Fukushima J. Med. Sci.,
Vol. 70, No. 2, 2024

[Original article]

Differentiation of ovarian serous carcinoma from ovarian clear cell carcinoma using a 10-gene signature selected by comprehensive gene expression analysis

Shinji Nomura[1)], Takafumi Watanabe[1)], Reiko Honma[2)], Susumu Matsukura[3)], Emi Ito[4)], Jun-ichi Imai[4)], Yuichiro Kiko[5)], Osamu Suzuki[5)], Yuko Hashimoto[5)], Manabu Kojima[1)], Shigenori Furukawa[1)], Shu Soeda[1)], Shinya Watanabe[4)] and Keiya Fujimori[1)]

[1)]Department of Obstetrics and Gynecology, Fukushima Medical University, Fukushima, Japan, [2)]Nippon Gene Co., Ltd., Chiyoda, Tokyo, Japan, [3)]Medicrome Inc., Fukushima, Japan, [4)]Translational Research Center, Fukushima Medical University, Fukushima, Japan, [5)]Department of Diagnostic Pathology, Fukushima Medical University, Fukushima, Japan

(Recieved August 26, 2023, accepted January 17, 2024)

Abstract

Aim : Ovarian serous carcinoma (OSC) and ovarian clear cell carcinoma (OCCC) are two major histological types of epithelial ovarian carcinoma (EOC), each with different biological features and clinical behaviors. Although immunostaining is commonly used for differential diagnosis between OSC and OCCC, correct identification of EOC with mixed-type histology is sometimes a diagnostic challenge. The aim of the present study was to explore candidate genes as potential diagnostic biomarkers that distinguish OSC from OCCC.

Methods : A total of 57 surgical specimens were obtained from EOC patients who had previously undergone primary debulking surgery. Total RNAs were extracted from fresh-frozen tissues of EOC patients, and were used for comprehensive gene expression analysis using DNA microarray technology.

Results : Ten candidate genes, *FXYD2*, *TMEM101, GABARAPL1*, *ARG2*, *GLRX, RBPMS*, *GDF15*, *PPP1R3B*, *TOB1*, and *GSTM3* were up-regulated in OCCC compared to OSC. All EOC patients were divided into two groups according to hierarchical clustering using a 10-gene signature.

Conclusion : Our data suggest that the 10 candidate genes would be an excellent marker for distinguishing OSC from OCCC. Furthermore, the molecular signatures of the 10 genes may enlighten us on the differences in carcinogenesis, and provide a theoretical basis for OCCC's resistance to chemotherapy in the future.

Key words : comprehensive gene expression analysis, diagnosis, gene signature, ovarian clear cell carcinoma, ovarian serous carcinoma

Introduction

Epithelial ovarian carcinoma (EOC) is one of the most common malignant tumors in women, and has the highest mortality rate[1)]. Ovarian serous carcinoma (OSC) and ovarian clear cell carcinoma (OCCC) are two major histological types of EOC, each with different biological features and clinical behaviors. OSC is the most commonly observed histological subtype of EOC around the world[2)]. Significant differences among ethnici groups have been observed in the incidence of OCCC ; it ac-

Corresponding author : Takafumi Watanabe E-mail : t-wata@fmu.ac.jp

counts for 11.7% of all EOC cases in Asians, compared to 4.4% of all cases in Caucasians[3]. High-grade OSC (HGOSC), which accounts for approximately 95% of all OSC cases, originates from the epithelial layer of the fallopian tube fimbriae, and is characterized by aggressive behavior and advanced stage at diagnosis[4]. Compared with HGOSC, low-grade OSC (LGOSC) occurs following a serous borderline tumor, and has both an indolent course and prolonged survival[5]. On the other hand, OCCC, which has been associated with endometriosis, tends to present at an earlier stage, and occurs in younger patients than HGOSC[6]. In addition, the efficacies of platinum-based chemotherapy for HGOSC and OCCC have been reported to be 20–50% and 70–80%, respectively, and late-stage OCCC has a worse prognosis compared with late-stage OSC[7,8]. Since the response to platinum-based chemotherapy is directly associated with prognosis in EOC patients who have undergone suboptimal surgery or neoadjuvant chemotherapy, accurate diagnosis is the most important factor for predicting prognosis.

The distinction between OSC and OCCC is sometimes a diagnostic challenge. Immunohistochemical markers, including hepatocyte nuclear factor 1-beta (HNF1β), WT1, estrogen receptor, progesterone receptor and TP53, are used to distinguish between OCCC and OSC[9]. In cases of mixed OSC and OCCC, molecular biomarkers may be useful for differential diagnosis, as it is difficult to make a clear diagnosis based only on morphology and immunohistochemistry. Recently, Zhou *et al.* reported distinct gene expression profiles associated with clinical outcomes in patients with OCCC and HGOSC, but did not report a differential diagnosis between them[10].

The aim of the current study was to explore candidate genes as potential diagnostic biomarkers that distinguish OSC from OCCC by comprehensive gene expression analysis using DNA microarray technology. Furthermore, we also present novel candidate biomarkers for chemoresistance and the development of new therapeutic targets for OCCC.

Materials and Methods

Clinical samples

The study population consisted of subjects who had been diagnosed with EOC between 2008 and 2015. A total of 57 Japanese patients, 39 OSC and 18 OCCC patients, who had undergone surgery in Fukushima Medical University Hospital, were enrolled. Informed consent from all study participants was documented in writing. Adjuvant therapy was determined according to the physician's treatment strategy. Evaluation of the response to treatment was assessed using the revised Response Evaluation Criteria in Solid Tumors guidelines (version 1.1). This study was approved by the Ethics Committee of Fukushima Medical University (No. 1953), which is guided by local policy, national law, and the World Medical Association Declaration of Helsinki. All analyses were performed in accordance with the relevant guidelines and regulations.

Comprehensive gene expression analysis

Fifty-seven frozen specimens were processed for total RNA using Isogen (Nippon Gene Co., Ltd., Tokyo, Japan), and poly(A)+RNA was purified using a MicroPoly(A) Purist kit (Ambion, Austin, TX, USA). DNA microarray and gene expression analyses were performed as previously published[11,12].

Hierarchical clustering

In order to select genes that distinguish OSC from OCCC, we analyzed DNA microarray data using log2 ratios. Firstly, the statistical differences between OSC and OCCC were analyzed using Student's *t*-test (two-tailed test), and genes corresponding to $p < 1.0$ E-5 were extracted. Secondly, we calculated the means of the values of the OSC and OCCC samples for each chosen gene, and then selected 29 genes in which the absolute value of the difference between these means was > 2.0. Finally, the standard deviation (SD) of the OSC samples was calculated, and 10 genes with SD < 1.0 were selected. Hierarchical clustering analysis was performed using the group average method with an Expression View Pro (MicroDiagnostic, Tokyo, Japan).

Construction of a gene expression scoring system to distinguish between OSC and OCCC

The log2 ratios of the 10 genes selected from the specimens were added as gene expression scores, which were arranged in ascending order[11]. To validate the diagnostic accuracy of the scoring system, a receiver operating characteristic (ROC) curve was used to determine the area under the curve (AUC). The optimal cut-off value for the definitive diagnosis between OSC and OCCC was set at a value where sensitivity and specificity were the closest to the value of the area under the ROC curve. ROC curves and group scatter plots were created using StatFlex ver. 6.0 software (Artech Co.,

Ltd., Osaka, Japan).

Statistical analysis

Statistical analyses of clinical data were performed using SPSS version 25 software (SPSS, Inc., Chicago, IL, USA). The differences in Tables 1 and 2 were assessed using the chi-square test or the Mann-Whitney U test. The confidence level was set at $P < 0.05$.

Results

Clinicopathological characteristics

A total of 57 EOC patients who had undergone surgery were enrolled in this study, and their clinicopathological characteristics are shown in Table 1. Among the 57 tumors, 39 were OSC (68%) and 18 were OCCC (32%). There were significant differences between the two groups of patients in terms of stage and whether they had undergone completion surgery, as well as clinical outcome in stage III/IV patients (Table 1).

Efficacy of platinum-based chemotherapy

A total of 34 patients with measurable disease, including 27 OSC and seven OCCC patients, underwent suboptimal surgery and received postoperative platinum-based chemotherapy. The overall response rate (ORR) in the OSC patients was 74% ($n = 20$), with a complete response (CR) rate of 51.9% ($n = 14$) and partial response (PR) rate of 22.2% ($n = 6$). On the other hand, the ORR in the OCCC patients was 14.3% ($n = 1$), with PR in 14.3% ($n = 1$). There was a significant difference in ORR between the OCCC and OSC patients ($P = 0.004$) (Table 2).

Table 1. Clinical characteristics and histological distribution in 57 Japanese patients with epithelial ovarian carcinoma

Characteristic	OSC ($n = 39$, 68%)	OCCC ($n = 18$, 32%)	*P*
Age at diagnosis (years), median (range)	62 (38-85)	61 (44-79)	0.32
Stage, n (%)			
I/II	5(12.8)	10 (55.6)	
III/IV	34 (87.2)	8 (44.4)	**<0.001**
Grade, n (%)			
Low	5 (12.8)	N/A	
High	34 (87.2)	N/A	
Completion surgery, n (%)			
optimal	12 (30.8)	11 (61.1)	
suboptimal	27 (69.2)	7 (38.9)	**0.03**
Clinical outcome (all), n (%)			
NED/AWD	30 (76.9)	12 (66.7)	
DOD	9 (23.1)	6 (33.3)	0.41
Clinical outcome (stage III/IV), n (%)			
NED/AWD	26 (76.5)	2 (40.0)	
DOD	8 (23.5)	6 (60.0)	**0.005**

OSC, ovarian serous carcinoma ; OCCC, ovarian clear cell carcinoma. NED, no evidence of disease ; AWD, alive with disease ; DOD, dead of disease. Significant *P* values ($P < 0.05$) are shown in **bold**.

Table 2. The difference in response to platinum-based chemotherapy in OSC and OCCC

Tumor responses	OSC ($n = 27$)	OCCC ($n = 7$)	*P* value
CR	14 (51.9%)	0 (0%)	
PR	6 (22.2%)	1 (14.3%)	
SD and PD	7 (25.9%)	6 (85.7%)	
ORR	20 (74.0%)	1 (14.3%)	0.004

OSC, ovarian serous carcinoma ; OCCC, ovarian clear cell carcinoma. CR, complete response ; PR, partial response ; SD, stable disease ; PD, progressive disease ; ORR, overall response rate.

Identification of genes to differentiate between OCCC and OSC

In order to detect a gene signature which distinguishes OCCC from OSC, we performed DNA microarray analysis using 57 tumor samples. A set of 10 genes that were up-regulated in OCCC compared to OSC was selected by statistical analysis as described in the Materials and Methods section (Table 3). The 10-gene signature was subjected to hierarchical clustering. All 57 samples were divided into two groups by hierarchical clustering (Fig. 1). Microarray data have been deposited to the DDBJ Genomic Expression Archive (GEA), and are available using accession numbers E-GEAD-556 and E-GEAD-576.

Validation of the gene expression scoring system

We constructed a gene expression scoring system to distinguish OSC from OCCC by using the 10 candidate genes. This gene expression scoring system was created by sorting the samples from left to right in order of decreasing score value (Fig. 2). ROC curve analysis of our gene expression scoring system yielded an optimal cut-off score of 3.39, with an AUC of 0.95, sensitivity of 88.9%, and specificity of 92.3% (Fig. 3).

Clinical features of five cases that deviated from hierarchical clustering

Although all 57 tumors were divided into two groups by hierarchical clustering using the 10-gene signature, only five cases were misclassified. Three OSC cases were categorized as OCCC, and two OCCC cases were categorized as OSC (Fig. 1). Their clinical features are summarized in Table 4. Tumor S37 had no response to platinum-based chemotherapy. Tumors S37 and S39 partially included OCCC in the tissue. Tumors S37 and S38 were LGOSC, and tumor C18 had PR to platinum-based chemotherapy.

Table 3. Ten genes that were up-regulated in OCCC compared to OSC by transcriptomic profiling

Gene symbol	Accession code	Description	Fold change	*P* value
FXYD2	NM_001680	FXYD domain containing ion transport regulator 2	3.62	9.01E-06
TMEM101	NM_032376	Transmembrane protein 101	3.09	1.95E-07
GABARAPL1	NM_031412	GABA type A receptor associated protein like 1	2.51	2.65E-08
ARG2	NM_001172	Arginase 2	2.44	2.48E-06
GLRX	NM_002064	Glutaredoxin	2.36	4.62E-08
RBPMS	D84109	RNA binding protein with multiple splicing	2.17	5.73E-08
GDF15	NM_004864	Growth differentiation factor 15	2.13	3.66E-06
PPP1R3B	AK091994	Protein phosphatase 1, regulatory (inhibitor) subunit 3B	2.05	3.64E-09
TOB1	NM_005749	Transducer of ERBB2, 1	2.04	6.36E-08
GSTM3	NM_000849	Blutathione S-transferase mu 3	2.02	5.52E-07

OCCC, ovarian clear cell carcinoma ; OSC, ovarian serous carcinoma.

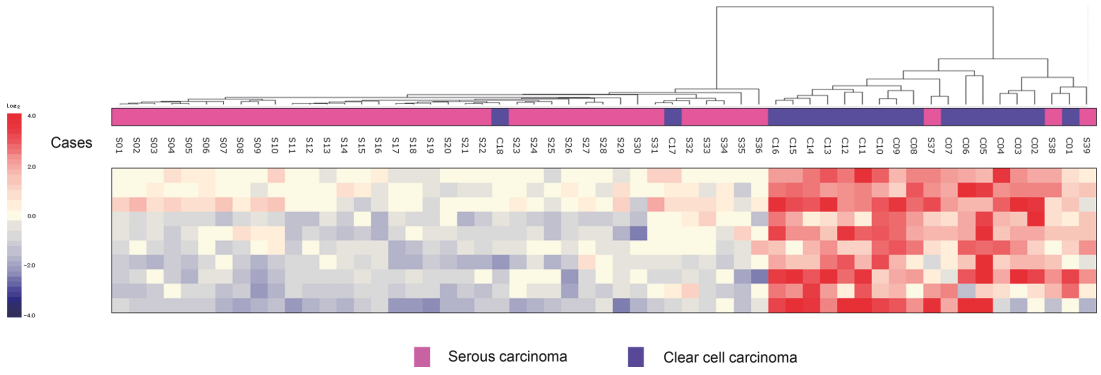

Fig. 1. Hierarchical clustering of 10 candidate genes with statistically differentiated expression in 39 ovarian serous carcinoma (OSC) and 18 ovarian clear cell carcinoma (OCCC) samples. On the heat map, red represents up-regulation and blue represents down-regulation. The color bar at the left side of the figure represents the grades of the relative expression levels : increased (red), and decreased (blue). The "S" or "C" at the beginning of each case indicates OSC or OCCC patient, respectively. Two main groups, OSC and OCCC, were formed.

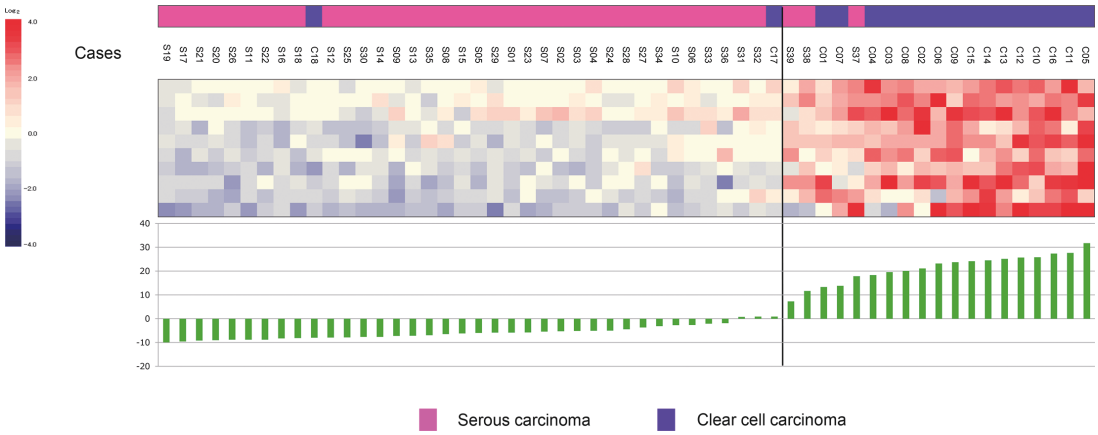

Fig. 2. Gene expression scoring system for 39 ovarian serous carcinoma (OSC) and 18 ovarian clear cell carcinoma (OCCC) samples. The green bars depict the gene expression score for each case. The black vertical line indicates the optimal cut-off score determined by receiver operating characteristic curve analysis.

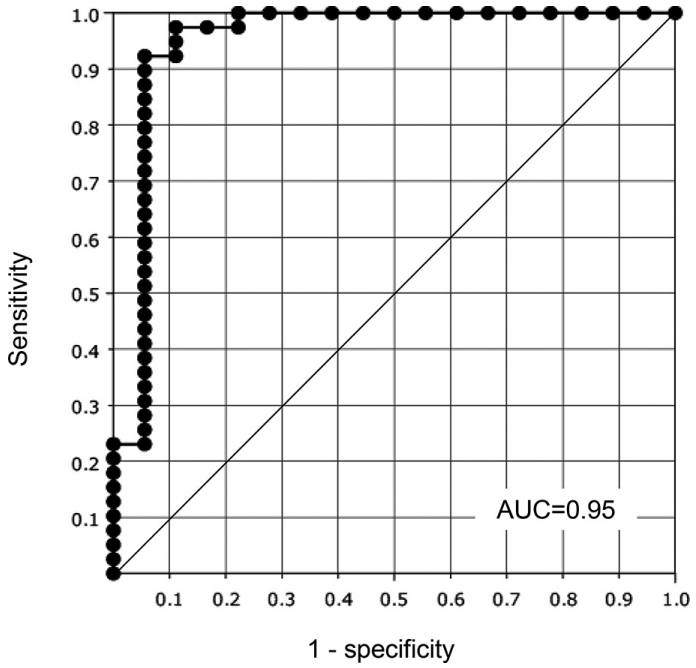

Fig. 3. Receiver operating characteristic curve analysis. The optimal cut-off score was 3.39. Area under the curve (AUC) was 0.95, with a sensitivity and specificity of 92.3%.

Table 4. Clinical features of five cases deviating from hierarchical clustering

Case No.	Stage	Histological finding	Clinical course
S37	IIIC	HGOSC with a partial of OCCC	No response of platinum-based chemotherapy
S38	I A	LGOSC	No evidence of disease
S39	I A	LGOSC with a partial of OCCC	No evidence of disease
C17	I A	OCCC	No evidence of disease
C18	IIIC	OCCC	Partial response of platinum-based chemotherapy

HGOSC, high-grade ovarian serous carcinoma ; LGOSC, low-grade ovarian serous carcinoma ; OCCC, ovarian clear cell carcinoma. The “S” or “C” at the beginning of each case indicates OSC or OCCC patient, respectively.

Discussion

In the current study, we confirmed clinical differences between OSC and OCCC. OCCC tends to be diagnosed earlier than OSC ; the rates of OSC and OCC diagnosed at stage I or II were 57–81% and 19–22%, respectively[13,14]. In general, HGOSC is an aggressive tumor that grows quickly and has often spread throughout the abdominal cavity by the time of diagnosis. Our results indicate that the OSC patients were at a significantly later stage and had a lower rate of completion surgery than the OCCC patients (Table 1). The clinical outcomes of OSC and OCCC significantly differed only in stage III/IV cases, but not in all cases (Table 1). In addition, platinum-based chemotherapy for patients with suboptimal surgical results was more effective in the OSC patients than in the OCCC patients (Table 2). These results support those of previous studies, which reported that OCCC is characterized by platinum resistance and poor prognosis in advanced stage[8].

In order to develop a diagnostic tool to differentiate between OCCC and OSC, we identified 10 genes obtained by differentially expressed gene analysis using DNA microarray technology. There have been several reports of comprehensive gene expression analysis for OCCC using cDNA microarrays[15–17]. The *FXYD2*, *RBPMS*, *GLRX* and *TOB1* genes were common in the 10 genes we detected.

The *FXYD2* gene encodes the γ-subunit of the Na+/K+-ATPase, which facilitates the egress of sodium, ingress of potassium, and maintenance of the transmembrane potential. Recently, it has been reported that FXYD2 overexpression in OCCC may serve as a promising prognostic biomarker, and can be a therapeutic target for cardiac glycosides that inhibit the Na+/K+-ATPase[18]. RBPMS protein is a member of a family of proteins that bind to the nascent RNA transcripts, and identify a selective marker of retinal ganglion cells[19]. GLRX protein acts as a glutathione (GSH)-dependent hydrogen donor for ribonucleotide reductase, and plays a role in the maintenance of cellular thiol redox homeostasis[20]. Hepatocyte nuclear factors are a subfamily of transcription factors that play multiple roles in the transcription of liver-specific genes[21]. Among these hepatocyte nuclear factors, HNF1β protein regulates expression of multiple genes implicated in cell differentiation, susceptibility to apoptosis, and glucose metabolism, and is associated with carcinogenesis of various tumors[22]. In EOC, the overexpression of HNF1β is specific for OCCC, and the incidence of HNF1β immunoreactivity has been reported to differ significantly between OCCC and other histologies[23]. Since *FXYD2*, *RBPMS*, and *GLRX* are associated with downstream targets of the HNF1β pathway, these genes may play an important role in differential diagnosis or carcinogenesis in OCCC[21].

The *TOB1* (ErbB-2,1) gene encodes a member of the erbB-2/B-cell translocation gene protein family of anti-proliferative factors that have the potential to regulate cell growth and differentiation. Although decreased expression of TOB1 was reported in various cancers, mostly thyroid, lung, and breast, there have been few reports of down-regulated TOB1 expression in EOC[24]. Results of the present study indicate that decreased TOB1 expression in OSC compared to OCCC may be associated with clinical features in OSC patients, such as aggressive behavior and advanced stage.

The six genes *GSTM3*, *GABARAPL1*, *ARG2*, *PPP1R3B*, *TMEM101* and *GDF15* have not previously been reported to be associated with cDNA microarray in EOC[15–17]. The GSTM3 gene has traditionally been considered to play a role in the detoxification of electrophiles by GSH conjugation[25]. Some studies have demonstrated that overexpression of GSTM3 was associated with resistance to cisplatin using a cell line model[26]. The GABARAPL1 protein is known as one of the homologs in the ATG8 protein, which plays a key role in autophagy processes, acts as a tumor suppressor, and inhibits Wnt signaling through promoting Dvl2 degradation[27]. UCA1 has been reported to be involved in cisplatin resistance mechanisms in ovarian cancer and bladder cancer, and one of the downregulated mRNAs was GABARAPL1[28–30]. The overexpression of GSTM3 and GABARAPL1 may reflect features of OCCC, such as platinum resistance and poor prognosis. Since there have been few reports on the associations of *ARG2*, *PPP1R3B*, *TMEM101* and *GDF15* with cancer or chemoresistance, we believe that it is important to accumulate more information on these genes in the future.

The 57 samples in our study were divided into OSC (n = 39) and OCCC (n = 18) by hierarchical clustering using a gene set consisting of a 10-gene signature (Fig. 1). Three (7.7%) of the 39 OSC cases and two (11.1%) of the 18 OCCC cases were excluded from the clustering. These five cases that were outliers of the clustering tended to be distributed around the cutoff value of the gene expression scoring system (Fig. 2). We performed a clinicopathological evaluation of the five cases that fell out-

side the clustering. Tumors S37, S38, and S39, which were in the OCCC cluster, showed LGOSC in two cases (S38 and S39) and a partial OCCC component in two cases (S37 and S39) (Table 4). Recently, a dualistic model has been proposed to divide EOC into two broad categories, called type I and type II. Type I ovarian tumors, which arise in a stepwise process from borderline neoplasms, include endometrioid, clear cell, mucinous, and transitional cell carcinomas, as well as LGOSC, while type II tumors, which develop de novo from the tubal and/or ovarian surface epithelium, comprise high grade serous carcinomas, undifferentiated carcinomas, and carcinosarcomas. Since cases S38 and S39 in the present study were pathologically LGOSC, their gene expression is expected to resemble OCCC included in type I more than HGOSC included in type II, considering their molecular biological classification. Although HGOSC is usually sensitive to platinum-based chemotherapy compared to OCCC, tumor S37 had no response. In our study, the ORRs in stage III/IV OSC and OCCC patients with suboptimal surgical results were 74% and 14%, respectively (Table 2). Tumor S37, grouped as OCCC by hierarchical clustering, had the OCCC characteristic of chemotherapy resistance. Tumor C18, grouped as OSC, also had the OSC characteristic of chemotherapy sensitivity. In the present study, we constructed a gene expression scoring system for distinguishing OSC from OCCC using 10 selected genes (Fig. 2). Introduction of the scoring system would make it easier to differentiate OSC from OCCC. Since there have been few studies in which a gene expression scoring system was constructed for use when diagnosing cancer, this scoring system would be a novel and powerful diagnostic tool[12].

There are several limitations to this study. First, the main limitations of our study were its retrospective design and relatively small sample size. Second, there was no independent cohort to validate the proposed biomarkers. Third, EOC is histologically heterogeneous, including not only OSC and OCCC but also endometrioid carcinoma and mucinous carcinoma. Furthermore, OSC is histologically classified as LGOSC and HGOSC, each with different clinical and molecular features. Since the frequency of mixed-type histology has been reported to be 6% of all EOC cases, the identification of a gene signature for five major pathological EOC subtypes may be necessary for better differential diagnosis[31].

In conclusion, OSC and OCCC are two major histological types of EOC, with distinctly different biological features and clinical behaviors. The results of our study suggest that the 10 candidate genes selected using DNA microarray technology would serve well to distinguish OSC from OCCC. Furthermore, the systemic identification of a differentially expressed 10-gene signature may shed light on variances in carcinogenesis and provide a theoretical basis for OCCC's resistance to chemotherapy.

Acknowledgments

Not applicable

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization and design : SN, TW, SW and KF. Collection of tissue samples and medical history : SN, MK, SN, SF and SS. Data curation : SN, TW RH, JI, EI, SM and SW. Methodology : TW, RH, JI, EI, SM and SW. Pathological diagnosis : YK, OS and YH. Supervision : SW and KF. Writing – original draft creation : SN and TW. All authors read and approved the final manuscript.

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