OTHERS

Significance of ERCC1 and Hormonal Receptor Expression in Ovarian Cancer

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Abstract : Background & Objectives : Ovarian carcinoma usually has a relatively poor prognosis. A rational approach to identify patients, who are likely to benefit from therapy, is urgently needed. Excision repair cross-complementation group 1 enzyme (ERCC1) has been proposed as a molecular predictor of clinical resistance to platinum-based chemotherapy. Steroid hormone receptors are important determinants of prognosis and predictive behavior in tumor tissues of several origins. The present study aimed to investigate the expression profile of ERCC1, ER & AR in patients with Ovarian carcinoma and their association with patient outcome. Methods : This is a prospective study which included 77 patients with ovarian carcinoma who were treated with platinum based chemotherapy at the National Cancer Institute (NCI) in Egypt during the period 7/2016- 7/2018. We evaluated the expression of ER, AR, and Excision repair cross-complementation group 1 enzyme (ERCC1) by immunohistochemistry. Expression profiles were compared to clinical, histologic and prognostic factors, the clinical outcome and survival. All patients received platinum containing chemotherapy regimen. Result : Of the 77 patients with ovarian cancer, 66.2 % (51/77) were ERCC1-positive, 49.4 % (38/77) were AR positive & 75.3 % (58/77) were ER positive. Platinum resistance was found in eight of the tumors with positive ERCC1 protein expression compared with two among the patients with negative tumor staining for ERCC1 (P = 0.643). There was significant association between ER & AR expression and pathological subtypes (p = 0.004, 0.007) respectively. There were no significant association between ER, AR& ERCC1 expression and PFS (P = 0.447,P = 0.162, P = 0.508 respectively) or OS (P = 0.781, P = 0.569, P = 0.381 respectively). Based on Cox proportional hazards regression analysis ERCC1, ER &AR were not independent factors affecting the prognosis of patients with ovarian carcinoma. Conclusion : These results demonstrate that positive ERCC1 expression is not associated with clinical resistance to platinum-based chemotherapy, ERCC1, AR& ER expression are not independent factors affecting the prognosis of patients with epithelial ovarian tumors and not associated with survival benefits. J. Med. Invest. 67 : 391-398, August, 2020

Keywords **:** *Excision repair cross-complementation (ERCC1)expression, ER & AR expression, Ovarian cancer, Platinum-resistance, Survival*

INTRODUCTION

Ovarian cancer is the leading cause of gynecologic cancer death in the United States. Ovarian cancer accounting for 3% of cancers among women in the United States, but is the fifth most common cause of cancer-related death. It was estimated that approximately 22,280 women were diagnosed with ovarian cancer in the United States in 2018, and that approximately 14,070 women died as a result of ovarian cancer in 2018 (1).

According to the National Population-Based Registry Program of Egypt 2008-2011, ovarian cancer represent 4.12% with crude rate 4.6. It is the 4th most common cancer in females. There is a progressive increase in number of incident ovarian cancer cases from 2288 in 2013 to 5957 in 2050, approximately 260%of 2013 incidence. Proportion of ovarian cancer was highest in upper Egypt (6.1%), and almost similar in middle Egypt (3.8%), and lower Egypt (3.9%) (2).

Platinum-based chemotherapy drugs are first-line treatments for ovarian cancer (3). However, a large number of patients do not respond to platinum-based chemotherapy due to drug resistance. Previous research shows that the nucleotide excision repair (NER) system plays an important role in platinum resistance to chemotherapy (4). It repairs platinum-induced DNA damage by removing the damaged fragments in the DNA molecule, and then synthesizing DNA by DNA polymerase. ERCC1 (excision repair cross complementation group 1) is a key gene involved in NER.

Endocrine factors play key roles in ovarian cancer development, with risk reduction related to multiparity and use of oral contraceptives (5,6).

Estrogen regulates growth and differentiation in the normal ovaries and has been demonstrated to have mutagenic effects. Progesterone, on the other hand, induces apoptosis and decreases cell membrane permeability, leading to decreased invasive potential (7). After menopause, when the estradiol level decreases, androgens are still produced and also seem to influence ovarian cancer development. Androgens promote cell proliferation, and androgen levels are decreased by the use of oral contraceptives (8).

The present study aimed to investigate the following :

1-Prognostic value of immunohistochemical expression of

Abbreviations
AR : Androgen Receptor ; EOC : Epithelial Ovarian Cancer ; OCSS : Ovarian Cancer Specific Survival ; ERCC1 : Excision repair cross-complementation group 1 ; IHC : Immunohistochemistry ; ER : Estrogen Receptor ; NER : nucleotide excision repair, PFS : progression-free survival, OS : Overall survival, HR : Hormonal Receptors

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ERCC1 and Sex steroid hormone receptors in the tumor tissue as regards progression free survival and overall survival.

2-Predictive value of ERCC1 expression as regards respose to platinum-based therapy.

MATERIALS AND METHODS

Patients

A total of 77 patients diagnosed with EOC were recruited between July 2016 and July 2018 in National Cancer Institute (Egypt). The median age at diagnosis was 53 years, ranged between 18–74 years. As presented in (Table 1), The tumors were classified according to the International Federation of Gynecology and Obstetrics classification system, with 16 (20.8%) samples classified as stage IA, 9 (11.7%) as stage IB, 8 (10.4%) as stage II, 19 (24.7%) as stage III and 25 (32.5%) as stage IV. The pathological types of the tumor samples were as follows : 56 (72.7%) Serous carcinoma samples (9 low G (G1), 7 intermediate (G2), 40 high G (G3)), 5 (6.5%) mucinous carcinoma, 12 (15.6%) endometrium cancer and 2 clear cell carcinoma, 2 transitional carcinoma. 67 (87%). Optimal radical surgery (PAH-BSO) was done in 67 patients (87%), while conservative surgery was done for 9 patients (11.6%) including 7 patients unilateral salpingoophrectomy (9%), 2 patients excised ovarian mass. Peritoneal biopsy was performed in 1 patients.

Table 1. Clinicopathological data of 77 patients with EOC

	Characteristics	Numbers	Percentage	Valid percent
Age				
	= < 53	42	54.5	
	> 53	35	45.5	
SA (n = 63)				
	< 1.8	28	36.4	44.4
	> = 1.8	35	45.5	55.6
BMI (n = 62)				
	< 30	26	33.8	41.9
	> = 30	36	46.8	58.1
CA 125 (n = 67)				
	0-35	12	15.6	17.9
	> 35	55	71.4	82.1
Stage				
	IA	16	20.8	
	IB	9	11.7	
	II	8	10.4	
	III	19	24.7	
	IV	25	32.5	
	I, II	33	42.9	
	III, IV	44	57.1	
Malignant ascites				
	present	28	36.4	
Peritoneal implants				
	present	24	31.2	
Omentum deposits				
	Present	25	32.5	
Distant metastasis				
	Pleural effusin (M1a)	5	6.5	20.0
	Liver (HFLs)	10	13.0	40.0
	Pulmonary nodules	4	5.2	16.0
	Splenic focal lesions	4	5.2	16.0
	Anterior abdominal wall	2	2.6	8.0
	Non regional LNs	13	16.9	52.0
Histopathology				
	Serous	56	72.7	
	Endometrioid	12	15.6	
	mucinous	5	6.5	
	others	4	5.2	
Grades				
	I	12	15.6	
	II	19	24.7	
	III	46	59.7	
ERCC1				
	N	26	33.8	
	P	51	66.2	
ER				
	N	19	24.7	
	P	58	75.3	
AR				
	N	39	50.6	
	P	38	49.4	

SA : Surface area, BMI : Body mass index, ER : Estrogen receptor, AR : Androgen receptor, ERCC1 : Excision repair cross-complementation group 1

66 patients (85.7%) received systemic platinum-based combination chemotherapy, following the surgical procedure, 37 (56.06%) patients received systemic chemotherapy as adjuvant treatment, 14 (21.21%) received as neo-adjuvant and 15 (22.7%) patients received systemic chemotherapy as adjuvant and neoadjuvant.

48 patients (72.2%) received 6 courses of chemotherapy or more.

Chemotherapy regimens consisted of 175 mg/m^2 taxol plus carboplatin calculated at AUC 5–6 every 3 weeks for 6–8 cycles or cycle every week for 18 weeks with AUC 2-3.

Most of patients (n = 37) (57.8%) received carboplatin with AUC 5-6 every 3 weeks and 27 (42.2%) patients received carboplatin weekly with AUC 2-3.

Ethical approval for the study was granted by the Cairo University ethics committee (Egypt), and all patients had given their written informed consent to participate in the study.

Immunohistochemical analysis

Tumor specimens were harvested from 77 patients prior to receiving platinum-based treatment.

1.Paraffin sections were made at 4 microns thickness and mounted on positive charged slides.

2.Immunostaining was done for all cases using Automated BenchMark ULTRA IHC/ISH system, and the following steps occurred automatically :

- Deparaffinization by using the EZ-prep solution.
- Cell conditioning (standard cell conditioning CC1) for 80 minutes.
- Antigen retrieval using reaction buffer (PH 7.4-7.8).
- Application of 100µ of each of the ready-to-use monoclonal antibodies used in the study under specific incubation temperature and time for each (Table 2).
- Application of Diaminobenzidine (DAB) as a chromogen (NexES Ultra View DAB Detection Kit).
- Counterstaining with Hematoxylin II for 8 minutes.
- Post counter staining with bluing reagent for 4 minutes.

3.Slides were extracted and arranged in racks.

4.Slides were washed in tap water and soap for 5 minutes and then dehydrated in the ascending grades of alcohol for 5 minutes in each container.

5.Slides were cleared in Xylene, and then cover slips were applied.

Chemotherapy outcome

Clinical curative effect was assessed by routine gynecological examination, imaging analysis (color ultrasound, computed tomography, magnetic resonance imaging or positron emission tomography-computed tomography for abdominal or pelvic regions) and detection of serum carbohydrate antigen (CA)-125 levels. No recurrence at 6 months post-chemotherapy was referred to as 'clinically sensitive' and included normal serum CA-125 levels, no new lesions, or the original residual lesions

Table 2. List of used immunohistochemical markers

Antibodies	Clone	Source	Incubation Temp	Incubation Time (min)	Visualization	Positive Control
AR (N-20)	Sc-816 Rabbit polyclonal	Santa Cruz Biotechnology	42°C	32	Nuclear	Prostatic carcinoma
ERCC-1	8F1 Mouse monoclonal	Gene Tex	37°C	32	Nuclear	Tonsil
ER	SP1 Rabbit monoclonal	Roche	37°C	36	Nuclear	Breast

had decreased in size or disappeared as identified by pelvic and imaging examination. By contrast, disease progression during chemotherapy, a continual increase in serum CA-125 levels or the appearance of new lesions identified by imaging at 6 months post-chemotherapy was recognized as 'clinical resistance'.

Follow-up

The final follow-up occurred on July 2019. The median follow up period was 22.8 months (range, 1.4 – 38.5 months). Disease PFS was described as the time from ovarian cancer surgery or the time from start neoadjuvant chemotherapy to disease recurrence or mortality, whichever came first. The time between surgery or start treatment and mortality or the end of follow-up was described as the overall survival time (OS).

Statistical analysis

Statistical analysis was done using IBM SPSS® Statistics version 22 (IBM® Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Pearson's Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables. For not normally distributed quantitative data, comparison between two groups was done using Mann-Whitney test (non parametric t-test). Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. Multivariate analysis was done using Cox-regression method for the factors affecting survival on univariate analysis. Hazard ratio (HR) with it 95% confidence interval (CI) were used for risk estimation. All tests were two-tailed. A p-value < 0.05 was considered significant.

RESULTS

Expression of ERCC1 and Relation to Outcome

Brown-yellow granules were observed in the majority of tumor cell cytoplasm and nuclei, and corresponded with positive ERCC1 expression (Fig. 1). Immunohistochemistry identified that 51/77 specimens (66.2%) were ERCC1 positive.

As presented in (Table 3), no significant association was identified between ERCC1 expression and age (P = 0.930), pathological type (P = 0.482), cell differentiation (P = 0.461), clinical stage (P = 0.316) and ER expression (P = 0.056) or AR expression (P = 0.127)

While there was significant association between ERCC1 expression and elevated serum level of CA 125 at the time of diagnosis (P = 0.046). Also, presence of omental deposits was significantly correlated with the positive ERCC1 expression in tumor tissue (P = 0.022)

As presented in (Table 4) (Fig.2), the number of resistant cases with positive ERCC1 expression (8/10 ; 80%) was not significantly greater than the number of sensitive cases with positive ERCC1 expression (41/63 ; 65.1%) (P = 0.351). For the 77 EOC cases, there

Figure 1. Positive reaction to ERCC1 in almost all tumor cells, both cytoplasmic and nuclear (X10).

Table 3. Correlation between ERCC1 expression and clinical pathological features.

Clinical feature	n	negative	positive	p-value
Age, years				0.930
=< 53	42	14	28	
> 53	35	12	23	
Stage				0.316
IA	16	9	7	
IB	9	3	6	
II	8	2	6	
III	19	5	14	
IV	25	7	18	
				0.164
I,II	33	14	19	
III,IV	44	12	32	
Pathological subtypes				0.482
serous	56	20	36	
endometrioid	12	2	10	
mucinous	5	1	4	
Grade				0.461
GI	12	5	7	
GII	19	8	11	
GIII	46	13	33	
ER				0.056
negative	19	3	16	
positive	58	23	35	
AR				0.127
negative	39	10	29	
positive	38	16	22	
CA 125				**0.046**
0-35	12	1	11	
> 35	55	21	34	
Omentum				**0.022**
absent	52	22	30	
present	25	4	21	

ER : Estrogen receptor, AR : Androgen receptor, ERCC1 : Excision repair cross-complementation group 1

was no significant difference in PFS and median OS between patients with positive ERCC1 expression and patients with negative expression (OS, P = 0.381 ; PFS, P = 0.508) (Fig. 3).

Table 4. Correlation between ERCC1 expression and platinum sensitivity.

	Sensitive	Resist	P-value
ERCC1			0.351
N (n = 24)(32.9%)	22 (34.9%)	2 (20%)	
P (n = 49)(67.1%)	41 (65.1%)	8 (80%)	

ERCC1 : Excision repair cross-complementation group 1

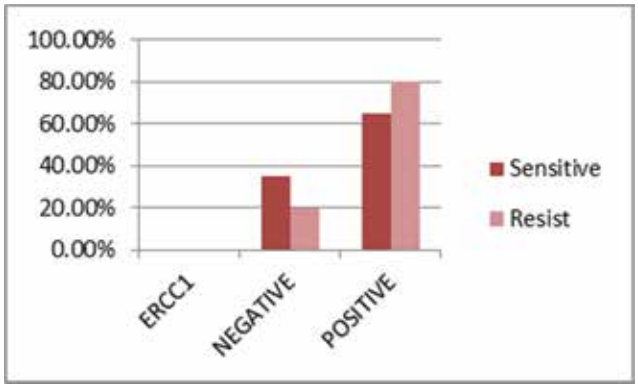

Figure 2. Correlation between ERCC1 expression and platinum sensitivity.

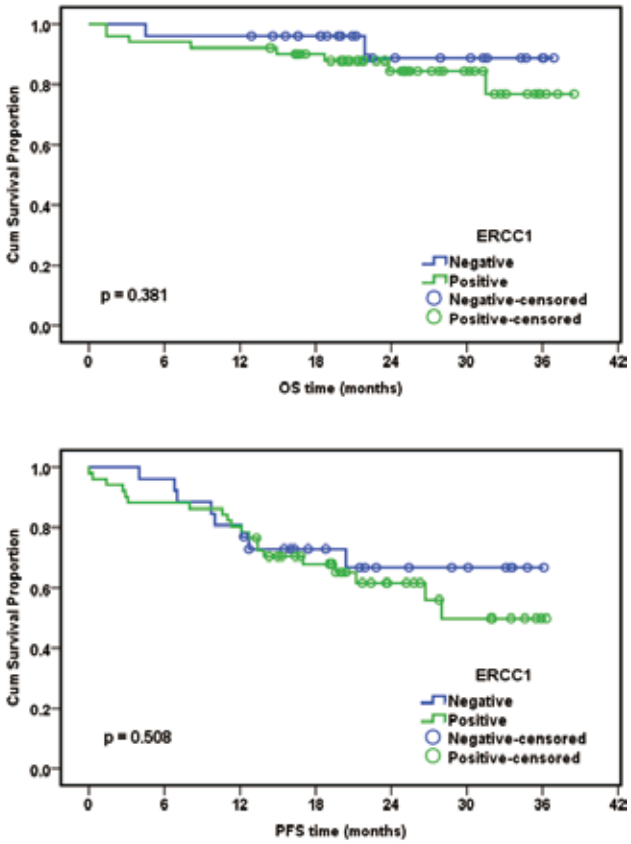

Figure 3. OS and PFS of patients with positive expression of ERCC1 vs. those with negative.

Expression of Sex Steroid Hormone Receptors and Relation to Outcome

The expression and the prognostic value were first assessed individually for each marker, with ER positivity detected in 58/77 (75.3%) (Fig 4) and AR positivity detected in 38/77 (49.4%) (Fig 5).

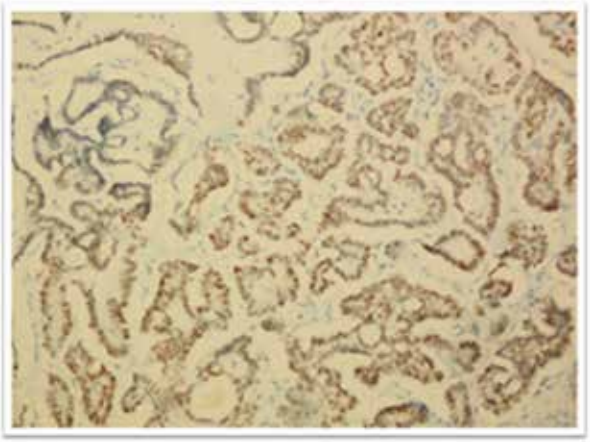

Figure 4. Moderate diffuse positive nuclear reaction to ER in most of tumor cells (X10).

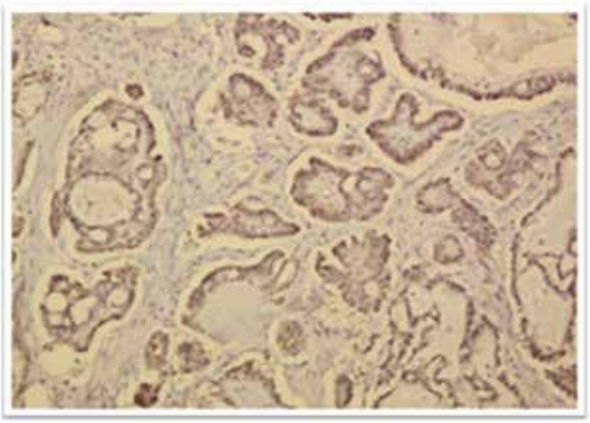

Figure 5. Positive reaction to AR in some tumor cells (X10).

The representation of stage, grade, age at diagnosis, histology and ERCC1 expression in relation to receptor status is outlined in (Table 5). No significant association was identified between AR expression and the clinical pathological features ---) age (P = 0.209), clinicl stage (P = 0.236), pathological subtypes (P = 0.318), pathological grade (P = 0.795), ERCC 1 expression (P = 0.127).

There is a significant association between AR expression and age (P = 0.050), ER expression (P = 0.004) and body surface area >= 1.8 (P = 0.028)

ER positivity was not significant association was identified between ER expression and the clinical pathological features ---) age (P = 0.847), clinicl stage (P = 0.815), pathological grade (P = 0.867), and border significant with ERCC 1 expression (P = 0.056).

There is a significant association between ER expression and pathological subtypes (P = 0.007), AR expression (P = 0.004), HB >= 10 (P = 0.026) and body surface area >= 1.8 (P = 0.049) (Table 6).

Table 5. Correlation between AR expression and clinical pathological features.

Clinical feature	n	negative	positive	p-value
Age, years				**0.050**
=<53	42	17	25	
>53	35	22	13	
SA				**0.028**
<1.8	28	19	9	
>=1.8	35	14	21	
Stage				0.236
IA	16	7	9	
IB	9	4	5	
II	8	2	6	
III	19	9	10	
IV	25	17	8	
				0.087
I-II	33	13	20	
II-IV	44	26	18	
Pathological subtypes				0.318
serous	56	25	31	
endometrioid	12	8	4	
mucinous	5	3	2	
Grade				0.795
GI	12	5	7	
GII	19	10	9	
GIII	46	24	22	
ER				**0.004**
negative	19	15	4	
positive	58	24	34	
ERCC1				0.127
negative	26	10	16	
positive	51	29	22	

SA : Surface area, ER : Estrogen receptor, AR : Androgen receptor, ERCC1 : Excision repair cross-complementation group 1

Table 6. Correlation between ER expression and clinical pathological features.

Clinical feature	n	negative	positive	p-value
Age, years				0.847
=<53	42	10	32	
>53	35	9	26	
SA				**0.049**
<1.8	28	11	17	
>=1.8	35	6	29	
Stage				0.815
IA	16	5	11	
IB	9	2	7	
II	8	1	7	
III	19	6	13	
IV	25	5	20	
I-II	33	8	25	0.939
III-IV	44	11	33	
Pathological subtypes				**0.007**
serous	56	9	47	
endometrioid	12	3	9	
mucinous	5	4	1	
Grade				0.867
GI	12	2	10	
GII	19	5	14	
GIII	46	12	34	
AR				**0.004**
negative	39	15	24	
positive	38	4	34	
ERCC1				0.056
negative	26	3	23	
positive	51	16	35	

SA : Surface area, ER : Estrogen receptor, AR : Androgen receptor, ERCC1 : Excision repair cross-complementation group 1

Expression of either ER or AR was not associated with improved PFS (P = 0.447, P = 0.162 respectively) (Fig 6) and OS (P = 0.781, P = 0.569 respectively) (Fig 7).

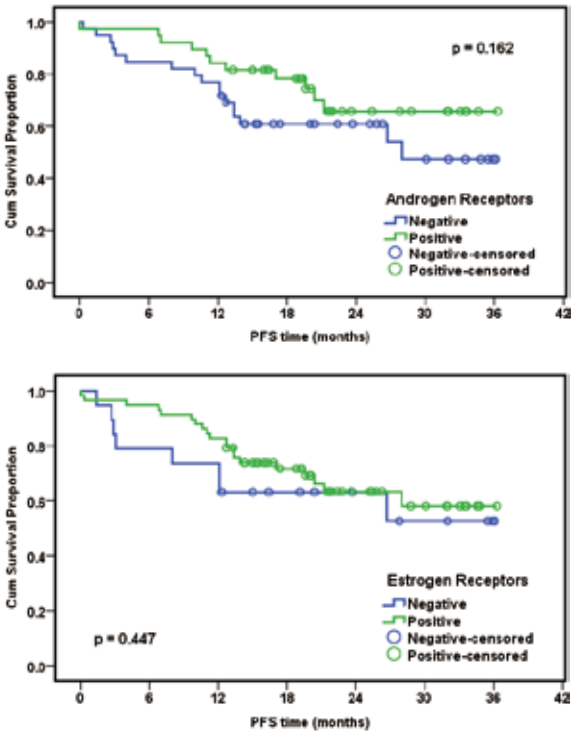

Figure 6. PFS of patients with positive expression of AR or ER vs. those with negative.

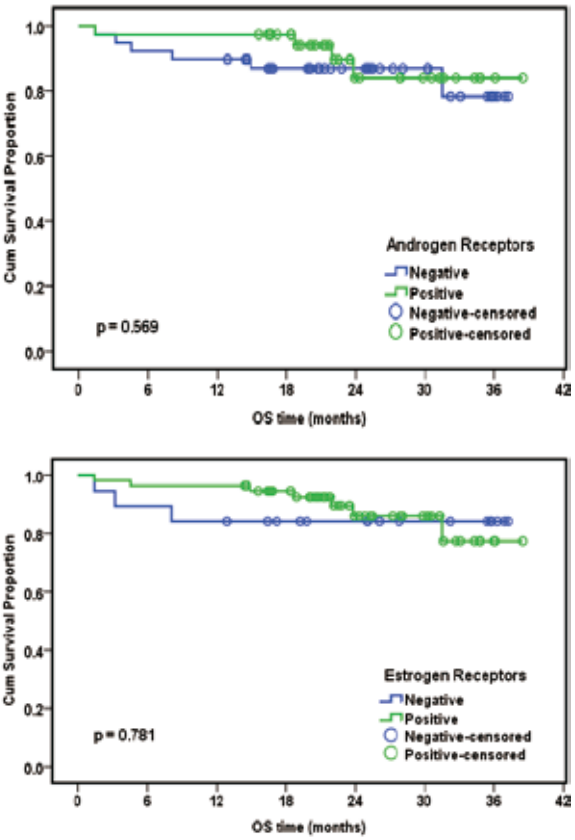

Figure 7. OS of patients with positive expression of AR or ER vs. those with negative.

ERCC1 expression, ER expression, AR expression, peritoneal deposits and platinum sensitivity. As presented in (Table 7), age, platinum sensitivity and received adjuvant chemotherapy were identified as independent factors significantly affecting the prognosis of patients (P = 0.048, P < 0.001 and P = 0.020, respectively), while other factors did not significantly affect prognosis.

Independent risk factors for patient survival time :

Cox proportional hazards regression was used to analyze possible risk factors, including age, histopathological type, degree of cancer cell differentiation, clinical stage, type of surgery and Cox regression analysis demonstrated that ERCC1 expression level, ER or AR expression were not an independent prognostic factor for the survival time of patients with EOC.

DISCUSSION

Chemotherapy drug resistance is a major factor restricting the improvement of patient survival rates, with 20–30% of patients with EOC undergoing primary platinum-resistance ; however, 80% of patients are likely to eventually encounter resistance (9,10). With the rapid development of pharmacogenomics and molecular biology, the mechanism of cisplatin resistance is closely associated with NER (11). In DNA repair, ERCC1 is a key gene of the NER pathway due to its binding with DNA repair endonuclease ERCC1-xeroderma pigmentosum group F (XPF) (12,13).

A number of studies have examined the association between ERCC1 expression (14-18) and clinical outcomes including response to platinum-based therapy, PFS and OS in patients with EOC (19). The outcomes of these studies were discriminative, ranging from increased rate of platinum resistance (22), worse PFS and overall OS (20-22), similar PFS (23-26), to similar OS (20-23). In our current study, we were unable to confirm any statistically significant association between ERCC1 expression and resistance to platinum-based chemotherapy. PFS and OS did not significantly differ between the positive and negative ERCC1 expression.

A previous meta-analysis evaluated whether response to platinum-based chemotherapy was associated with ERCC1 expression in patients with ovarian cancer (24). It was observed that patients with negative ERCC1 expression had a significantly greater response to platinum-based chemotherapy compared with patients with positive ERCC1 expression (24), indicating that ERCC1 protein expression status is correlated with response to platinum-based chemotherapy in ovarian cancer. Zhao *et al*. (25) identified a negative correlation between ERCC1 expression and clinical chemosensitivity in EOC.

Stadlmann *et al*. analyzed 80 samples of ovarian cancer utilizing 8F-1 antibody for immunohistochemy and found low overall ERCC1 expression (20.3%) and no association between protein expression and platinum responsiveness (p = 0.21) (16), which correlates with our results. In a study of Steffensen *et al*., immunohistochemy with the 8F-1 antibody against ERCC1 was used to examine 100 tumor specimens : 45% of specimens were positive, which was associated with a significantly poorer response to platinum-based chemotherapy but not with a worse OS (15). Lin *et al*. corroborated these findings by demonstrating that low ERCC1 protein expression was significantly associated with drug sensitivity in 63 patients (26).

In a study of Rubatt *et al*. (27), in which patients who participated in GOG-172 and GOG-182 trials and provided tumor samples for translational research were included, 27% of tumors were ERCC1-positive. ERCC1 expression was not associated with clinical characteristics or platinum responsiveness. Women

Table 7. Univariate analysis for survival time.

							95% CI for Exp (B)	
	B	SE	Wald	df	P-value	Exp (B)	Lower	Upper
Age.53	.365	.380	.923	1	.337	1.440	.684	3.031
Stage(III, IV vs I,II)	.822	.419	3.854	1	.050	2.276	1.001	5.172
Surgery (other vs PAH+BSO)	.862	.462	3.477	1	.062	2.368	.957	5.861
Histopatholoy			1.413	2	.493			
Path(serous vs mucinous)	.745	1.022	.531	1	.466	2.106	.284	15.613
Path(Endometrod vs mucinous)	.137	1.156	.014	1	.905	1.147	.119	11.054
Grade:			2.330	2	.312			
Grade(1 vs III)	-1.130	.746	2.295	1	.130	.323	.075	1.394
Grade(II vs III)	-.193	.444	.189	1	.664	.824	.345	1.970
Peritoneal involvement	1.208	.406	8.841	1	.003	3.347	1.509	7.420
ERCC1 expression	.276	.419	.434	1	.510	1.318	.580	2.996
ER.AR expression:			2.555	2	.279			
ER.AR(either vs both +ve)	.063	.450	.019	1	.889	1.065	.440	2.575
ER.AR (Both –ve vs both +ve)	.698	.466	2.242	1	.134	2.011	.806	5.017
AR (-ve vs +ve)	.535	.387	1.904	1	.168	1.707	.799	3.646
ER	.317	.419	.571	1	.450	1.373	.603	3.123
Platinum sensitivty	2.773	.471	34.658	1	**< 0.001**	16.005	6.358	40.290
Adj.cth	.906	.388	5.452	1	**.020**	2.475	1.157	5.297

CI : confidence interval ; SE : standard error, df : degrees of freedom, ER : Estrogen receptor, AR : Androgen receptor, ERCC1 : Excision repair cross-complementation group 1, PAH-BSO : Pan abdominal hysterectomy bilateral salpingoophorectomy

with ERCC1-positive versus negative tumors had similar median PFS (17.9 months versus 17.5 months, respectively, p = 0.59), median OS (52 months versus 47 months, respectively, p = 0.30), risk of disease progression [adjusted hazard ratio (HR) = 0.90, 95%CI = 0.71-1.15, p = 0.41), and risk of death (adjusted HR = 0.81, 95% CI = 0.61-1.07, p = 0.14)

However, Muallem *et al*. (28) demonstrated that there were no significant differences in the PFS between patients with low, intermediate and high H-scores for ERCC1 expression.

The prognostic value of sex steroid hormone receptor expression in ovarian cancer is not fully defined. In this study, we can however demonstrate that expression of ER and AR not predicts PFS and OS.

In the present study, no information on use of endocrine treatment was available, precluding analyses of possible effects of endocrine treatment on the findings reported. However, endocrine treatment is not standard in ovarian cancer and is unlikely to have been administered to the study cohort to such an extent that it has influenced the results (29,30).

The finding that aromatase inhibition appears slightly more effective than tamoxifen in ovarian cancer likely reflects the more efficient hormone inhibition of aromatase inhibitors. In support of this notion, epidemiological studies indicate that reduced circulating levels of androgens decrease the risk of developing ovarian cancer, but clinical studies have shown only limited effects of androgen deprivation (32,34,35).

The presence and prognostic value of AR expression in ovarian cancer vary in different studies, but increased AR expression seems to generally be associated with a favorable prognosis (29,31,33), contrary to the results in the present study.

Zhaojun, *et al*., (2017) who investigated the correlation between ER expression and epithelial ovarian cancer prognosis in thirty-five studies with a total of 5824 patients were included, and demonstrated that the expression of ER, especially ER α, was a positive predictor of overall survival among epithelial ovarian cancer patients (36), contrary to the results in the present study.

In conclusion, the present study demonstrated that high ERCC1 expression in patients with EOC was not associated with resistance to platinum-based chemotherapy or with survival time. In addition, it was also observed that ERCC1 protein expression was not an independent factor affecting the prognosis of patients. We demonstrate a prognostic role of PR and AR expression in ovarian cancer, with independent effects on PFS and OS and the best outcome for patients whose tumors displayed coexpression of ER and AR.

Further studies with larger sample sizes and improved study designs are required to investigate whether or not ERCC1 may function as a predictor for chemotherapy against EOC.

And our data define a basis for further evaluation of the role of sex steroid hormone receptors, and in the future possibly endocrine treatment, in ovarian cancer and support that such studies may be subtype specific to comprehensively evaluate the potential clinical benefit.

STATEMENT CONFLICT OF INTEREST

No conflict of interest.

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