

# Low-grade serous ovarian carcinoma is a rare histological subtype in Japan

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## Summary

**Purpose of investigation:** To compare low-grade serous ovarian carcinomas (LGSC) and high-grade serous ovarian carcinomas (HGSC). **Materials and Methods:** Between 1985 and 2013, patients with LGSC and HGSC were identified through pathological review using the 2014 World Health Organization classification. The clinical outcome of patients with LGSC and HGSC was retrospectively compared. **Results:** A total of 174 cases, 5 (2.9%) cases of LGSC and 169 (97.1%) cases of HGSC (97.1%) were identified for our study. The proportion of patients who underwent optimal surgery was higher for LGSC than HGSC ( $p = 0.03$ ). We found no other statistically significant differences in the characteristics of the two groups. Survival analysis revealed that the histological subtype was not an independent prognostic factor of Progression-free survival ( $p = 0.28$ ) or overall survival ( $p = 0.43$ ). **Conclusions:** LGSCs may be a rare histological subtype in Japan and may not be associated with a different prognosis than HGSC. Larger scale studies are needed to examine the clinical significance of LGSC.

**Key words:** Ovarian carcinoma; Ovarian serous carcinoma; Low grade serous carcinoma; High grade serous carcinoma; Prognosis.

## Introduction

Ovarian carcinoma remains the leading cause of death among gynecologic malignancies [1]. The prognosis of patients with ovarian carcinomas has not significantly improved even with aggressive treatments [2-4]. The prognostic factors for ovarian carcinoma include age, performance status, stage of disease, histological subtypes, tumor grade, and residual tumor after surgery [5-8]. Among them, histological subtypes are important to identify in order to develop new treatment in view of their different molecular profiles. The most prevalent histological subtype is ovarian serous carcinoma, which has high capacity for disease progression and higher response rates to platinum-based chemotherapies than other histological subtypes [9-13].

Traditionally, the grading system for ovarian serous carcinoma has been the three-tiered system proposed by Shimizu-Silverberg or the one proposed by the International Federation of Gynecology and Obstetrics (FIGO) [14, 15]. The Shimizu-Silverberg grading system was based on the architectural features, the nuclear/cytologic atypia, the mitotic index, or a combination of these features [14]. The FIGO grading system was based on architectural patterns, and the grade depended on the ratio of glandular or papillary structures and solid tumor growth within the individual tumors [15]. In 2004, Malpica *et al.*, proposed a two-tiered grading system which classified ovarian serous carcinomas into low-grade serous ovarian carcinomas (LGSC) or high-grade serous ovarian carcinomas (HGSC) [16]. Sev-

eral subsequent reports have confirmed that this system has higher reproducibility than the traditional grading systems [17, 18]. Furthermore, while HGSC frequently had genomic instability based on *TP53* and *BRCA* mutations, LGSC often has *KRAS* or *BRAF* mutations. There are strong correlations between the morphologic features and the molecular profiles [19-21]. Thus, this two-tier grading system was incorporated into the 2014 World Health Organization (WHO) criteria [22]. However, the incidence of LGSCs is low, therefore, its clinicopathological features are still unclear [23].

The object of this study is to evaluate the frequency and clinical outcomes of LGSC compared to HGSC through review of pathology reports of ovarian serous carcinomas and serous borderline tumors (SBT) at our hospital using the 2014 two-tiered WHO grading system.

## Materials and Methods

The patients who underwent primary surgeries for ovarian serous carcinomas and SBTs at our hospital between January 1985 and August 2013 were identified. Pathological review for these patients were conducted by three observers (M.M., H.I., and H.T.) according to 2014 WHO criteria [22] without additional clinical information. Figure 1 shows representative images of LGSC and HGSC.

Patients complicated with other cancers, those without clinical information, and those who received neoadjuvant chemotherapy were excluded. Clinical summary was ob-

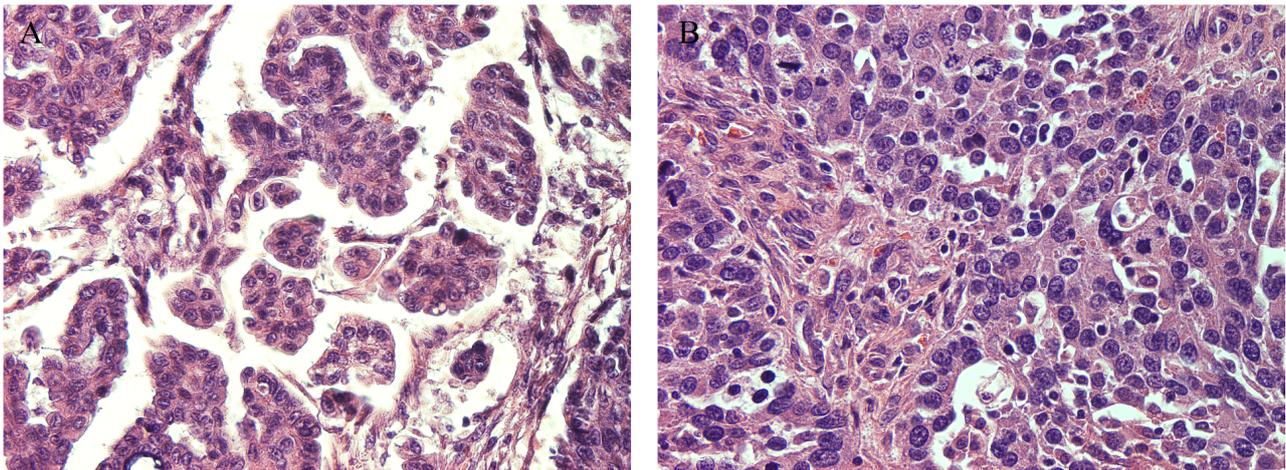


Figure 1. — Representative images of low-grade serous ovarian carcinomas (LGSC) and high-grade serous ovarian carcinomas (HGSC) according to the 2014 World Health Organization classification. (A) LGSC: uniform nuclei and infrequent mitotic figures with low nuclear atypia of well-differentiated tumors (200 $\times$ ). (B) HGSC: nuclear pleomorphism and frequent mitotic figures. Nuclear atypia is characteristic of high-grade tumors (200 $\times$ ).

tained from medical records. The stage of the disease was determined using the 2014 FIGO classification [24], and performance status was assigned using the Eastern Cooperative Oncology Group scale [25]. Residual tumors < 1 cm was defined as optimal surgery and  $\geq$  1 cm as suboptimal primary debulking surgery (PDS).

The JMP<sup>®</sup> Pro ver. 14.0.0 (SAS Institution Inc., NC, USA) was used for statistical analyses. The chi-squared test or Fisher's exact test was used to compare several variables between LGSCs and HGSCs. The duration from primary diagnosis of the disease to the diagnosis of clinical relapse, progression, or death was defined as progression-free survival (PFS). The duration from primary diagnosis of the disease to death or the date of last follow-up was defined as overall survival (OS). Survival curves of PFS and OS using the Kaplan-Meier method were compared using the log-rank test. Univariate and multivariate analysis of PFS and OS were performed using the Cox regression hazard model. Statistical significance was defined as a  $p$  value of < 0.05.

Institutional Review Board approval from the National Defense Medical College obtained and all study subjects provided written informed consent.

## Results

There were a total of 216 patients with ovarian serous carcinomas and 13 with SBTs. Twenty patients who received neoadjuvant chemotherapy were excluded. Furthermore, 35 patients were excluded due to histological diagnosis other than HGSC and LGSC as determined through pathological review. Among them were 17 patients with SBT, 7 with endometrioid carcinoma, 6 with clear cell carcinoma, 2 with mucinous carcinoma, 1 with carcinosarcoma, and 2 with adenocarcinoma not otherwise speci-

fied. Ultimately, 174 patients were entered in this study: 5 (2.9%) patients with LGSC and 185 (97.1%) patients with HGSC (Figure 2). One out of 5 cases with LGSC was originally diagnosed as SBT (1/13, 7.7%) and the remaining 4 cases were originally diagnosed as ovarian serous carcinoma (4/169, 2.4%).

The characteristics of the patients with LGSC or HGSC was shown in Table 1. There were no statistical differences in age, performance status, FIGO stage, and frequency of recurrences. The proportion of patients who underwent optimal surgery was higher for LGSC than HGSC ( $p = 0.03$ ). A majority of the patients received platinum-based chemotherapy: 4 cases of LGSC (80.0%) and 164 cases of HGSC (97.0%), respectively. Among them, patients with evaluable tumors included 1 patient with an LGSC and 103 patients with HGSC. Responses (complete and partial response) to chemotherapy were observed in the 1 (100%) patient with LGSC and 75/103 (72.8%) patients with HGSC. There were no statistical significances in PFS ( $p = 0.32$ ) and OS ( $p = 0.46$ ) between the two groups (Figure 2). Univariate analysis revealed that the histological subtype was not a significant prognostic variable for PFS (Hazard ratio (HR) 0.50,  $p = 0.28$ ) or OS (HR 0.59,  $p = 0.43$ ). Multivariate analysis demonstrated that FIGO stages III and IV were independent prognostic factors (PFS: HR 2.28,  $p < 0.01$ ; OS: HR 2.94,  $p < 0.01$ ) (Table 2).

## Discussion

Our study demonstrated that the incidence of LGSC was 2.9% through pathological review of previously diagnosed cases of ovarian serous carcinoma and SBT. We did not identify statistically significant differences in clinicopathological features and prognosis between LGSC and HGSC. However, the number of cases with LGSC is small.

Table 1. — Characteristics of the patients with low-grade serous and high-grade serous carcinomas.

Characteristic	LGSC (n = 5)		HGSC (n = 169)		p-value
Age, mean (range)	46	(38–68)	56	(29–83)	0.08
Performance status (%)					
≤ 1	5	(100)	167	(98.8)	0.99
> 2	0	(0.0)	2	(1.2)	
FIGO stage (%)					
I	2	(40.0)	18	(10.7)	0.15
II	0	(0.0)	17	(10.1)	
III	3	(60.0)	95	(56.2)	
IV	0	(0.0)	39	(23.1)	
Chemotherapy					
Done	4	(80.0)	164	(97.0)	0.16
Not done	1	(20.0)	5	(3.0)	
Residual tumor status (%)					
Optimal surgery	4	(80.0)	66	(39.0)	0.03
Suboptimal surgery	1	(20.0)	103	(61.0)	
Recurrence/Disease progression (%)					
Yes	2	(40.0)	105	(62.1)	0.37
No	3	(60.0)	64	(37.9)	

Abbreviations. FIGO: International Federation of Gynecology and Obstetrics, HGSC: High-grade serous carcinoma, LGSC: Low-grade serous carcinoma.

In 2004, Malpica *et al.* recommended a two-tiered grading system for ovarian serous carcinomas. Subsequently, several researchers reported the results of pathology review of ovarian serous carcinomas. Seidman *et al.*, reported that 10/113 (8.8%) patients were diagnosed with LGSC using pathology review of previously diagnosed ovarian serous carcinoma FIGO stage III and found no difference in prognosis of HGSC and LGSC [26]. They concluded that LGSC is a rare histologic type and a larger-scale study was needed in order to properly examine possible prognostic differences. Hence, Bodurka *et al.*, reported the results of a re-

view of a total of 392 patients on the carboplatin/paclitaxel arm of Gynecologic Oncology Group (GOG) Protocol 158. As a result, 21/241 (8.7%) patients were diagnosed with LGSC and their prognosis was better when compared to patients with HGSC [27]. Furthermore, Hannibal *et al.*, reported on data using the population-based, nation-wide Danish Pathology Data Bank [28]. This report did not perform pathology reviews and assigned the grade of the tumor as either LGSC if the original diagnosis was well-differentiated carcinoma or HGSC if the initial diagnosis was moderately or poorly differentiated carcinoma. Con-

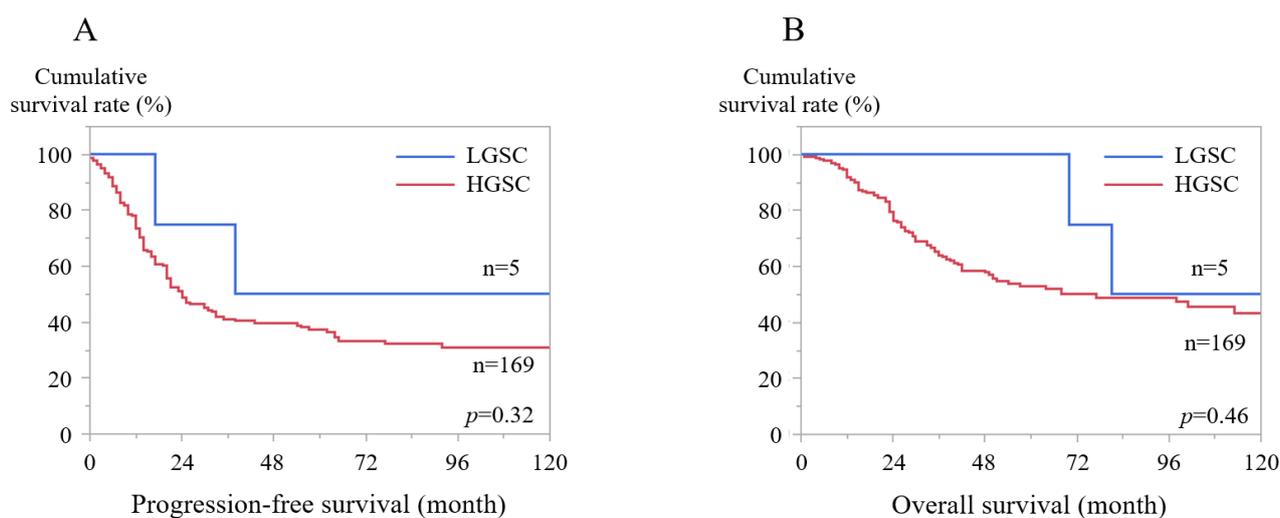


Figure 2. — Progression-free survival (Figure 2A) and overall survival (Figure 2B) of patients with ovarian low-grade serous carcinomas and high-grade serous carcinomas. There were no statistically significant differences between the PFS ( $p = 0.32$ ) and OS ( $p = 0.46$ ) groups.

Table 2. — Variables predictive of progression-free and overall survival in univariate and multivariate analyses.

Variables	Progression-free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Age								
≥ 55 vs. < 55	1.19(0.82 – 1.74)	0.37			1.12(0.73 – 1.74)	0.59		
FIGO stage								
III, IV vs. I, II	2.85(1.66 – 5.34)	< 0.01	2.28(1.27 – 4.47)	< 0.01	3.78(1.88 – 9.04)	< 0.01	2.94(1.39 – 7.40)	< 0.01
Residual tumor status								
Optimal vs. Suboptimal	0.5 (0.33 – 0.75)	< 0.01	0.68(0.43 – 1.03)	0.07	0.47(0.29 – 0.73)	< 0.01	0.64(0.39 – 1.04)	0.07
Histology								
LGSC vs. HGSC	0.5 (0.08 – 1.59)	0.28			0.59(0.53 – 10.2)	0.43		

Abbreviations. HR: hazard ratio, CI: Confidence interval, FIGO: International Federation of Gynecology and Obstetrics, HGSC: High-grade serous carcinoma, LGSC: Low-grade serous carcinoma.

sequently, 279 women with LGSC and 2,029 women with HGSC were identified and the frequency of LGSCs was 12.1% (279/2308), with the prognosis of LGSC being better than that of HGSC. Therefore, LGSC is a rare histologic type of ovarian cancer and there is controversy over the association the two-tiered grading system with prognosis. Our study showed that the proportion of LGSCs in our hospital was only 2.9% of ovarian serous carcinomas. We found no statistically significant differences in prognosis between LGSC and HGSC. In view of the small number of cases with LGSC we cannot reach a definitive conclusion about prognosis. We found that the rarity of LGSC is similar to several previous reports. As Diaz-Padilla *et al.* stated, multi-institutional, prospective, population-based studies using uniform pathological criteria and more accurate clinical staging information are needed in order to clarify this issue [23].

Ovarian histological subtypes can vary between countries and ethnicities. For example, the incidence of ovarian clear cell carcinoma in the United States is 4.8% in Caucasians, 3.1% in African-Americans, and 11.1% in Asians [29]. However, the incidence rate of ovarian clear cell carcinoma in Japan is more than 25% [30]. On the other hand, the rate of LGSC among ovarian serous carcinomas ranges from 8.7% to 12.1% in Western countries [26-28]. In a Chinese report, the proportion of LGSC among ovarian serous carcinomas was 9.2% [31]. We found a much lower proportion of LGSC than seen in other countries. Further research to identify differences based on country and ethnicity need to be performed.

Gershenson *et al.*, analyzed 112 LGSC at stage II-IV and reported that LGSC were characterized by a younger age at diagnosis and prolonged OS (median PFS 19.5 months; median OS: 81.8 months), and that persistent disease after primary chemotherapy was the only factor associated with shorter OS times [32]. Schmeler *et al.*, demonstrated that 88% of patients with LGSC had stable disease as the best response to platinum containing neoadjuvant chemother-

apy and that LGSC is not as responsive to conventional chemotherapy as HGSCs [33]. Therefore, the best management for LGSC is optimal surgery, as it is for HGSC, and the development of better chemotherapy against LGSC is needed. In our study, LGSC tended to be diagnosed at a younger age and achieved a higher rate of optimal surgery although it did not reach statistical significance. Our study included only 1 patient with residual tumor who received chemotherapy. Therefore, because our study is small and patients with LGSC occasionally respond to conventional chemotherapy, we cannot make a definitive statement about chemotherapy response.

LGSC often have *KRAS* or *BRAF* mutations [19-21]. Also, *KRAS* and *BRAF* are upstream regulators of mitogen-activated protein kinase (MAPK). These gene mutations result in activation of the MAPK pathway [34]. Based on these facts, a phase II study for LGSC was performed to examine the efficacy of selumetinib, an inhibitor of mitogen-activated protein kinase kinase (MEK) 1/2 [35]. It demonstrated that 15% of patients had objective responses, 65% of patients had stable disease, and adverse effects were tolerated. Although LGSC is a rare histological subtype, the classification is useful in developing new target-therapy based on molecular profile.

Some low-grade serous tumors of the ovary could display a macropapillary form of invasion which could be misdiagnosed as serous adenofibroma [36]. Also, because the distinction of low-grade from high-grade serous carcinoma is dependent on nuclear features [16], classification tumors with intermediate grade nuclei to low-grade or high-grade serous carcinoma can be difficult. However, high kappa values have been obtained among different reviewers using the 2-tier grading system [37]. Thus, the ease and reproducibility of using the 2-grade system was adopted in 2014 by the WHO. Our study included no cases originally diagnosed as LGSC. The rarity of LGSC might be one of causes for the diagnostic difficulty. Therefore, making this diagnosis requires close attention by the pathologist.

The limitations of our study include a small number of cases and being a single-institution study. Particularly, the survival analysis in our study is limited due to small-case study. However, our study is the first to evaluate LGSC in Japan through review of previously diagnosed cases of ovarian serous carcinoma and SBT. In order to further clarify the clinical characteristics and behavior of LGSC, multi-institutional studies should be performed.

## Conclusions

LGSC might be rare type of ovarian cancer type in Japan. Its prognosis might not be different from than that of HGSCs. Due to its rarity, further research is necessary to clarify its prevalence and clinicopathological features in Japan.

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## Conflict of Interest

The authors declare no competing interest.

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