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RESEARCH

Clinical and Prognostic Value of the Presence of Irregular Giant Nuclear Cells in pT1 Ovarian Clear Cell Carcinoma

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Abstract In the early stages of epithelial ovarian cancer, histopathological grading is important. However, the grading of ovarian clear cell carcinoma (OCCC) remains controversial. We aimed to identify irregular giant nuclear cells (IGNCs) by a simple method in clinical practice, and to evaluate the prognostic value of IGNCs in pT1 OCCC. Eighty-seven pT1 OCCC patients who underwent initial surgery at Jikei University Kashiwa Hospital, Chiba, Japan, were retrospectively assessed. Paraffin-embedded tissue sections (PTSs) stained with hematoxylin and eosin were reviewed. Giant nuclear cells (GNCs) were defined as cells with a nuclear length of more than twice the median nuclear length. GNCs with irregular nuclear circumferences were defined as IGNCs. Cases where one or more GNCs existed and where IGNCs accounted for >10% of the GNCs were classified as IGNC-positive. We also attempted to identify IGNCs on touch imprint cytology smears (TICSs). Among the 87 cases, 68 were IGNC-negative and 19 were IGNC-positive. The 5-year disease-free and overall survival rates were 88.9% and 90.3% in the total patients, 98.3% and 100% in the IGNC-negative group, and 59.7% and 62.0% in the IGNC-positive group, respectively. These survival rates were significantly lower in the IGNC-positive group than in the IGNC-negative group (adjusted hazard ratio=14, 95% confidence interval=2.7–124 and adjusted hazard ratio=25, 95% confidence interval=2.9–768, respectively). Prognostic differences were not identified for other factors. IGNC identification on 28 available TICSs predicted IGNC identification on PTSs (sensitivity=50.0%, specificity=100%, P=0.007). The presence of IGNCs has clinical and prognostic value for pT1 OCCC.

Keywords Intraoperative diagnosis · Nuclear morphometry · Ovarian cancer · Pathology · Touch imprint cytology

Abbreviations

CI	confidence interval
DFS	disease-free survival
EOC	epithelial ovarian cancer
GNC	giant nuclear cell
HR	hazard ratio
IGNC	irregular giant nuclear cell
OCCC	ovarian clear cell carcinoma
OS	overall survival
PTS	paraffin-embedded tissue section

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Introduction

Ovarian clear cell carcinoma (OCCC), which was defined by the World Health Organization in 1973 [1], is recognized as a distinct subtype of epithelial ovarian cancer (EOC). Some of its characteristics are poor prognosis, chemoresistance, high incidence of early-stage detection, relatively high occurrence in younger women and high prevalence in Asians. OCCC accounts for 11% of all EOCs among Asians but only 5% of all EOCs in general [2]. In Japan, OCCC occurs at an even higher rate of up to 22% [3]. Although OCCC is often diagnosed early, its prognosis is frequently worse than those of other histological subtypes of EOC. Moreover, the histopathological grading system for OCCCs remains controversial in terms of its usefulness, and is therefore not recommended by the World Health Organization [4]. OCCC is considered to be a high-risk cancer, regardless of its grade or pT1 substage. Therefore, even for stage IA or IB OCCC, adjuvant chemotherapy is indicated. Furthermore, surgeons almost uniformly perform retroperitoneal lymphadenectomy and hesitate to conduct less-invasive operations like fertility-sparing surgery.

Liu et al. [5] analyzed the nuclear shapes in pathological tissue specimens obtained from 40 OCCC patients using image measurement software. In addition, they evaluated the prognostic value of the presence of giant nuclei and nuclear irregularities in OCCC and found that these factors were related to a poor prognosis. In the present study, we aimed to identify irregular giant nuclear cells (IGNCs) by employing a simple method that is easily applicable in clinical practice and to evaluate the clinical and prognostic value of IGNCs in pT1 OCCC.

Methods

Among the primary EOC patients who initially underwent surgery between 1995 and 2008 at Jikei University Kashiwa Hospital, Chiba, Japan, 151 were diagnosed with OCCC. The pathological diagnoses were determined by

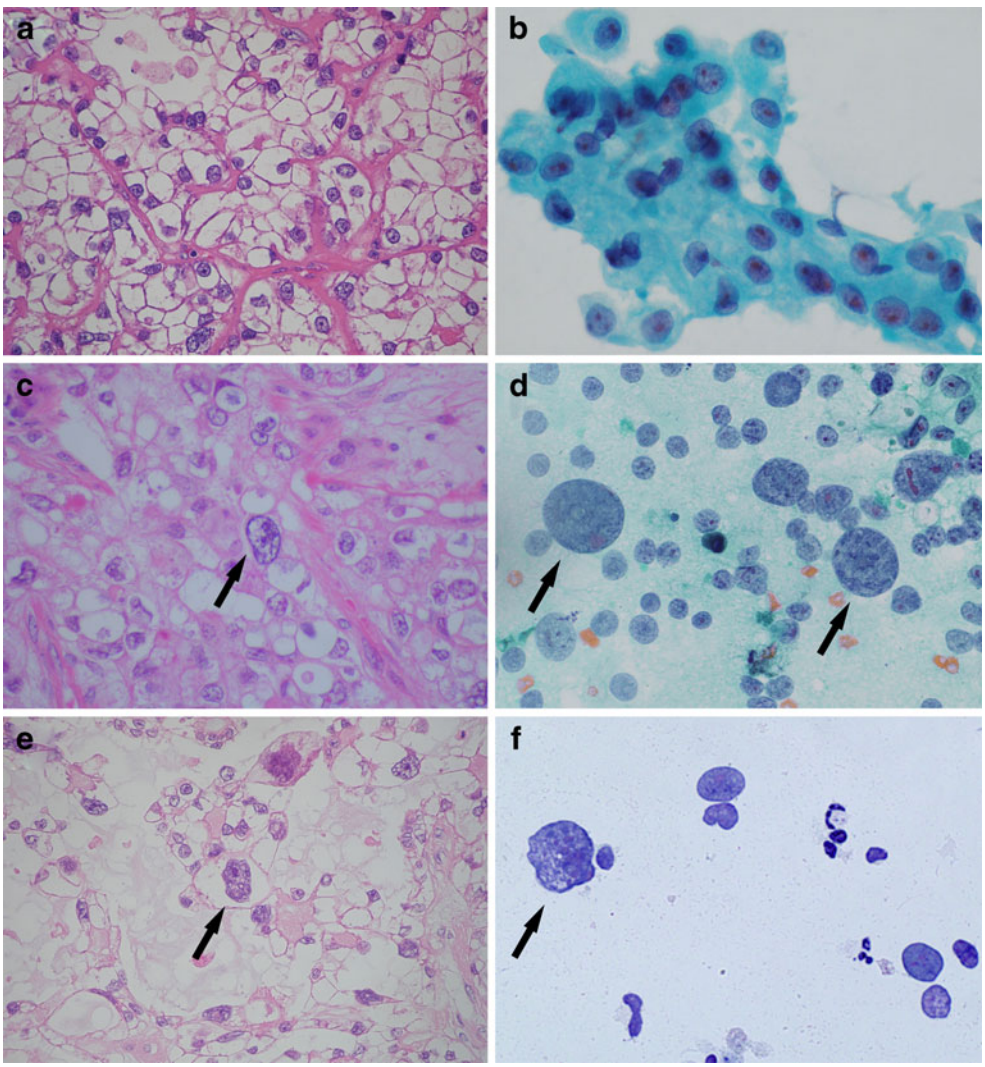

Fig. 1 Representative histological and cytological images. **a** An ovarian clear cell carcinoma (OCCC) without giant nuclear cells (GNCs) (tissue pathology, hematoxylin and eosin staining [H&E], ×400). **b** An OCCC without GNCs (touch imprint cytology, Papanicolaou staining [Pap], ×400). **c** An OCCC with GNCs (tissue pathology, H&E, ×400). **d** An OCCC with GNCs (touch imprint cytology, Pap, ×400). **e** An OCCC with irregular giant nuclear cells (IGNCs) (tissue pathology, H&E, ×400). **f** An OCCC with IGNCs (touch imprint cytology, Pap, ×400)

pathologists of the Department of Clinical Pathology at the hospital. Among the 151 patients, 87 had pT1 tumors, and their cases were retrospectively analyzed. For all cases, paraffin-embedded hematoxylin and eosin-stained tissue sections were archived and available for pathological review. These sections were reviewed by two independent pathologists and the pathological diagnoses were verified (see the Acknowledgments). For morphometric assessment, the paraffin-embedded tissue sections (PTSs) were examined under a double-headed microscope by two of the authors who were blinded to the patients' clinical data. All available sections that included cancer cells were reviewed for each patient. Giant nuclear cells (GNCs) were defined as cells with a nuclear length of more than twice the median nuclear length. Moreover, GNCs with irregular nuclear circumferences, bizarre nuclear forms or obviously distorted nuclear membranes were defined as IGNCs. Cases where one or more GNCs existed and where IGNCs accounted for more than 10% of the GNCs were classified as IGNC-positive. All the other cases were classified as IGNC-negative. If the initial opinions of the authors were conflicting in the classification of a case, a consensus decision was taken. The prognosis was evaluated on the basis of the IGNC grouping and other factors.

In addition, we attempted to identify IGNCs by touch imprint cytology in cases where touch imprint cytology smear (TICS) specimens were available. These smears, which were prepared ex vivo by touching the cut surface of the excised tumors, were stained by the Papanicolaou method.

The associations between the IGNC grouping or characteristic factors and the outcomes were analyzed using Student's *t*-test, Fisher's exact test and the chi-square test. To assess the prognosis, the disease-free survival (DFS) and overall survival (OS) rates were analyzed using the Kaplan-Meier method, log-rank test and multivariate Cox proportional hazards model. Hazard ratios (HRs) were calculated in multivariate analyses adjusted for patient age, pT1 substage, retroperitoneal lymphadenectomy, first-line chemotherapy regimen and IGNC grouping. All the tests were two-tailed and values of $P<0.05$ were considered statistically significant.

Results

Representative photographs of PTSs and TICSs for cases with no GNCs, with GNCs, and with IGNCs are shown in Fig. 1. The patients' characteristics are listed in Table 1 and the profiles of nine relapse cases are shown in Table 2. GNCs and IGNCs were seen most frequently in the sixth case shown in Table 2. For this case, we counted total tumor cells, GNCs, and IGNCs on prints of 20 vision fields (×200 magnification) for each of the PTSs and the TICSs.

Table 1 Characteristics of the 87 patients who received initial operations and were diagnosed with pT1 ovarian clear cell carcinoma

Characteristics	No. of patients				
	Total	(%)	IGNC grouping		*P*
			Negative	Positive	
Total (%)	87	(100)	68 (78.2)	19 (21.8)	
Age (y)					
Mean ± standard deviation	54.0±10.5		54.5±10.2	52.4±11.5	0.44[a]
Range	27–84		33–75	27–84	
pT1 substage					
pT1a	20	(23.0)	16	4	1.0[b]
pT1c	67	(77.0)	52	15	
Lymph node involvement					
N0	74	(85.1)	60	14	0.12[c]
Nx	10	(11.5)	7	3	
N1	3	(3.4)	1	2	
Retroperitoneal lymphadenectomy					
Performed	69	(79.3)	57	12	0.061[b]
Not performed	18	(20.7)	11	7	
First-line chemotherapy regimen					
Taxane and carboplatin	67	(77.0)	56	11	0.44[d]
Conventional cisplatin-based regimen	12	(13.8)	9	3	
Irinotecan hydrochloride and cisplatin	1	(1.1)	0	1	
Not performed	6	(6.9)	2	4	
Unknown	1	(1.1)	1	0	

[a] Calculated using Student's *t*-test

[b] Calculated using Fisher's exact test

[c] Calculated using the chi-square test

[d] Calculated using Fisher's exact test to compare the group that received taxane and carboplatin with the group that received the conventional cisplatin-based regimen

IGNC, irregular giant nuclear cell

Table 2 Characteristics of the 9 relapse cases

IGNC grouping	Age (y)	pTNM stage	Initial operation	First-line chemotherapy (courses)	Area of recurrence	Outcome	Disease-free survival (months)	Overall survival (months)
Positive	84	pT1cNxM0	TH + BSO + OM	None[a]	Peritoneal dissemination	Dead	4	7
Positive	54	pT1cN1M0	TH + BSO + OM + PL + PAL	DC (6)	Virchow's and mediastinal lymph nodes	Unknown[b]	5	More than 9
Negative	51	pT1cN0M0	TH + BSO + OM + PL	PC (6)	Peritoneal dissemination	Alive	10	More than 27
Positive	52	pT1cN0M0	TH + BSO + OM + lymph node biopsy	PC (6)	Para-aortic lymph nodes	Dead	11	33
Positive	61	pT1cN0M0	TH + BSO + OM + PL + PAL	DC (6)	Liver parenchyma	Dead	13	33
Positive	49	pT1cN0M0	TH + BSO + OM + PL	CAP (5)	Peritoneal dissemination	Dead	14	32
Positive	48	pT1cN1M0	TH + BSO + OM + PL	Irinotecan hydrochloride + cisplatin (6) [c]	Para-aortic lymph nodes	Dead	21	25
Positive	64	pT1cN0M0	TH + BSO + OM + PL	CAP (5)	Liver parenchyma and para-aortic lymph nodes	Dead	44	47
Negative	48	pT1aN0M0	TH + BSO + PL	CAP (5)	Peritoneal dissemination	Dead	71	82

[a] Because of old age (84 y)

[b] Nine months after the surgery, the hospital records of the patient were not available

[c] Because of taxane allergy

IGNC, irregular giant nuclear cell; pTNM, pathological tumor-nodes-metastasis classification; TH, total hysterectomy; BSO, bilateral salpingo-oophorectomy; OM, omentectomy; PL, pelvic lymphadenectomy; PAL, para-aortic lymphadenectomy; DC, docetaxel + carboplatin; PC, paclitaxel + carboplatin; CAP, cyclophosphamide + adriamycin + cisplatin

The numbers (percentages) of total tumor cells, GNCs, and IGNCs in these specimens were 1447, 12 (0.83%), 3 (0.21%) and 1253, 31 (2.5%), 4 (0.32%) in the PTSs and TICSs, respectively. The median observation period was 46 months (range, 3–136 months). Six patients underwent fertility-sparing surgery, while the remaining patients underwent standard operations, including total hysterectomy, bilateral salpingo-oophorectomy and omentectomy (or biopsy), as the initial procedures. Sixty-nine patients underwent retroperitoneal lymphadenectomy (50 pelvic, 19 both pelvic and para-aortic), and lymph node involvement was observed in three cases. Eight patients underwent a retroperitoneal lymph node biopsy and lymph node involvement was not observed. The remaining 10 cases did not undergo pathological exploration of retroperitoneal lymph nodes. Postoperative adjuvant chemotherapy was administered to 80 patients. No significant differences were observed between the IGNC-positive and IGNC-negative groups with respect to patient age, pT1 substage, lymphadenectomy or first-line chemotherapy regimen.

Table 3 shows the associations between the prognostic factors of interest and the recurrence or survival rates. In the total patients, the 5-year DFS and OS rates were 88.9% and 90.3%, respectively. The mean ages of the patients with tumor recurrence or death did not differ significantly from those of the patients without recurrence or death (P=0.41 and P=0.30, respectively, Student's t-test). Multivariate analyses with the Cox proportional hazards model revealed that patient age was not related to the rates of recurrence or death (HR for a one-unit [1-year] increase in age [one-unit HR]=1.01, 95% confidence interval [CI]=0.90–1.13 and one-unit HR=1.02, 95% CI=0.88–1.19, respectively). Tumor recurrence and death were more common in the IGNC-positive group than in the IGNC-negative group (relative risk=12.5, 95% CI=2.8–56 and relative risk=21.5, 95% CI=2.7–168, respectively). The DFS and OS rates were significantly lower in the IGNC-positive group than in the IGNC-negative group (Fig. 2). There were no prognostic differences in terms of the pT1 substage (pT1a vs. pT1c) or whether lymphadenectomy was performed. The DFS and OS rates tended to be lower in the group receiving a conventional cisplatin-based regimen as the first-line chemotherapy than in the group receiving taxane and carboplatin. However, multivariate analyses with the

Table 3 Univariate and multivariate analyses of prognostic factors using the Kaplan-Meier method and Cox proportional hazards model

Factors	*n*	Events		DFS				OS			
				Kaplan-Meier		Cox[a]		Kaplan-Meier		Cox[a]	
				5-year				5-year			
		Recurrence	Death	DFS (%)	*P*[b]	HR	95% CI	OS (%)	*P*[b]	HR	95% CI
pT1 substage											
pT1a	20	1	1	100	0.41	1		100	0.58	1	
pT1c	67	8	6	85.9		0.73	0.068–17	87.6		0.34	0.012–9.4
Retroperitoneal lymphadenectomy											
Performed	69	7	5	89.2	0.78	1		91.3	0.48	1	
Not performed	18	2	2	88.5		0.37	0.015–3.1	87.2		0.72	0.018–9.6
First-line chemotherapy regimen											
Taxane and carboplatin	67	4	2	93.4	0.14	1		95.6	0.051	1	
Conventional cisplatin-based regimen	12	3	3	83.3		1.8	0.31–9.6	83.3		4.1	0.47–59
IGNC grouping											
Negative	68	2	1	98.3	<0.001	1		100	<0.001	1	
Positive	19	7	6	59.7		14	2.7–124	62.0		25	2.9–768

[a] Multivariate analysis using the Cox proportional hazards model adjusted for patient age and other factors

[b] Calculated using the univariate log-rank test

DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval

Cox proportional hazards model revealed no significant differences in this regard. The overall results of univariate and multivariate analyses adjusted for patient age and other factors indicated that only the IGNC grouping was significantly related to the prognosis.

The screening values of IGNC identification were calculated. With respect to predicting lymph node involvement, the sensitivity was 66.7%, specificity was 84.8% and likelihood ratio was 4.4 (Fig. 3a). However, these results were not statistically significant. TICSs were available in 28 cases (32.2%). Among these cases, three (10.7%) were identified to be IGNC-positive on TICSs, and all of them were identified to be IGNC-positive on PTSs. With respect to predicting IGNC identification on PTSs, the sensitivity of IGNC identification on TICSs was 50.0%, but the specificity was 100% (Fig. 3b).

Discussion

In the early stages of EOC, it is essential to accurately predict each patient's prognosis and select appropriate

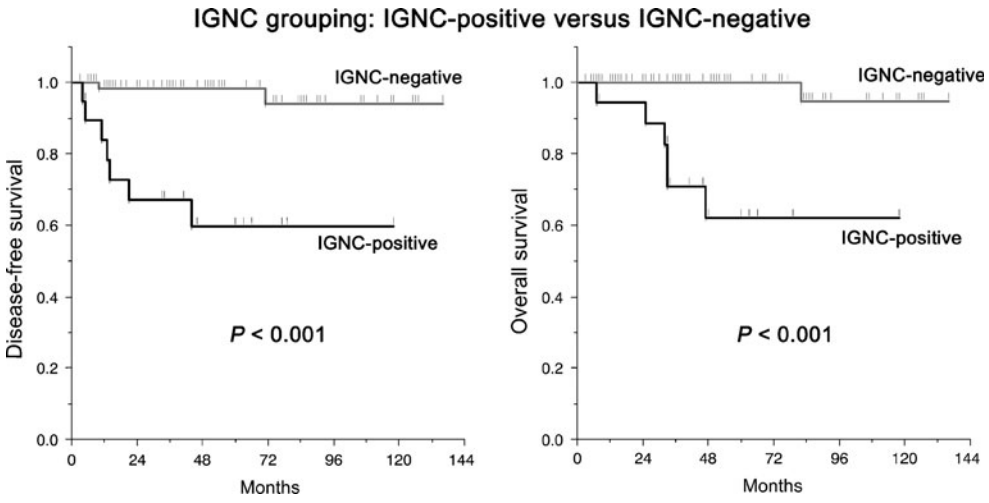

Fig. 2 Prognostic analysis performed using the Kaplan-Meier method and log-rank test. IGNC, irregular giant nuclear cell

a Lymph node involvement

		N1	N0	Total
IGNC	Positive	2	10	12
	Negative	1	56	57
	Total	3	66	69

$P = 0.076$

Sensitivity	66.7%
Specificity	84.8%
Positive predictive value	16.7%
Negative predictive value	98.2%
Likelihood ratio	4.4

b IGNC on paraffin tissue sections

		Positive	Negative	Total
IGNC on touch smears	Positive	3	0	3
	Negative	3	22	25
	Total	6	22	28

$P = 0.007$

Sensitivity	50.0%
Specificity	100%
Positive predictive value	100%
Negative predictive value	78.6%
Likelihood ratio	Not available

Fig. 3 **a** Screening value of IGNC identification for lymph node involvement. **b** Screening value of touch imprint cytology for histopathological IGNC identification. *P* values were calculated using Fisher's exact test. IGNC, irregular giant nuclear cell

treatment to avoid unnecessary invasive therapy and ensure a good outcome. Young et al. [6] suggested that women with low-risk cancers, defined as stage IA or IB, grade 1 or 2, or non-clear-cell histology, do not need further adjuvant therapy, and the currently used clinical therapeutic strategies are based on this approach [7, 8]. Moreover, the clinical implications of EOC grades are widely accepted with respect to non-clear-cell histology [9–11]. However, the grading of OCCC remains controversial. It is more difficult to grade OCCCs than other histological subtypes of EOCs because a single specimen contains various structures, and nuclear abnormalities tend to be moderate or severe. In the present study, we revealed the prognostic value of the presence of IGNCs in pT1 OCCC by employing a method that is easy to use in clinical practice.

The paclitaxel and carboplatin regimen is generally administered concomitantly to EOC patients as a first-line adjuvant chemotherapy [12]. The regimen is also prescribed to patients with OCCC [13, 14]. However, the efficacy of this therapy has not always been satisfactory in cases of OCCC [15]. In the present study, the 5-year recurrence rate was 1.7% in the IGNC-negative group, suggesting a very good prognosis for this group. Therefore, it seems doubtful that every tumor with a clear-cell histology belongs to a high-risk group and needs to be uniformly treated by adjuvant chemotherapy even in stage I cases. Omission of adjuvant chemotherapy should be considered for IGNC-negative tumors at stage I because they pose a low risk. In contrast, this therapeutic strategy was inappropriate for the IGNC-positive group, which was ascertained to be a very high-risk group.

Total hysterectomy, bilateral salpingo-oophorectomy and omentectomy are considered to be standard initial procedures. In addition, retroperitoneal lymphadenectomy is generally performed and is considered to have diagnostic value. However, its therapeutic value is controversial and there is no consensus on whether lymphadenectomy improves outcomes. Maggioni et al. [16] conducted a randomized study on the value of lymphadenectomy for treating patients with stage I and II EOC (n=268). Although the systemic lymphadenectomy group in their study tended to have a better prognosis than the lymph node biopsy group, the difference was not significant. On the basis of the results of a large-scale non-randomized epidemiological survey (n=6,686), Chan et al. [17] suggested that lymphadenectomy for stage I disease improved survival in non-clear-cell EOC patients but not in OCCC patients. In a retrospective study (n=205), Suzuki et al. [18] concluded that patients with early-stage OCCC who underwent lymphadenectomy did not show a significant improvement in survival. Therefore, the therapeutic value of retroperitoneal lymphadenectomy in patients with early-stage OCCC remains unclear. Lymph node involvement is observed in approximately 5–8% of patients with pT1 OCCC [19, 20], which is lower than the rate of 13.7% observed for pT1 EOCs in general [21]. In the present study, lymph node involvement was detected in three of 87 (3.4%) pT1 cases and three of the 69 (4.3%) lymphadenectomy cases, but just one of the 57 (1.8%) IGNC-negative cases in which a lymphadenectomy was performed. Therefore, we questioned whether lymphadenectomy needs to be performed uniformly in patients with pT1 OCCC. The results of the present study suggest that lymph node involvement may be predicted by IGNC identification in patients with pT1 OCCC.

Our results for IGNC identification on TICSs suggest that if IGNCs are identified on TICSs, they will also be identified on PTSs. For example, in cases where a tumor is diagnosed as OCCC on the basis of intraoperative frozen-section pathological analysis [22, 23] or tumor cytology [24], we consider that IGNC identification by intraoperative touch imprint cytology can provide us with valuable clinical information that would aid the decision on whether excessively invasive operations can be avoided.

In renal cell carcinoma, Fuhrman et al. [25] found that the existence of large or irregular nuclei was associated with a poor prognosis. Subsequently, the prognostic value of the Fuhrman nuclear grading system has well been recognized. However, the interobserver reproducibility is not considered to be satisfactory because of the complexity of the four-tiered grading system [26–28]. In the present

study, we have proposed an easy and simplified stratification using identification of IGNCs for OCCC. We hope to carry out a prospective and larger-scale study to assess the interobserver reproducibility as well as consolidate the prognostic value of IGNCs in the future.

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