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Role of ERCC1 in Epithelial Ovarian Cancer

[1]Mandalia Toral, [2]Shah Rutu, [1]Gajjar Kinjal, [2]Jethva Disha, [3]Patel Jayendra

[1]Research Assistant, [2]Junior Research Fellow, [3]Senior Scientific Officer and Head

Molecular Diagnostics & Research Lab-II, Cancer Biology Department

The Gujarat Cancer & Research Institute (GCRI), Ahmedabad, Gujarat, India

Abstract:

Mortality rate of ovarian cancer is highest among all gynaecological malignancies. Excision Repair Cross-Complementation Group1 (ERCC1) enzyme is an important component in Nucleotide Excision Repair (NER) pathway that reflects NER repair activity level. ERCC1 expression levels in human tumor tissues may have a role in clinical resistance to platinum compound. Various studies have examined the prognostic significance of ERCC1 gene in many malignancies. However, rare studies have elucidated its prognostic role in ovarian cancer. Therefore, this study aimed to explore the significance of ERCC1 expression in Epithelial Ovarian Cancer (EOC) patients.

This study consists of 54 untreated EOC patients and 23 benign ovarian tumors. Quantitative real time RT-PCR was used to detect the messenger RNA (mRNA) expression levels of ERCC1 in ovarian cancer tissues and their relationships with clinicopathological parameters were analysed. The association of ERCC1 expression with disease-free survival (DFS) and overall survival (OS), was investigated by Kaplan-Meier survival analysis. Data was statistically analysed by SPSS software.

ERCC1 mRNA expression was found to be significantly higher in EOC patients as compared to benign ovarian tumor (P=0.049) and the ROC curve also confirmed its differentiating efficacy between the benign epithelial ovarian diseases and EOC. ERCC1 mRNA expression was not significantly associated with any of the clinicopathological parameters of EOC patients with exception to inflammation and histological grade where, it showed a positive trend of significance with inflammation (P=0.068), indicating an increased ERCC1 mRNA expression with presence of inflammation. However, a trend of higher ERCC1 expression was observed in well differentiated tumors as compared to moderately differentiated tumors (p=0.076) and poorly differentiated tumors (p=0.084), respectively. Moreover, there was no statistically significant correlation of ERCC1 expression with DFS (P=0.390) or OS (P=0.139) of the studied patients.

The results of the study reveal that, ERCC1 can be used as a marker for differentiating patients with benign ovarian disease and EOC. However, further investigation in a larger cohort with longer follow up period is required to determine the role of ERCC1 in prognosis and prediction of therapy in EOC patients.

Keywords: ERCC1, Epithelial ovarian cancer, ERCC1 mRNA expression

Introduction:

Ovarian cancer is one of the most common causes of cancer-related deaths in women of developed nations. According to Globocan 2020 Ovarian cancer accounts for an estimated 313,595 new cases and 207,252 deaths worldwide (1, 2). It ranks 8th among all malignancies in India with 45,701 new cases and 32,077 deaths per year (2). Incidence of ovarian cancer in The Gujarat Cancer & Research Institute (GCRI) was 5.8% according to the hospital based cancer registry. In fact, ovarian cancer is accountable for more deaths than any other type of female reproductive cancer. Ovarian malignancies are associated with significant morbidity and carry the worst prognosis and highest mortality of all the gynaecological cancers. For better chances of curing and to evade such high rates of morbidity and mortality, they should be diagnosed promptly (3). Hence, early identification is essential to improve the survival rates and prognosis. Diagnosis remains challenging due to the asymptomatic nature of early disease, late presentation in women and limitations in imaging modalities for differentiating ovarian benign and malignant lesions (4). Benign ovarian tumors usually grow slowly and may be precursors and etiological risk factors for ovarian cancer (5). EOCs are supposed to arise from a single

layer of cells that covers the ovary or that lines cysts immediately beneath the ovarian surface (6). The four most common histological types of EOC are serous, mucinous, endometrioid and clear cell carcinoma (7). The standard line of care treatment includes surgery and platinum-based chemotherapy; however, anti-angiogenic bevacizumab and Poly (ADP-ribose) polymerase (PARP) inhibitors have gained momentum in the management of this gynaecological malignancy in the past decade (8). Platinum compounds induce their cytotoxic effect by binding to DNA molecules in the form of a platinum DNA adduct. Although the mechanism of platinum resistance in vivo is not clearly understood, laboratory studies on cancer cell lines suggest that NER is the main mechanism responsible for this resistance by increased platinum DNA adduct removal (9). ERCC1 gene is critical within NER and serves a leading role in this pathway (10). Excision of platinum-DNA adducts are performed by NER proteins that recognize the DNA damage and excise the platinum DNA adducts from the damaged DNA strand (11). ERCC1 expression in relationship to patient survival have shown a correlation of its increased expression with reduced survival in lung, colon, pancreatic, gastric, bladder, and esophageal cancer (9). Recently, accumulative studies have investigated the prognostic significance of ERCC1 gene in many malignancies. To date, only limited research has been performed on the prognostic role of ERCC1 gene in ovarian cancer, furthermore, the results remain unpredictable (12).

Hence the aim was to explore the role of ERCC1 mRNA expression in EOC patients by studying its prevalence in patients with benign epithelial ovarian diseases and EOC by qRT PCR and correlate the results with the established clinicopathological parameters and survival in EOC patients.

Materials and methods:

This retrospective study consisted of 54 EOC patients and 23 patients having benign epithelial ovarian tumors, diagnosed and treated at GCRI. The study was approved by the Institutional review committee and ethics committee. The detailed clinical history such as patient's age, menopausal status, and histopathological findings was recorded from the case files maintained at the Institutional Medical Record Department. Patients diagnosed with other types of ovarian carcinoma were excluded from the study. Seropositive patients were also excluded from the study. Follow up details of EOC patients were noted for a period of 5 years or until death within that period. Complete follow-up details were obtained in 83% (45/54) of EOC patients and hence were included for survival analysis.

Primary tumor tissue samples of histopathologically confirmed EOC patients were collected from the operation theatre and selected by the pathologists of Oncopathology department, GCRI. The selected tissue samples were collected in RNA later, immediately snap frozen in liquid nitrogen and stored at -80°C until further analysis.

RNA was extracted from tumor tissues using RNA isoplus reagent (Takara). The extracted RNA was quantified using Qubit fluorimeter 3.0 (Invitrogen). Reverse transcription for cDNA synthesis was carried out from 2µg of total RNA sample using High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, cat # 4368814) as per protocol. The thermal cycling conditions included incubation at 25˚C for 10 min, 37˚C for 120 min, 85˚C for 5 min followed by final hold at 4˚C.

The real-time quantitative PCR of cDNA was performed by using QuantiNova SYBR Green PCR Kit (Qiagen, Cat #208052). The primer sequences for ERCC1 and GAPDH (used as housekeeping reference gene for normalization) were ERCC1 forward: 5'-CCCTGGGAATTTGGCGACGTAA-3' and reverse: 5'-CTCCAGGTACCGCCCAGCTTCC-3' and GAPDH forward: 5'-AAGGTCGGAGTCAACGGATTTG-3' and reverse: 5'- GCCATGGGTGGAATCATATTGG-3'. The cycling conditions included PCR initial activation step at 95˚C for 2 min, followed by 40 cycles of denaturation at 95◦C for 5 seconds and combined annealing/extension at 60◦C for 10 seconds. The relative expression was calculated as $2^{-\Delta\Delta Ct}$.

Statistical analysis:

The statistical data analysis was performed with the help of SPSS (Statistical Package for the Social Sciences) software (release 19; Chicago, USA). The independent t test was performed to evaluate correlation of ERCC1 expression between two groups of patients and also with the clinicopathological parameters. Receiver's operating characteristic (ROC) curves were constructed to determine the discriminating efficacy of ERCC1 expression. Kaplan-Meier survival curve comparison analysis was used for survival data, and the log-rank test was used for comparing survival analysis data. $P \leq 0.05$ was considered to be significant.

Results:

Detailed patient and clinicopathological characteristics of benign and EOC are shown in Table 1.

Table 1: Clinical characteristics of patients with benign ovarian tumors (N=23)

Characteristics	N (%)
Age	
≤ 47	12 (52)
> 47	11 (48)
Menopausal status	
pre-menopausal	07 (30)
post-menopausal	16 (70)

Detailed patient and clinicopathological characteristics of EOC are shown in Table 2. The median age of patients enrolled in the study was 47 years and was used as cut off to categorize the patients in younger age group (≤47) and older age group (>47). Accordingly, 52% (N=28) of patients were in younger age group and 48% (N=26) were in older age group. Seventy percent (N=38) of the females were post-menopausal while 30% (N=16) were having pre-menopausal status.

Table 2: Clinicopathological characteristics of patients with epithelial ovarian cancer (N=54)

Characteristics	N (%)	Characteristics	N (%)
Age		**Vascular permeation**	
≤47 years	28 (52)	Absent	42 (78)
>47 years	26 (48)	Present	12 (22)
Menopausal status		**Capsular Invasion**	
Pre menopause	16 (30)	Absent	27 (50)
Post menopause	38 (70)	Present	27 (50)
Tumor size		**Necrosis**	
Small tumor size [T1 (N=34)+T2 (N=6)]	36 (67)	Absent	33 (61)
Large tumor size [T3 (N=15)+T4 (N=0)]	18 (33)	Present	21 (39)
Nodal status		**Inflammation**	
Absent	49 (91)	Absent	44 (82)
Present	05 (09)	Present	10 (18)
Metastasis		**Fallopian tube**	
Absent	53 (98)	Absent	31 (57)
Present	01 (02)	Present	23 (43)
Stage		**Uterus**	
Early [Stage I (N=32) + Stage II (N=6)]	35 (65)	Absent	38 (70)
Advanced [Stage III (N=17)+ Stage IV(N=0)]	19 (35)	Present	16 (30)
Histological grade		**Cervix**	
Well differentiated	19 (35)	Absent	47 (87)
Moderately differentiated	08 (15)	Present	07 (13)
Poorly differentiated	27 (50)	**Omentum**	
Histological types		Absent	34 (63)
Serous Adenocarcinoma	40 (74)	Present	20 (37)
Mucinous adenocarcinoma	08 (15)	**Peritoneum**	
Endometrioid carcinoma	05 (09)	Absent	34 (63)
Clear cell adenocarcinoma	01 (02)	Present	20 (37)
Serous adenocarcinoma		**Pelvic Organs**	
Low grade serous adenocarcinoma	11 (20)	Absent	35 (65)

High grade serous adenocarcinoma	29 (54)	Present	19 (35)
Lymphocytic stromal response		**Ascites**	
Absent	45 (83)	Absent	23 (43)
Present	09 (17)	Present	31 (57)
Lymphatic permeation		**Malignant cells Ascites**	
Absent	41 (76)	Absent	37 (69)
Present	13 (24)	Present	17 (31)
HE-4		**CA 125**	
<69 pmol/L	02 (04)	<35 U/ml	04 (07)
≥69 pmol/L	24 (44)	≥35 U/mL	41 (76)
Not known	28 (52)	Not known	09 (17)

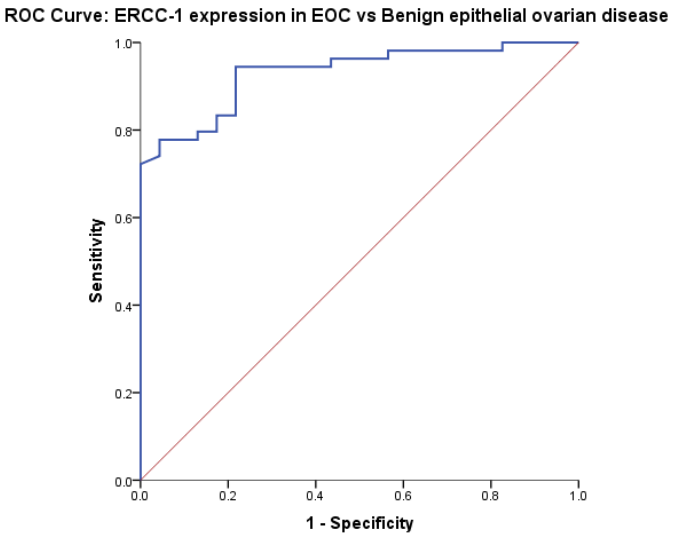
Correlation of ERCC1 mRNA expression between patients with benign ovarian tumor and EOC

The relative expression of ERCC1 was found to be significantly higher in EOC patients (70%) as compared to benign patients (30%) (P= 0.049) [Table 3].

Table 3: Correlation of ERCC1 expression between patients with benign ovarian tumors and EOC

Patients	**ERCC1**		
	N (%)	Mean ± SE	**P value**
Benign ovarian disease	23 (30)	1.77 ± 0.45	**0.049**
EOC	54 (70)	356.79 ± 176.29	

The ROC curves were generated to reveal the efficacy of significantly higher ERCC1 mRNA expression in order to differentiate the benign and EOC patients. The results demonstrated that ERCC1 mRNA expression could significantly differentiate patients with benign ovarian diseases from the EOC patients (AUC = 0.931; P< 0.001) [Figure: 1].



Test result variable	Area under curve	Std. Error	Asymptotic Significance (P value)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
ERCC1	0.931	0.028	<0.001	0.877	0.985

Figure 1: ROC curve of ERCC1 expression in benign vs EOC patients

Correlation of ERCC1 mRNA expression with clinicopathological parameters in EOC patients

A trend of higher ERCC1 mRNA expression was observed in EOC patients having well differentiated tumors (M±SE = 931.14 ± 481.05) as compared to moderately differentiated tumors (M±SE = 24.07 ± 17.63) (P= 0.076) and poorly differentiated tumors (M±SE = 51.21 ± 12.33) (P= 0.084). Moreover, when compared between individual groups of patients, no significant difference in ERCC1 mRNA expression was observed between moderately and poorly differentiated tumors (P=0.227). There was trend observed in higher ERCC1 mRNA expression between EOC patients having absence (M±SE =431.39 ± 278.25) and presence of inflammation (M±SE = 28.57 ± 123.19) (P=0.068). However, ERCC1 mRNA expression did not correlate significantly with rest of the clinicopathological parameters in the studied EOC patients (Table 4).

Table 4: Correlation of ERCC1 mRNA expression with clinicopathological parameters in EOC patients

Parameter	**N (%)**	**ERCC1**	
		Mean ± SE	P value
Age (Range: 25- 70 years)			
≤47 years	28 (52)	178.24 ± 97.37	0.321
>47 years	26 (48)	522.59 ± 327.69	
Menopausal status			
Pre menopause	16 (30)	84.54 ± 37.09	0.132
Post menopause	38 (70)	471.42 ± 248.65	
Tumor size			
Small tumor size	36 (67)	456.03 ± 260.99	0.283
Large tumor size	18 (33)	158.31 ± 81.80	
Nodal status			
Absent	49 (91)	344.87 ± 192.92	0.698
Present	05 (9)	473.58 ± 258.12	
Stage			
Early	35 (65)	468.02 ± 268.28	0.265
Advanced	19 (35)	151.90 ± 77.64	
Histological grade			
Well differentiated	19 (35)	931.14 ± 481.05	**0.076**
Moderate differentiated	08 (15)	24.07 ± 17.63	
Moderate differentiated	08 (15)	24.07 ± 17.63	0.227
Poorly differentiated	27 (50)	51.21 ± 12.33	
Well differentiated	19 (35)	931.14 ± 481.05	**0.084**
Poorly differentiated	27 (50)	51.21 ± 12.33	
Histological types			
Serous adenocarcinoma	40 (74)	406.74 ± 230.50	0.115
Mucinous adenocarcinoma	08 (15)	34.03 ± 15.55	
Serous adenocarcinoma			
Low grade	11 (20)	1363.27 ± 791.39	0.126
High grade	29 (54)	43.92 ± 11.46	
Lymphocytic stromal response			
Absent	45 (83)	416.11 ± 210.54	0.457
Present	09 (17)	60.16 ± 55.62	
Lymphatic permeation			
Absent	41 (76)	445.36 ± 230.74	0.124
Present	13 (24)	77.45 ± 43.01	
Vascular permeation			
Absent	42 (78)	434.81 ± 225.43	0.134

Parameter	N (%)	ERCC1	
		Mean ± SE	P value
Present	12 (22)	83.70 ± 46.26	
Capsular Invasion			
Absent	27 (50)	554.96 ± 346.77	0.269
Present	27 (50)	158.62 ± 58.54	
Necrosis			
Absent	33 (61)	476.66 ± 278.25	0.314
Present	21 (39)	168.42 ± 1193.15	
Inflammation			
Absent	44 (82)	431.38 ± 278.25	**0.068**
Present	10 (18)	28.57 ± 123.19	
Fallopian tube			
Tumor absent	31 (57)	405.02 ± 295.29	0.725
Tumor present	23 (43)	291.77 ± 123.19	
Uterus			
Tumor absent	38 (70)	405.90 ± 242.21	0.869
Tumor present	16 (30)	240.16 ± 160.02	
Cervix			
Tumor absent	47 (87)	408.36 ± 201.72	0.869
Tumor present	07 (13)	10.47 ± 6.66	
Omentum			
Tumor absent	34 (63)	471.65 ± 276.28	0.285
Tumor present	20 (37)	161.53 ± 74.07	
Peritoneum			
Tumor absent	34 (63)	471.66 ± 276.28	0.285
Tumor present	20 (37)	161.29 ± 74.08	
Pelvic organs			
Absent	35 (65)	517.76 ± 269.24	0.099
Present	19 (35)	60.26 ± 17.37	
Ascites			
Absent	17 (34)	1135.06 ± 523.30	0.831
Present	33 (66)	1307.69 ± 508.77	
Malignant cells in Ascites			

Parameter	N (%)	ERCC1	
		Mean ± SE	P value
Absent	37 (69)	432.05 ± 254.44	0.379
Present	17 (31)	192.99 ± 86.67	
CA 125			
<35 U/ml	04 (07)	48.08 ± 14.68	0.149
≥35 U/ml	41 (76)	387.36 ± 230.06	
Not known	09 (17)		
HE-4			
<69 pmol/L	02 (3)	33.92 ± 31.28	0.171
≥69 pmol/L	24 (44)	584.97 ± 388.95	
Not known	28 (52)		

Association of ERCC1 mRNA expression with disease free and overall survival in EOC patients

Kaplan-Meier survival analysis was evaluated for DFS and OS in EOC patients. The median values of ERCC1 expression was used as cut-off value to divide the EOC patients into low (< 50) and high (≥ 50) expression groups, respectively. The difference in survival curves was analysed using the log rank test. ERCC1 was the not significant prognosticator for OS (Log rank=2.188, df=1, P=0.139) while, it was not able to predict DFS (Log rank=0.738, df=1, P=0.390) in the EOC patients. Further, the Kaplan-Meier survival analysis and the log rank test revealed that, ERCC1 mRNA expressions in EOC patients were not able to predict DFS or OS in the EOC patients (Table 5).

Table 5: Association of ERCC1 mRNA expression with disease free and overall survival

ERCC1 mRNA expression	N	Patients relapsed N (%)	Patients expired N (%)
Low	22	7 (32)	3 (14)
High	23	8 (35)	6 (26)
Log rank test statistics		Log rank=0.738, df=1, P=0.390	Log rank=2.188, df=1, P=0.139

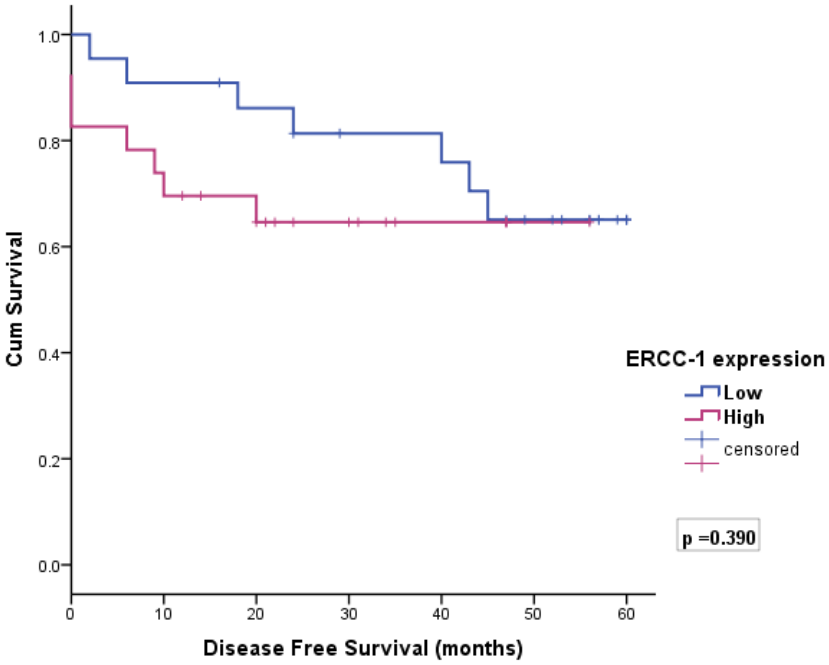


Figure 2: Kaplan-Meier survival analysis for DFS in EOC patients

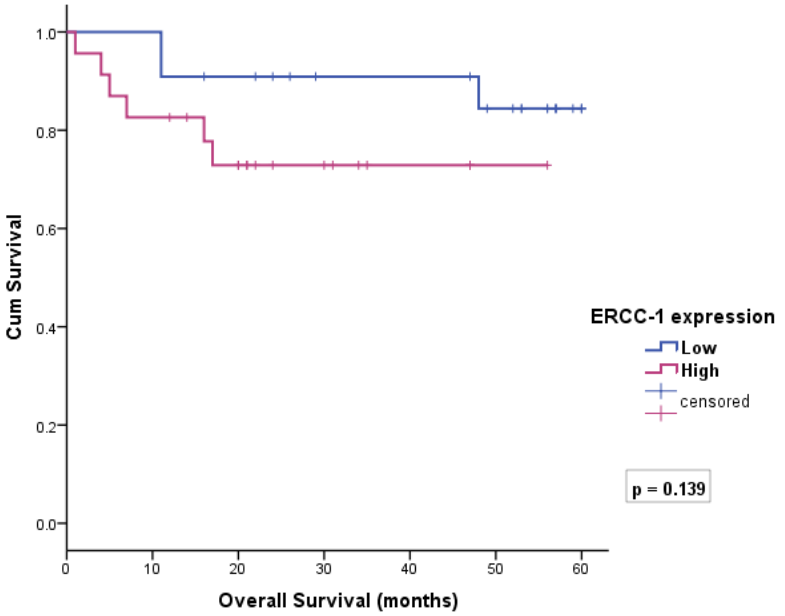


Figure 3: Kaplan-Meier survival analysis for OS in EOC patients

Discussion:

Ovarian cancer is a lethal reproductive tumor affecting women worldwide. However, the advancement in presentation and occurrence of chemoresistance are the key factors for poor survival among ovarian cancer women (13). EOC is the commonest type, highly heterogeneous, and often linked to genetic instability (14). Serous EOC has traditionally been graded as well, moderately, and poorly differentiated from the standpoint of pathogenesis (15). ERCC1 is widely recognized as a key gene regulating NER and is closely associated with platinum metabolism. However, DNA damage by platinum is the main anti-cancer mechanism and the damage can be repaired by the NER pathway. Therefore, individual differences in NER capacity will lead to individual differences in response to platinum and thus to different prognoses (16). However, it has been reported that the ERCC1 gene is involved in the repair of DNA damage caused by platinum drugs which thus reduces the efficacy of chemotherapy (17).

Based on this understanding, the current study aimed to evaluate the role of ERCC1 gene in EOC patients. The results indicated that ERCC1 expression was significantly higher in EOC patients as compared to the benign ovarian tumors (P= <0.001) which is concordant with the study of Zhao, et al (2018) (12).

In the present study, the predominant histological type of EOC was serous adenocarcinoma (74%) which was similar to the study of Muallem et al (2014), where 92.9% of EOC patients had serous papillary carcinoma out of which about 96% had low grade disease. However, in present study 54% of patients had high grade serous carcinoma.

A number of studies have examined the association between ERCC1 expression and clinicopathological parameters in patients with EOC. In the study of Zhang et al (2019) (18), majority of the EOC patients included were of advance stage and ERCC1 expression was significantly positively associated with FIGO stage and CA125 levels, which is not consistent with the current results. However, no significant correlation of ERCC1 expression was observed with age, menopause, tumor size, stage etc. Similarly, Steffensen et al (2009) (11), Scheil-Bertram et al (2010) (19), Xie c et al (2011) (20), Rubatt et al (2012) (21) and Du et al (2016) (10) also found no significant correlation with age, tumor size or stage of ovarian cancer patients.

Findings by Ganzinelli et al. (2011) suggested that higher levels of ERCC1 correlated with the vital state (22). Stratifying according to the stage, in stage III patients, lower levels of ERCC1 was associated with higher tumour grade. Similar to this, in the present study higher levels of ERCC1 was associated with early stage and low grade serous adenocarcinoma in EOC patients. In parallel to this, Smith et al. (2007) (23) also observed higher ERCC1 expression in early stage EOC patients. Moreover, they observed lower ERCC1 expression in serous carcinoma as compared to non-serous EOC patients, which is contradictory to the present results.

Further, in accordance to the present study, Ju et al. (2016) (24) observed that although not significant, the expression of ERCC1 was higher in serous adenocarcinoma patients and early stage EOC patients as compared to mucinous and advanced stage EOC patients, respectively. They also observed increased ERCC1 expression in well differentiated tumors as compared to moderate/poorly differentiated tumors, but the difference was not statistically significant. The statistical analysis of the current data also revealed that ERCC1 mRNA expression was not significantly correlated with histological grade. However, a trend of higher ERCC1 mRNA expression in well differentiated tumors as compared to moderately differentiated (P= 0.076) as well as poorly differentiated tumors (P= 0.084) of EOC patients. Contradictorily, Wu et al. et al (2020) noted that there was no significant association between expression of ERCC1 and histological grade of the malignant tumors (17).

A trend of higher ERCC1 mRNA expression (P=0.068) was observed in EOC patients having absence of inflammation. However, ERCC1 mRNA expression did not correlate significantly with rest of the clinicopathological parameters in the studied EOC patients.

In the study carried out by Zho et al. (2018), it was shown that high ERCC1 mRNA expression was correlated with a worse overall survival among all ovarian cancer patients (P<0.001) (12), which is not consistent with the current results.

Milovic-Kovacevic et al (2011) studied that DFS was significantly longer in the patient group with low expression of ERCC1 compared with patients with high ERCC1 expression (log rank, P=0.01) and OS was significantly longer in patients with low expression of ERCC1 protein compared with patients to high expression of ERCC1 (log rank, P=0.01) (25). However, in the current study, no such association was observed between the ERCC1 mRNA expression and DFS or OS of EOC patients, which was similar to the study of DU et al (2016) (10) where there was no statistically significant difference in progression free survival (P=0.099) or OS (P=0.103) between the high and low expression groups.

Hence, the results of the present study in concordance with observations by other researchers, demonstrate that ERCC1 expression is associated with early phases of EOC like low grade serous adenocarcinoma, early stage and well differentiated tumors. Moreover, previous studies have demonstrated that high ERCC1 expression in patients with EOC are associated with resistance to platinum-based chemotherapy. As platinum chemotherapy is the first-line therapy administered for EOC, ERCC1 expression may be widely used as a predictor of neoadjuvant therapy. These findings suggest that evaluating the ERCC1 expression may guide individualized treatment, avoid administration of invalid chemotherapy and eventually improve treatment for patients in the early phase of EOC before it progresses to advanced stage disease. However, further extended study enrolling more number of patients with a longer follow up period is essential to explore the ultimate role of ERCC1 as a predictive and prognostic marker in EOC.

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