Original Article

Recurrence Pattern In Women With Early-Stage Epithelial Ovarian Cancer In South Of Iran

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Abstract

Background: Ovarian cancer is the deadliest gynecologic cancer. Approximately 30% of patients are diagnosed with early-stage of disease. We designed this study to identify recurrence patterns of early-stage epithelial ovarian cancer (EOC) and significant clinicopathologic factors that influenced disease recurrence.

Methods: This retrospective study evaluated eligible patients who underwent surgery ± adjuvant chemotherapy between 2007 and 2017. Data was collected from medical records and follow-up visits. Data analysis was performed by SPSS 22.

Results: Two hundred and eight patients met inclusion criteria. During the follow-up period, recurrence was seen in 35 patients (16.8%). Recurrence rate within the first year of following period was 40%. Serous carcinoma was the most common histologic type in recurrence group (51.4%). The most frequent stage was IC3 (31.4%). In multivariate analysis, the recurrence rate was significantly higher in stage IC3 and IIB than IA (OR=22.4, and 7.82 respectively) and lower in endometrioid Carcinoma compared to clear cell carcinoma (OR=0.13). Disease recurrence was significantly higher in patients with positive peritoneal cytology compared with negative cytology (OR=4.17). The most common site for recurrence was peritoneal dissemination and intra-pelvic peritoneal recurrence was seen in 62.8%.

Conclusions: Peritoneal dissemination, especially intrapelvic peritoneal relapse is the most common pattern of recurrence in early-stage of EOC patients, and positive peritoneal cytology for malignancy is a predictive factor for tumor recurrence. Maximum efforts for complete primary staging is necessary to identify microscopic foci of tumors lead to disease recurrence.

Keywords: Epithelial ovarian carcinoma, recurrence, early stage, recurrence patterns.

INTRODUCTION

Ovarian cancer is the deadliest gynecologic cancer.(Baghal-Sadriforoush, Bagheri, Rad, & Nejadnematalahi, 2022; Khalafi-Nezhad, Ebrahimi, Ahmadpour, Momtahan, Robati, Saraf, et al., 2020; Zhang, Huo, Huang, Cheng, Liu, & Bao, 2019) and accounts for an incidence rate, 9.2 per 100,000, in Asian/Pacific Islander women.(Torre, Trabert, DeSantis, Miller, Samimi, Runowicz, et al., 2018) Approximately 30% of patients are diagnosed with early stage of disease. (International Federation of Gynecology and Obstetrics [FIGO] stage I, II).(Ditto, Leone Roberti Maggiore, Bogani, Martinelli, Chiappa, Evangelista, et al., 2019; Kajiyama, Mizuno, Shibata, Umezu, Suzuki, Yamamoto, et al., 2014) Although these patients possess generally favorable prognosis, with a 5-year overall survival rate about 70 to 90%, disease relapse may occur ranging from 13 to over 31% in different studies.(Ditto, et al., 2019; Hirose, Tanabe, Nagayoshi, Hirata, Narui, Ochiai, et al., 2018; Kajiyama, et al., 2014) The main primary treatment for early-stage of

epithelial ovarian cancer (EOC) is surgical, and patients should undergo total abdominal hysterectomy, bilateral salpingo-oophorectomy and comprehensive surgical staging.(Ditto, et al., 2019; Hirose, et al., 2018; Jonathan S. Berek, 2020) With adequate surgical staging and correct selection of patients with early-stage of EOC for adjuvant chemotherapy, disease recurrence is partly avoided.(Bakkum-Gamez, Richardson, Seamon, Aletti, Powless, Keeney, et al., 2009; Ditto, et al., 2019; Hirose, et al., 2018; Trimbos, Vergote, Bolis, Vermorken, Mangioni, Madronal, et al., 2003) Based on recent studies, stage at diagnosis, post-operative disease residue volume, histologic grading and positive peritoneal cytology affect patients survival.(Baharara, Amini, & Mousavi, 2015; Chan, Tian, Monk, Herzog, Kapp, Bell, et al., 2008; Kajiyama, et al., 2014; Vergote, De Brabanter, Fyles, Bertelsen, Einhorn, Sevelda, et al., 2001) Acquaintance of recurrence site and patients characteristic details in relapsed cases of early-stage EOC is needed to promote therapeutic strategy for these group of patients. In spite of all that, there are some limitations and biases such as small sample size, inclusion of border line tumors in the most studies and there have been few reports focusing on the recurrence pattern details in early-stage EOC patients.(Angiolo Gadducci, Cosio, Zola, Sostegni, Fuso, & Sartori, 2013; A. Gadducci, Sartori, Maggino, Zola, Landoni, Fanucchi, et al., 1997; Schilder, Thompson, DePriest, Ueland, Cibull, Kryscio, et al., 2002) In the current study, we analyzed retrospectively, a relatively large series of patients with early-stage of EOC to identify significant clinicopathologic factors that influence disease recurrence pattern.

Materials and methods:

This retrospective study was done at Shiraz University of Medical Science (medical referral center of southern Iran). We evaluated eligible subjects diagnosed with early-stage (stage I, II) EOC using the FIGO classification (published in 2014), and underwent surgery ± adjuvant chemotherapy, and followed up between 2007 and 2017 in Shahid Motahari academic tumor clinic in Shiraz. Before collecting the data, the purpose of research was explained for all participants clearly, and written informed consent was obtained. This study was approved by Shiraz University Medical Science Ethics Committee. (Ethic code: IR.SUMS.REC.1399.1240) Patients with border line tumors, and non-epithelial ovarian malignancies, and lack of essential clinical data were excluded. Data were collected from medical records and follow-up visits. We utilized the World Health Organization (WHO) criteria for histologic tumor types. Types of surgical procedure were classified to: 1- hysterectomy, bilateral salpingo-oophorectomy, and omentectomy (Basic surgery), 2-Basic surgery + Pelvic lymphadenectomy (PLNX), 3- Basic surgery + PLNX + Para-aortic lymph node dissection (PANX), and 4- Fertility preserving surgery (Limited surgery).

Recurrence site classification included four categories: 1-Peritoneal involvement (finding a lesion in intra and/or extrapelvic peritoneum by imaging, and cases with ascites + elevated Cancer Antigen 125 level based on Gynecological Cancer Inter Group critera [GCIG] for recurrence), 2-Lymphagenous (retroperitoneal [pelvic and para-aortic lymph nodes], and inguinal, mediastinal lymph node involvement with recurrence), 3-Hematogenous (recurrence in liver, spleen, lung, bone, and others), 4-Others including positive pleural cytology in cases with only pleural effusion, and patients with rising the CA125 level according to GCIG criteria. Patients with overlapping recurrence sites were designated in each classification reiteratively.

Statistical analysis:

Median (minimum and maximum) and frequency (relative frequency) were used to describe quantitative and qualitative variables, respectively. Logistic regression, multivariate logistic regression, and Chi-square tests were used to evaluate the associations, to control for confounding all variables with p-value < 0.2 resulted from univariate analysis were entered in backward elimination regression with α=0.1 removal and significance level 0.05. SPSS v.22re uses and significance level was considered 0.05 for all tests.

Results

Two hundred and eight patients with early-stage of EOC met inclusion criteria during the study period. The characteristics of enrolled patients were summarized in table 1. The median age was 47 years, ranging from 18 to 81, and 77 patients (37%) were in a menopausal state. The median follow-up period was 53 months (range: 2-133 months). In our study, the FIGO stage distribution was shown that tumors of stage IA were most frequent, in 63 patients (30.3%)

and serous carcinoma (47.1%) was the most common histotype reported, followed by mucinous carcinoma in 21.2% of cases. While 77 patients (37%) had a grade 1 tumor, grade 2 and 3 were seen in 79 (38%) and 52 (25%) respectively. Fifty-three (25.5%) women had positive washing cytology/ ascites. In all patients, 174 (83.7%) underwent basic surgery + pelvic lymphadenectomy and 155 (74.5%) received chemotherapy. The causes for not ordering of chemotherapeutic agents in 25.5% of patients judged based on disease stage, histologic type, age, complications and patient's desires. During the follow-up period, recurrence was seen in 35 patients (16.8%) out of the 208 cases with early-stage of EOC. The characteristics of 35 recurrence cases were described in table 2. The median age of recurrence patients was 45 years (range: 18-69 years) and the median follow-up time was 47 months (range from 13 to 101). We detected recurrence within the first year of follow-up period in 14 patients (40%), at 1-2 years in 7 patients (20%), at 2-3 years in 9 cases (25.7%) and at 3 years and over, in 5 patients (14.3%). The median time to recurrence was 20 months (ranging from 3 to 50). Serous carcinoma was the most common histologic type in recurrence group, seen in 18 patients (51.4%), followed by mucinous carcinoma in 6 cases (17.1%), and the most frequent stage was IC3 in 11 patients (31.4%), and the second frequent stage was IIB in 7 cases (20%). From 35 patients with recurrence, 32 cases (91.4%) underwent basic surgery + pelvic lymph node dissection, and fertility sparing surgery was done for 3 patients (8.6%). Para-aortic lymph node dissection was designated for none of them. In all of 28 patients (80%) received adjuvant chemotherapy, carboplatin + paclitaxel regimen was used. Table 3 presents the association of age, histologic type, and grade, FIGO stage, surgical techniques and adjuvant therapy with recurrence that analyzed by univariate and multivariate logistic regression. In multivariate analysis, the recurrence rate was significantly higher in stage IC3 and IIB than IA (OR=22.42, and 7.82 respectively) and significantly lower in endometrioid carcinoma compared to clear cell carcinoma (OR=0.13). Disease recurrence was significantly higher in the patients with positive peritoneal cytology compared with negative cytology (OR= 4.17). We found some rare sites for disease recurrence in our study including: recurrence in gluteal muscle, rectus muscle and adrenal gland that confirmed with trucut biopsy. There were four recurrence site categories in our study, Peritoneal, Lymphogenous, Hematogenous, and Others in 31 (88.6%), 12 (34.3%), 10 (28.6%) and 2 (5.7%) patients respectively. Classification of recurrence sites was tabulated in table 4. Fifteen patients participated in more than one classification, for example, both peritoneal and lymphogenous recurrence occurred in 10 patients. The most common site for recurrence was peritoneal dissemination, and intrapelvic peritoneal recurrence was seen in 22 cases (62.8%), equivalent with more than the half of all recurrences.

Discussion

The current research was done to identify the recurrence sites of early stage of EOC in a regional population of these patients in a referral center for gynecologic oncology in Sothern Iran, Shiraz. In our study the recurrence rate was 16.8% in 208 patients with stage IA-IIB EOC, and peritoneal relapse was the most frequent site (88.6%). Several studies have evaluated the recurrence sites of early-stage of EOC.(Chan, et al., 2008; Ditto, et al., 2019; Hirose, et al., 2018; Skírnisdóttir & Sorbe, 2007; Tropé, Kaern, Hogberg, Abeler, Hagen, Kristensen, et al., 2000; Wei, Li, Sun, Li, Xu, & Wu, 2017) But details of this subject have been lesser investigated. In one available study, among of 467 FIGO stage IA-IIA patients, recurrence was found in 87 (19%) of cases and intrapelvic peritoneal dissemination was occurred in 44% of recurrence cases.(Angiolo Gadducci, Cosio, Zola, Sostegni, Fuso, & Sartori, 2013) In another research in Japan, 602 FIGO stage I patients, were followed up and recurrence was seen in 70 (11.6%) cases, and 70% of all them showed peritoneal recurrence.(Hirose, et al., 2018) Gadducci and et.al reported 17% recurrence rate, that is similar to our study, including intrapelvic recurrence in 54% of all relapse cases in a retrospective study of 224 FIGO stage I patients.(A. Gadducci, et al., 1997) In these studies, peritoneal dissemination is the most frequent route for recurrence and one of the reasons for it may be insufficient exploration of peritoneal cavity for occult involvement. Gaemmaghami et al, in a descriptive analytic study concluded that without staging surgery including peritoneal biopsies, occult metastasis may be missed and lead to inadequate treatment.(Gaemmaghami, Yousefi, Gilani, Mosavi, & Shariat, 2011) The National Comprehensive Cancer Network (NCCN) guideline and Gynecology Oncology Group (GOG) surgical manual advised to multiple peritoneal surface biopsies during surgery including: paracolic gutters, under-surface of diaphragm (or sweeping it for papanicolaou test alternatively), right and left pelvic side wall, cul-de-sac and urinary bladder peritoneum.(Morgan, Armstrong, Alvarez, Bakkum-Gamez, Behbakht, Chen, et al., 2016) The lack of taking these biopsies, or incompleteness of them, conduce to undiagnosed upstaged disease in patients

without gross peritoneal lesions.(Lee, Kim, Chung, Kim, Park, & Song, 2014; Shroff, Brooks, Zighelboim, Powell, Thaker, Mutch, et al., 2011) Similar to nationwide epidemiologic studies, in our survey, serous carcinoma was in the top of histologic types with a view to frequency, both in primary under-study population (47.1%), and in recurrence group (51.4%), and it is contrary to reports about Asian women that serous carcinoma incidence is lowest in them.(Torre, et al., 2018) Arab et al, reported that the most common epithelial ovarian cancer in Iran were serous (47.6%) and mucinous carcinoma (9.2%) in 2010.(Arab, Khayamzadeh, Hashemi, Hosseini, Tabatabaeefar, Anbiaee, et al., 2010) Karimi-zarchi et al conducted a cross-sectional, description-analytic study on 120 patients in 2015, and declare that serous adenocarcinoma was observed in 57.6% of all epithelial ovarian carcinoma (the most frequent histologic subtype).(Karimi-Zarchi, Mortazavizadeh, Bashardust, Zakerian, Zaidabadi, Yazdian-Anari, et al., 2015) Statistical reports discrepancies between Iranian and other Asian investigations such as Japanese studies may be due to genetic and environmental factors. Differences between dietary habits, and use of oral contraceptives, and pregnancy rate may be influence ovulation rate and menstruation duration that played a role to developing endometriosis as a precursor for clear cell carcinoma, the most common histologic subtype in Japan.(Machida, Matsuo, Yamagami, Ebina, Kobayashi, Tabata, et al., 2019) In our study recurrence rate was significantly higher in stage IC3 and IIB, than stage IA. Ditto et al, in a retrospective study showed that FIGO stage is a relevant prognostic factor for recurrence in early stage of EOC patients.(Ditto, et al., 2019) Chan et al, in a study derivative from two Gynecology Oncology Group trials, concluded that higher stage and positive peritoneal washing for malignancy were independent prognostic factors for recurrence.(Chan, et al., 2008) Patients with positive peritoneal cytology are in a higher risk for disease recurrence and have poorer survival in comparison with negative washing, essentially.(Kajiyama, Suzuki, Yoshikawa, Kawai, Nagasaka, & Kikkawa, 2019)

As these results, we showed that positive peritoneal cytology for malignancy associated with higher recurrence rate compared to negative washing, because of widely spreading seeds of tumor cells in the peritoneal cavity. We showed recurrence rate was lower in endometrioid carcinoma than the clear cell carcinoma. In a Japanese study, Sou et al, found the same result.(Hirose, et al., 2018) This difference is explained with less sensitivity of clear cell carcinoma to chemotherapeutic agents such as platinum-based drugs with low response rate (<50%).(Hirose, et al., 2018; Hogen, Vicus, Ferguson, Gien, Nofech-Mozes, Lennox, et al., 2019)

Conclusion

As we showed, peritoneal dissemination, especially intrapelvic peritoneal relapse was the most common pattern of recurrence in early stage of EOC patients, and positive peritoneal cytology for malignancy is a predictive factor for tumor recurrence. Despite our study limitation, such as retrospective nature and single-study design, our findings of recurrent pattern may be led to improve the management of patients with early stage of EOC. Further multicentric, prospective researches for confirming these findings should be designed. In conclusion, maximum effort for complete primary staging surgery is necessary to identify microscopic foci of tumors lead to disease recurrence.

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Table 1. Characteristics of study population

Characteristics	Value
Age(year)(n=208)	47(18-81)
<50 year	123(59.1%)
≥50 year	85(40.9%)
Menopause status yes	77(37%)
no	131(63%)
Follow-up period(month)(n=208)	53(2-133)
FIGO sub-stage	
IA	63(30.3%)
IB	13(6.3%)
IC1	22(10.6%)
IC2	32(15.4%)
IC3	22(10.6%)
IIA	35(16.8%)
IIB	21(10.1%)
Grade I	77(37%)
II	79(38%)
III	52(25%)
Histology	
Serous	98(47.1%)
Mucinous	44(21.2%)
Endometrioid	36(17.3%)
Clear cell	12(5.8%)
Transitional.cell-brenner	6(2.9%)
Mix	8(3.8%)
others	4(1.9%)
Positive peritoneal cytology yes	53(25.5%)
No	155(74.5%)
Surgery	
Basic surgery	8(3.8%)
Limited surgery	22(10.6%)
Basic surgery+ PLNX	174(83.7%)
Basic surgery+ PLNX+ PANX	4(1.9%)
Chemotherapy regimen	
Carboplatin+ Paclitaxel	154(74%)
Cisplatin+ Paclitaxel	1(0.5%)
No chemotherapy	53(25.5%)

Values are presented as median (min-max) or number (%).

FIGO, International Federation of Gynecology and Obstetricians; PLNX, Pelvic lymphadenectomy; PANX, Para-aortic lymphadenectomy.

Table 2. Characteristics of patients with recurrence

characteristics	Value
Age(year)	45(18-69)
Follow-up period(month)	47(13-101)

FIGO sub-stage	*35(100%)*
IA	5(14.3%)
IB	1(2.9%)
IC1	3(8.6%)
IC2	2(5.7%)
IC3	11(31.4%)
IIA	6(17.1%)
IIB	7(20%)
Histology	*35(100%)*
Serous	18(51.4%)
Mucinous	6(17.1%)
Endometrioid	3(8.6%)
Clear cell	5(14.3%)
Mix	2(5.7%)
Transitional.cell-brenner	0(0%)
Other	1(2.9%)
Surgery	*35(100%)*
Basic surgery	0(0%)
Limited surgery	3(8.6%)
Basic surgery+ PLNX	32(91.4%)
Basic surgery+ PLNX+ PANX	0(0%)
Chemotherapy regimen	*35(100%)*
Carboplatin+ Paclitaxel	28(80%)
Cisplatin+ Paclitaxel	0(0%)
No chemotherapy	7(20%)

Values are presented as median (range) or number (%).

FIGO, International Federation of Gynecology and Obstetricians; PLNX, Pelvic lymphadenectomy; PANX, Para-aortic lymphadenectomy.

Table 3. The association between recurrence and patients characteristics.

Variable(n)	Univariate analysis			Multivariate analysis*		
	OR	95% C.I	p-value	OR	95% C.I	p-value
Age(year)(n=208)	0.99	0.96-1.02	0.42	0.99	0.96-1.03	0.70
FIGO sub-stage						
IA(reference)(n=63)	1.0	1.0	-	-	-	-
IB(n=13)	0.97	0.1-9.03	0.97	1.35	0.14-13.43	0.79
IC1(n=22)	1.83	0.4-8.39	0.43	3.29	0.64-16.82	0.15
IC2(n=32)	0.77	0.14-4.22	0.76	0.62	0.11-3.52	0.59
IC3(n=22)	11.6	3.36-40.01	<0.001	22.42	5.57-90.22	<0.001
IIA(n=35)	2.4	0.57-8.52	0.17	3.41	0.88-13.17	0.07
IIB(n=21)	5.8	1.6-21.01	0.007	7.82	1.98-30.94	0.003
Grade						
Grade I(reference category)(n=77)	1.0	1.0	-	-	-	-
Grade II(n=79)	3.75	0.94-13.53	0.06	3.82	1.01-14.54	0.04
Grade III(n=52)	18.09	5.04-64.97	<0.001	17.94	4.97-64.71	<0.001
Histology						
Clear cell(reference)(n=12)	1.0	1.0	-	-	-	-

Mucinous(n=44)	0.22	0.05-0.93	0.03	0.26	0.06-1.14	0.07
Endometrioid(n=36)	0.13	0.25-0.66	0.01	0.14	0.03-0.72	0.0.2
Serous(n=98)	0.31	0.09-1.11	0.07	0.40	0.11-1.49	0.17
Transitional.cell-brenner(n=6)	0	0-0	>0.99	0.0	0.0-.0.0	>0.99
Mix(n=8)	0.47	0.06-3.34	0.44	0.52	0.98-4.28	0.6
Others(n=4)	0.47	0.04-5.9	0.55	0.52	0.04-6.8	0.62
Positive peritoneal cytology(n=208)	4.85	2.26-10.42	<0.001	4.17	2.39-11.22	<0.001
Surgery						
Basic surgery(reference)(n=8)	1.0	1.0	-	-	-	-
Limited surgery(n=22)	0	0.0-.	>0.99	∞	0.0-.	0.99
Basic surgery+ PLNX(n=174)	0.7	0.19-2.51	0.58	∞	0.0-.	0.99
Basic surgery+ PLNX+ PANX(n=4)	0.0	0.0-.	>0.99	0.73	0.0-.	>0.99
Adjuvant chemotherapy						
observation(reference group)(n=53)	1.0	1.0	-	-	-	-
chemotherapy(n=155)	1.45	0.56-3.75	0.43	1.77	0.64-4.92	0.27

∞Too big OR

*adjusted on marital status

FIGO, International Federation of Gynecology and Obstetricians; PLNX, Pelvic lymphadenectomy; PANX, Para-aortic lymphadenectomy; C.I, Confidence interval; OR, Odds ratio.

Table 4. Classification of recurrence sites.

variables	No. (%)
Peritoneal dissemination	31(88.6%)
Intrapelvic peritoneum only	22(62.8%)
Intra-and extrapelvic peritoneum	4(11.4%)
Ascites only	5(25.8%)
Hematogenous recurrence	*10(28.6%)*
Liver	3(8.6%)
Spleen	1(2.9%)
Lung	1(2.9%)
Bone	1(0%)
Others	4(0%)
Lymphogenous recurrence[a]	12(34.3%)
Para-aortic lymph nodes	7(20%)
Pelvic lymph nodes	7(20%)
Inguinal lymph nodes	1(2.8%)
Mediastinal lymph nodes	0(0%)
Others	*2(5.7%)*
CA125 only	2(5.7%)
Pleural effusion	0(0%)

[a] two common cases experiencing Para-aortic lymph nodes& Pelvic lymph nodes, and one common case experiencing Pelvic lymph nodes & Inguinal lymph nodes.