at risk of lymph node metastasis [9, 10].

Studies have shown that patients with Stage I low-grade endometrioid ovarian cancer have a favorable prognosis, and adjuvant chemotherapy and staging lymphadenectomy do not improve the survival rates. Research by Bizzarri et al. has indicated that staging lymphadenectomy in patients with moderately differentiated OEC is associated with improved DFS (Disease-Free Survival) and OS (Overall Survival). Moderate differentiation might be considered as two distinct entities that could benefit differently from various surgical staging procedures [11]. In this context, the prognostic role of lymph node dissection in early-stage OEC continues to be a matter of debate [12, 13].

Our study exclusively focused on patients diagnosed with Stage I OEC. We aimed to gather sufficient evidence to make strong, well-supported recommendations to support or refute the results of a single published study that demonstrated a significant overall survival (OS) benefit for patients with stage I OEC. In addition, we sought to identify the clinical characteristics and prognostic factors associated with stage I OEC that may affect OS in this patient cohort. To address these issues, a retrospective survey was conducted using a population from the internationally recognized Surveillance, Epidemiology, and End Results (SEER) database.

2. Materials and methods

2.1 Data sources

The SEER database collects incidence data from 18 population-based cancer registries and tumor clinicopathological information, accounting for approximately 27.8% of the U.S. population(https://seer.cancer.gov). The data used in this study were publicly available and excluded identifying information from the individual patients. Therefore, there was no requirement for written informed consent from patients or approval from an Institutional Review Board. This study collected data using the SEER*Stat (Version 8.4.3) program using research data submitted to SEER by November 2021. Because the SEER database is a large, population-based cancer registry with patient-level data, the results can be better extrapolated to the general population than studies conducted in single centers.

2.2 Study population

Due to database limitations, our analysis was restricted to a sample from January 1, 2004, to December 31, 2015. We selected all patients with ICD-O-3 Hist/behav malignant codes 8380/3, 8381/3, 8382/3, and 8383/3 with ovarian endometrioid carcinoma from the SEER database. The database contains information on the patient registration number, personal information, primary lesion site, tumor size, tumor code, treatment regimen, and cause of death.

The inclusion criteria for the study cases were: 1) diagnosis of OEC; 2) stage I; 3) diagnosed between 2004 and 2015. Exclusion criteria were: 1) cancer diagnosed at autopsy; 2) missing month of cancer diagnosis; 3) presence of only precancerous or in situ lesions; 4) prior diagnosis of any cancer. Tumor staging was based on the 6th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. Among the eligible cases, the following variables were ascertained from the SEER database: age, race, marital status, degree of differentiation, tumor size, whether hysterectomy was performed, whether chemotherapy was administered, and survival outcome. Survival outcome included overall survival (OS), which was defined as the time interval between endometrial cancer diagnosis and death for any reason (all-cause). The screening process is illustrated in Fig. 1.

2.3 Statistical analysis

Clinical and demographic features were compared across subgroups using chi-square or Fisher's exact test. Overall survival was estimated using the Kaplan-Meier method (with right-censored data for those who died after data submission or dropped out). Hazard ratios (HR) and 95% confidence intervals (CIs) were determined using univariate Cox proportional hazard models. Cox proportional hazards models were fitted for all predictor variables using the forward stepwise selection procedure. Data analysis was performed using R software (version 4.1.3). Statistical significance was set at $P < 0.05$, and a P-value of less than 0.01 was considered highly significant.

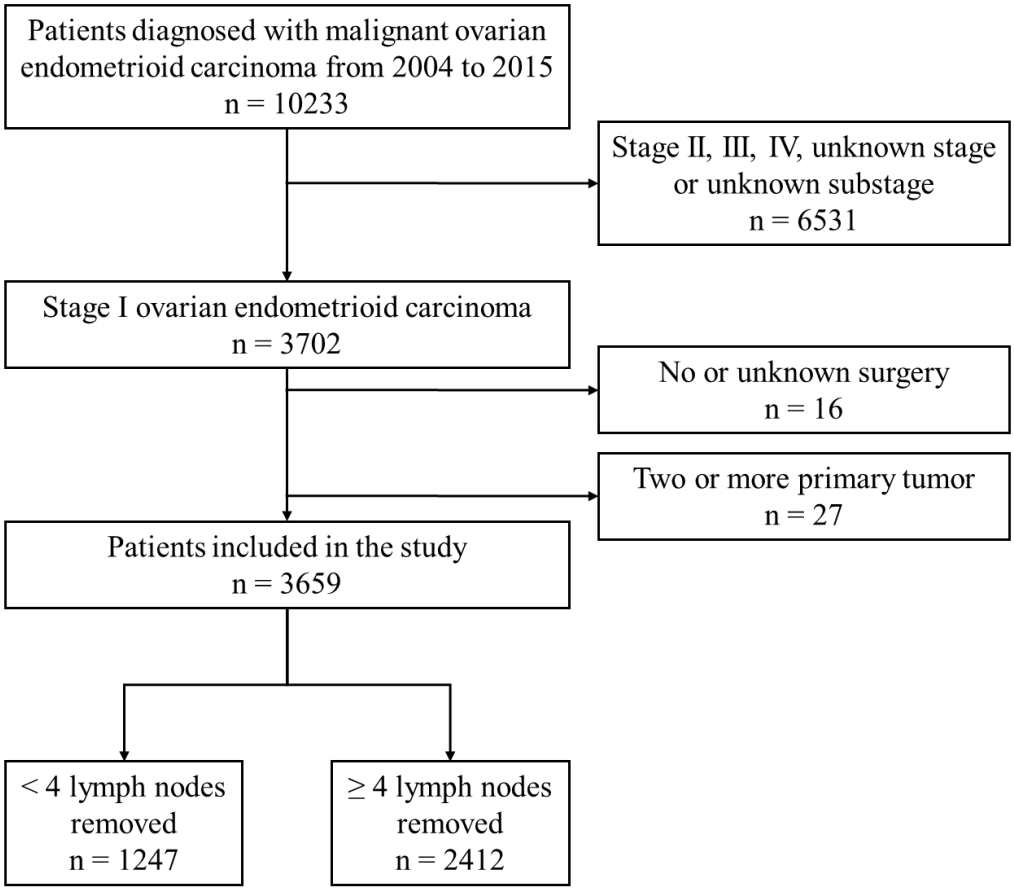

Figure 1. Flowchart of patient selection from the SEER database.

3. Results

3.1 Summary statistics

In total, 3659 patients with stage I OEC who fulfilled all the inclusion criteria were identified: 1247 (34.1%) underwent resection of < 4 lymph nodes and 2412 (65.9%) underwent resection of ≥ 4 lymph nodes. The follow-up period for the cohort ranged from 1 to 179 months with a mean follow-up of 91.99 months. In this population, 1335 (36.5%) were aged < 50 years, 1199 (32.8%) were aged 50-60 years, 712 (19.5%) were aged 60-70 years, and 413 (11.3%) were aged ≥ 70 years. Most patients were white (n = 3078; 84.1%), followed by other races (n = 408; 11.2%) and black (n = 173; 4.7%). Most patients were married (n = 1974; 53.9%), 832 (22.7%) were single, and 853 (23.3%) were listed as others. The number of patients with histological grade I (well-differentiated), II (moderately differentiated), III (poorly differentiated), IV (undifferentiated or anaplastic), and unknown disease was 1425 (38.9%), 1310(35.8%), 438(12.0%), 73 (2.0%), and 413 (11.3%), respectively. A total of 1595 (43.6%) patients had tumors < 10 cm in size and 1483 (40.5%) had tumors ≥ 10 cm in size. 1740 (47.6%) received chemotherapy, while 1919 (52.4%) did not. Patient characteristics are presented in Table 1.

In this cohort, except for radiotherapy ($P = 0.552$), lymph node resection ($P < 0.001$), age ($P < 0.001$), race ($P = 0.004$), marital status ($P < 0.001$), grade ($P < 0.001$), tumor size ($P = 0.017$), chemotherapy ($P = 0.004$), and hysterectomy ($P = 0.002$) were significantly correlated with survival outcomes of patients.

Table 1. Epidemiologic and clinicodemographic characteristics of patients with Stage I OEC

Subject	Total	Alive	Dead	P-value
Lymph nodes removed				<0.001
< 4	1247 (34.1)	944 (31.0)	303 (49.7)	
≥ 4	2412 (65.9)	2105 (69.0)	307 (50.3)	
Age (years)				<0.001
< 50	1335 (36.5)	1158 (38.0)	177 (29.0)	
50-60	1199 (32.8)	1054 (34.6)	145 (23.8)	
60-70	712 (19.5)	584 (19.2)	128 (21.0)	
≥ 70	413 (11.3)	253 (8.3)	160 (26.2)	
Race				0.004
Black	173 (4.7)	134 (4.4)	39 (6.4)	
White	3078 (84.1)	2556 (83.8)	522 (85.6)	
Others	408 (11.2)	359 (11.8)	49 (8.0)	
Marital status				<0.001
Single	832 (22.7)	714 (23.4)	118 (19.3)	
Married	1974 (53.9)	1694 (55.6)	280 (45.9)	
Others	853 (23.3)	641 (21.0)	212 (34.8)	
Grade				<0.001
Well differentiated	1425 (38.9)	1234 (40.5)	191 (31.3)	
Moderately differentiated	1310 (35.8)	1091 (35.8)	219 (35.9)	
Poorly differentiated	438 (12.0)	324 (10.6)	114 (18.7)	
Undifferentiated or anaplastic	73 (2.0)	47 (1.5)	26 (4.3)	
Unknown	413 (11.3)	353 (11.6)	60 (9.8)	
Tumor Size (cm)				0.017
< 10	1595 (43.6)	1360 (44.6)	235 (38.5)	
≥ 10	1483 (40.5)	1219 (40.0)	264 (43.3)	
Unknown	581 (15.9)	470 (15.4)	111 (18.2)	
Radiotherapy				0.552
Yes	63 (1.7)	54 (1.8)	9 (1.5)	
No	3582 (97.9)	2982 (97.8)	600 (98.4)	
Unknown	14 (0.4)	13 (0.4)	1 (0.2)	
Chemotherapy				0.004
Yes	1740 (47.6)	1483 (48.6)	257 (42.1)	
NO	1919 (52.4)	1566 (51.4)	353 (57.9)	
Surgery				0.002
Hysterectomy	2943 (80.4)	2474 (81.1)	469 (76.9)	
No_Hysterectomy	586 (16.0)	461 (15.1)	125 (20.5)	
Unknown	130 (3.6)	114 (3.7)	16 (2.6)	

3.2 Survival analysis

Survival analysis was performed using the Kaplan-Meier estimate for OS (Fig. 2). Among stage I OEC patients, those who had more than four lymph nodes removed had better overall survival (OS) than those with fewer than four lymph nodes removed ($P < 0.001$). Younger patients (< 50 years) exhibited better OS after 50 months than older patients (≥ 50 years), with no significant difference before 50 months ($P < 0.001$). Patients with tumor grades I-II had better OS than those with grades III-IV ($P < 0.001$). Patients with tumors < 10 cm had better OS than those with tumors ≥ 10 cm ($P = 0.01$). Patients who underwent hysterectomy had better OS ($P = 0.008$). However, race and marital status did not significantly affect survival ($P > 0.05$). Our research indicates that patients with stage IC disease who undergo chemotherapy have better survival rates ($P = 0.015$, Fig.3).

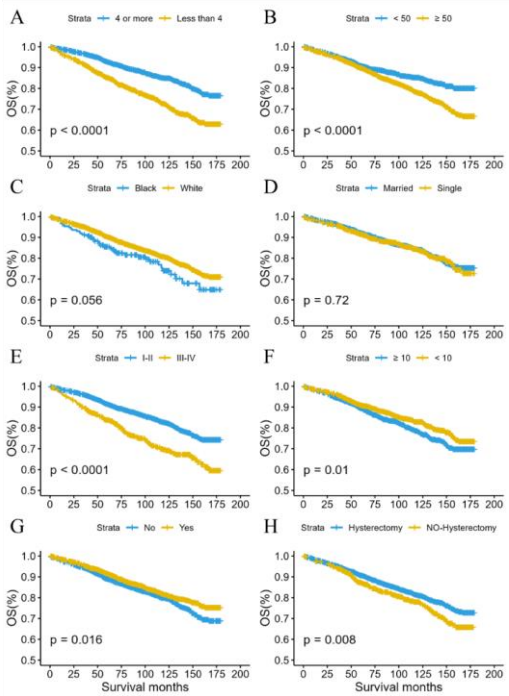

Figure 2. OS curves of patients with Stage I OEC compared according to (A) Lymphadenectomy, (B) Age, (C) Race, (D) Marital status, (E) Grade, (F) Tumor size, (G) Chemotherapy, (H) Surgery. OS = overall survival.

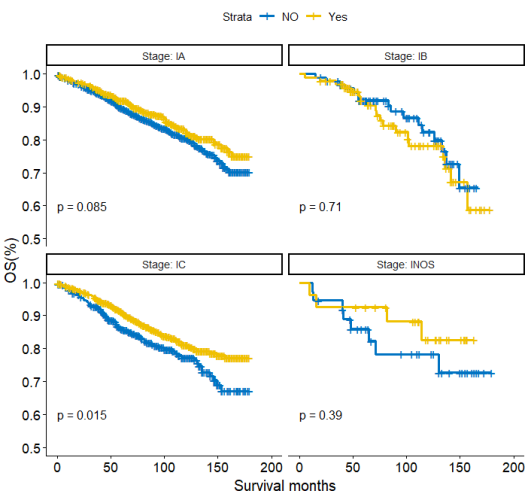

Figure 3. Subgroup analysis according to chemotherapy.

Furthermore, we used Kaplan-Meier survival analysis to estimate overall survival (OS) based on whether more than four lymph nodes were removed, in conjunction with other variables (Fig. 4). The results indicate that, in addition to tumor grade, the removal of more than four lymph nodes improves survival in stage I OEC patients, regardless of age, race, marital status, tumor size, and whether chemotherapy or hysterectomy was performed (P < 0.001).

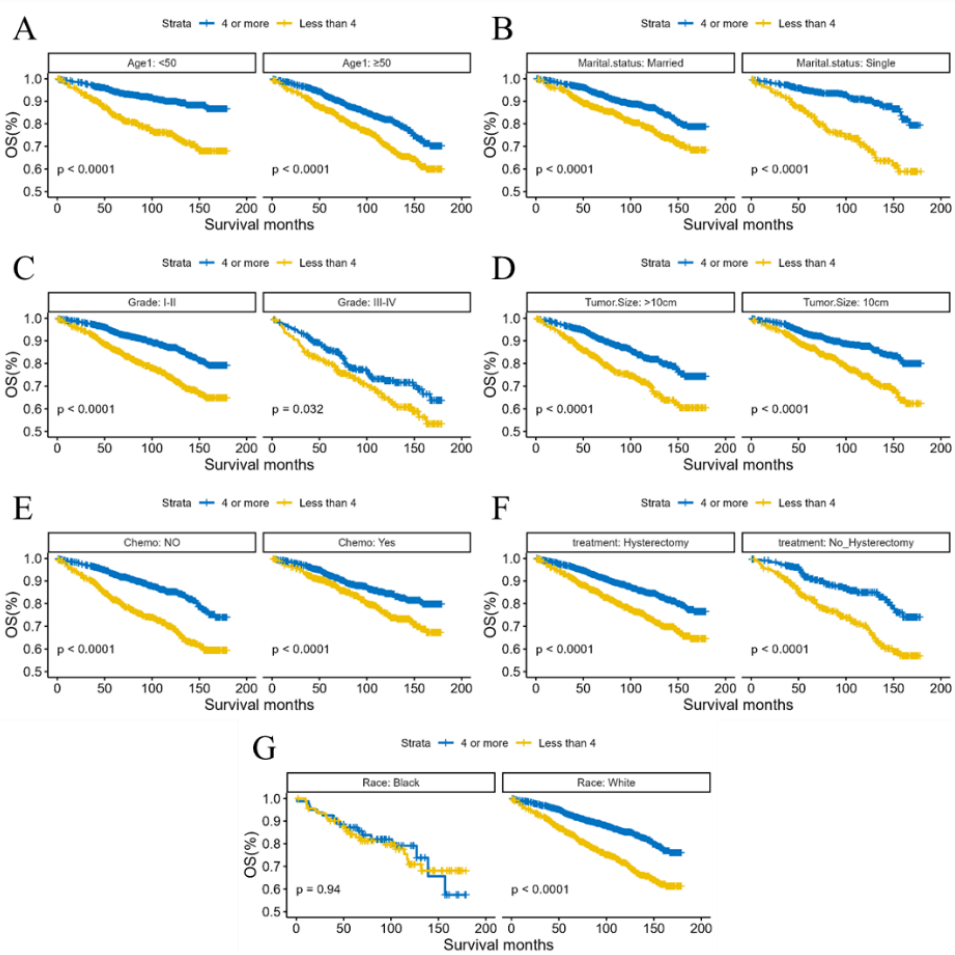

Figure 4. Subgroup analysis according to lymphadenectomy.

3.3 Univariate and multivariate analysis

This study utilized Univariate and multivariate Cox regression analyses were used to explore the impact of predictive factors on the survival of patients with stage I Ovarian Endometrioid Carcinoma (OEC). Univariate analysis results indicated that the removal of more than four lymph nodes (HR, 0.443; CI, 0.347-0.564; P < 0.001) was associated with a lower risk and better prognosis. Factors associated with a higher risk and poorer prognosis included age ≥ 50 years (HR, 1.85; CI, 1.403-2.439; P < 0.001), grade III-IV (HR, 1.593; CI, 1.201-2.113; P = 0.001), and tumor size ≥ 10 cm (HR, 1.391; CI, 1.089-1.776; P = 0.008), all of which were significantly associated with survival time (Table 2).

We employed multivariate Cox regression analysis complemented by a forest plot to investigate the independent effects of various clinical factors on patients with stage I OEC (Fig. 5). The forest plot vividly illustrated that the hazard ratios (HRs), 95% confidence intervals (CIs), identifying lymphadenectomy (P < 0.001), age (P < 0.001), grade (P = 0.007), tumor size (P = 0.016), and chemotherapy (P = 0.044) were significant independent predictors of survival. Our findings emphasize the importance of removing more than four lymph nodes in the prognosis and management of patients with stage I OEC.

Table 2. Univariate analysis of overall survival for Stage I OEC.

Variable	HR (95% CI)	Univariate P value
Age (years)		
< 50	1 [Reference]	NA
≥ 50	1.85(1.403-2.439)	<0.001
Race		
Black	1 [Reference]	NA
White	0.625(0.382-1.022)	0.060
Marital status		
Married	1 [Reference]	NA
Single	1.079(0.831-1.40)	0.569
Grade		
I-II	1 [Reference]	NA
III-IV	1.593(1.201-2.113)	0.001
Tumor Size (cm)		
< 10	1 [Reference]	NA
≥ 10	1.391(1.089-1.776)	0.008
Radiotherapy		
No	1 [Reference]	NA
Yes	0.856(0.319-2.298)	0.758
Chemotherapy		
No	1 [Reference]	NA
Yes	0.815(0.638-1.040)	0.100
Lymph nodes removed		
< 4	1 [Reference]	NA
≥ 4	0.443(0.347-0.564)	<0.001
Treatment		
No_Hysterectomy	1 [Reference]	NA
Hysterectomy	0.771(0.567-1.050)	0.099

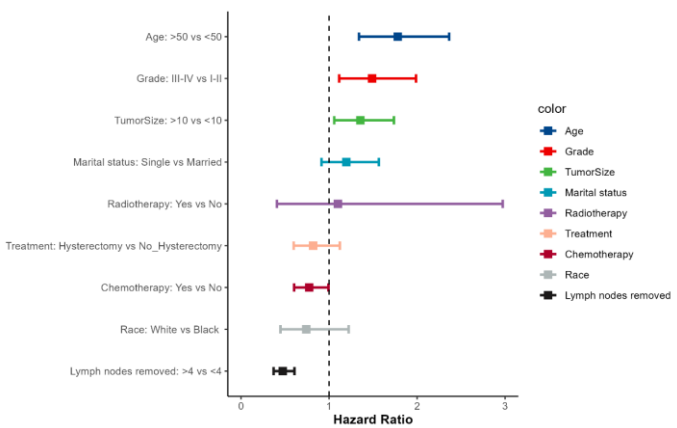

Figure 5. Full-model averaged Cox proportional hazard ratios with 95% confidence intervals. There is a dashed line for an equivalent hazard ratio (HR = 1).

4. Discussion

The 3659 patients with stage I OEC who were included in the present study accounted for 35.8% of all patients with this subtype of tumor during the same period, which is consistent with the previously reported range of 34-47% and is significantly higher than the percentage of stage I patients with ovarian serous carcinoma (9-12%) [14-18]. These findings indicate that a considerable proportion of patients with OEC are diagnosed at an early stage. In this study, we analyzed the risk factors of patients with stage I OEC. This study identified five independent prognostic factors affecting overall survival: lymphadenectomy, age, grade, tumor size, and chemotherapy. The results indicated that patients with older age, lower differentiation, larger tumors, no chemotherapy, and either no lymphadenectomy or minimal lymph node removal had lower survival rates. Our research also showed that removing more than four lymph nodes can improve the survival rates of patients with stage I OEC, regardless of the patient's age, race, marital status, tumor size, and whether they underwent chemotherapy or hysterectomy.

Considering the prognostic value of lymph node status, systematic lymphadenectomy is an essential component of the treatment guidelines for all patients with ovarian cancer. However, the effectiveness of lymph node dissection remains controversial. The rate of lymph node metastasis in stage I OEC is 2.1% [19]. A retrospective analysis of patients with stage I G1/2 OEC suggests that patients with stage I G1/2 OEC have a good prognosis, and adjuvant chemotherapy and staging lymphadenectomy do not improve survival rates [20]. Additionally, studies have shown that patients undergoing pelvic and para-aortic lymph node dissection do not exhibit a significant improvement in overall survival rates, and lymph node dissection does not affect the prognosis of patients [21]. Conversely, Bizzarri et al. reported a higher lymph node metastasis rate (5.5%) and found that lymph node dissection significantly affects DFS and OS [11]. Zhao et al. showed that lymphadenectomy was an independent protective factor for postoperative relapse in Stage I OEC ($p = 0.0041$), but the number of dissected lymph nodes was not [22]. Our study indicated that lymph node dissection is an independent prognostic factor affecting the overall survival with OEC. Further subgroup analysis revealed that the prognosis of all patients with stage I OEC improved with the removal of more than four lymph nodes, except for those of African American descent. However, the data for this study were obtained from the SEER database, and the specific sites of lymph node removal were not clear. Therefore, the specific lymph node surgical strategy in patients with stage I OEC requires further investigation.

A retrospective study in China showed that the incidence rate of OEC in individuals under 50 years old is on an annual increase (about 1.02% each year), while the incidence rate in individuals aged 50 years and above is decreasing (by 8.01% each year), suggesting a trend towards a younger age of onset [23]. The age of onset for OEC is between 40 and 50 years, with an average age of onset lower than that for HGSOC, and there are regional differences in the age of onset. International studies indicate that the average age of onset for OEC is 55 years [24], while domestic reports claim an average age of onset of 50 years [23]. In our study, the average age of the patients with stage I OEC selected from the SEER database was 55 years. Additionally, a study based on the French ESMEUnicancer database found that age is one of the prognostic factors affecting the overall survival (OS) of patients with OEC; patients diagnosed at age ≥ 50 years had a lower OS than those under 50 years (HR = 1.36, 95% CI 1.03-1.80, $P < 0.05$) [25]. Recent research has shown that older patients have a poorer prognosis, with statistically significant survival differences among the three age groups (< 61 years, 61-73 years, ≥ 74 years) ($P < 0.05$), and worse prognosis in the older age-group [26]. This is consistent with our findings in patients with stage I OEC.

Tumor lesions in patients with OEC are usually unilateral, large in volume (with an average size of 11 cm), and may have a smooth surface, the cut section often shows a solid and cystic appearance, with widespread hemorrhage or necrosis [25]. Our results indicate that tumor size is also an independent prognostic factor for OEC, with larger tumors associated with a lower overall survival rate. Early stage OEC often presents no obvious symptoms as the disease progresses and the tumor enlarges, and common clinical manifestations may include pelvic pain (52.9%), gastrointestinal symptoms (41.6%), palpable masses (40.3%), abdominal bloating (39.4%), vaginal bleeding (19.9%), and dysmenorrhea (18.1%) [27].

Most endometrioid tumors are well or moderately differentiated [28]. Our study showed that 74.7% of stage I OEC (Ovarian endometrioid Carcinoma) are well or moderately differentiated. One study indicated that 56% of OECs are poorly differentiated, which is less than the proportion of serous adenocarcinomas (64%) [14]. Malkasian et al. conducted a multivariate analysis on a sample of 1938 women with epithelial ovarian cancer, among which 958 were ovarian serous adenocarcinomas and 75 were ovarian endometrioid carcinomas, which grouped histological types based on combinations of stage and grade, and the results showed no difference in survival rates between

the different histological subtypes [29]. However, patients with endometrioid tumors in stage IA, grade 2, stage IB/C, grade 2, stage III, and grade 3 had better survival rates than patients with serous adenocarcinoma. Nevertheless, owing to the small number of patients and multiple statistical comparisons, Malkasian et al. advised a cautious interpretation of these results.

Surgery combined with chemotherapy is the most commonly used strategy for the treatment of OEC. After comprehensive staging surgery, based on clinicopathological staging and histological grading, patients received different adjuvant treatments. Patients with stage IA/IB grade G1 OECs do not require adjuvant chemotherapy; those with stage IA/IB grade G2 or stage IC grade G1 OECs may consider chemotherapy (3-6 cycles) or observation. A regimen of carboplatin combined with paclitaxel or docetaxel intravenous chemotherapy is recommended. Our research indicates that chemotherapy can improve the overall survival rate of patients with stage IC OEC. Additionally, studies have shown that resistance to platinum-based drugs is rare in patients with stage I OEC, and among 68 patients who received postoperative platinum-based combination chemotherapy, only three cases (4.3%) developed resistance to platinum chemotherapy drugs [22]. There was no difference in disease-free survival (DFS) between patients who received less than four cycles and more than four cycles of platinum-based chemotherapy [22]. Another study showed that after comprehensive staging surgery, chemotherapy did not extend the 5-year survival rate of patients with stage IA to IIA OECs (HR 1.092; 95%CI, 0.954-1.249; P=0.201). Patients with early stage OEC do not require adjuvant chemotherapy after comprehensive staging surgery [30]. Whether postoperative chemotherapy and the optimal cycle of postoperative chemotherapy should be administered to patients with stage I OEC with different prognostic risk factors requires further research.

This study had several limitations in the utilization of the SEER database for research on patients with early stage Ovarian Endometrioid Carcinoma (OEC). Primarily, the absence of data regarding endocrine therapy for patients with OEC within the SEER database precludes our ability to evaluate the efficacy of endocrine treatments in early stage OEC, indicating the need for further clinical studies to explore the potential benefits of such therapy. Additionally, the database lacks detailed information on lymph node dissection specifics, such as the count and location of nodes dissected in patients with OEC, thus restricting our in-depth analysis of the impact of lymph node dissection. Finally, the lack of comprehensive postoperative chemotherapy details hinders our capacity to delve into the effect of chemotherapy on survival rates among these patients. These limitations highlight that while the SEER database remains a valuable resource for research, a more thorough understanding of certain therapeutic interventions for OEC necessitates reliance on alternative data sources or future investigations.

5. Conclusions

A comprehensive analysis of patients with Stage I ovarian endometrioid carcinoma (OEC) underscores the complexity of predicting survival outcomes. While lymphadenectomy, age, grade, tumor size, and the application of chemotherapy have emerged as significant predictors, our findings advocate for a more tailored approach to treatment planning. Specifically, the role of lymphadenectomy, despite being a traditional practice, may necessitate reevaluation given its limited impact on the overall survival of certain patients. Age, tumor grade, and tumor size are crucial factors that directly influence survival rates, emphasizing the need for personalized treatment strategies that consider these variables. Moreover, the nuanced application of chemotherapy, especially in low-grade cases where its necessity is debated, calls for a strategic approach that weighs the potential benefits against risks. In light of these insights, our study suggests a movement towards more individualized care protocols, aiming to optimize survival outcomes while minimizing unnecessary interventions for patients with Stage I OEC.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

Ethical approval

No ethical approval or informed consent was required for this study because of the public availability of data in the SEER database.

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Author contributions

All the authors contributed to the conception and design of the study. Materials were prepared by J.Z. Data were collected and analyzed by J.Z. and P.Y. Results explanations were provided by J.Z. and H.L. The first draft of the manuscript was written by J. Z., and all authors commented on the previous versions of the manuscript. All authors have read and approved the final manuscript.

Data availability

Publicly available datasets were analyzed in this study. These data are available at https://seer.cancer.gov.

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