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Value of fertility-sparing surgery for young females with epithelial ovarian cancer: a comparative study.

Valor de la cirugía de preservación de la fertilidad en mujeres jóvenes con cáncer de ovario epitelial: un estudio comparativo

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Abstract

OBJECTIVE: In the current study, we aimed to compare between radical surgery and fertility saving surgery in females with stage 1A-C EOC regarding recurrence rate and patients survival rates in addition to evaluating reproductive and obstetric outcomes for stage I EOC females who were managed by fertility saving surgery.

PATIENTS AND METHODS: We prospectively identified 60 patients diagnosed with stage I EOC aged ≤ 40 years. Patients in the fertility-preservation group underwent salpingo-oophorectomy on the side of the affected ovary in addition to incisional biopsy or wedge excision of the ovary on the other side. Patients in the radical surgery group underwent total hysterectomy and bilateral salpingo-oophorectomy. We followed up all patients for 5 years to assess their reproductive and oncological outcomes.

RESULTS: Patients in the fertility preservation surgery group were significantly younger (30 ± 4 *versus* 35 ± 5) ($p < 0.001$), their tumor sizes were smaller 3.4 ± 1.3 versus 6.0 ± 2.6 ($p < 0.001$), of lower grade ($p = 0.011$), earlier stage ($p < 0.001$) and has more mucinous histology than patients in the radical surgery group. There were no statistically significant differences between both groups regarding tumor recurrence or survival rates. Of 25 patients underwent fertility preservation surgery, 18/25 (72%) tried to get pregnant. 15/18 (83%) pregnancies were recorded, including 13 live births, 1 miscarriage, and 1 intrauterine fetal death.

CONCLUSION: Fertility sparing surgery could be adequate alternative to radical surgery for young females with stage I EOC.

KEYWORDS: Epithelial ovarian cancer (EOC); Fertility preservation; radical surgery; outcome.

Resumen

OBJETIVO: Comparar la cirugía radical con la cirugía conservadora de la fertilidad en mujeres con cáncer de ovario epitelial en estadio 1A-C con respecto a la tasa de recurrencia y las tasas de supervivencia. Además, evaluar los desenlaces reproductivos y obstétricos para las mujeres con cáncer de ovario epitelial en estadio I tratadas con una conducta conservadora de la fertilidad.

PACIENTES Y MÉTODOS: Estudio prospectivo efectuado en pacientes con cáncer de ovario epitelial, estadio I, con edad ≤ 40 años. A las pacientes del grupo de preservación de la fertilidad se les practicó salpingooforectomía del lado del ovario afectado y una biopsia por incisión o escisión en cuña del ovario contralateral. A las pacientes del grupo de cirugía radical se les practicó la histerectomía total y salpingooforectomía bilateral. Para evaluar los desenlaces reproductivos y oncológicos se dio seguimiento a todas las pacientes durante cinco años.

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RESULTADOS: Se estudiaron 60 pacientes; las del grupo de cirugía de preservación de la fertilidad eran significativamente más jóvenes (30 ± 4 en comparación con 35 ± 5) (p < 0.001), el tamaño de sus tumores era más pequeño 3.4 ± 1.3 en comparación con 6.0 ± 2,6 (p < 0.001), de menor grado (p < 0.001). = 0.011), estadio más precoz (p < 0.001) y con más histología mucinosa que las pacientes del grupo de cirugía radical. No hubo diferencias estadísticamente significativas entre ambos grupos en cuanto a la recurrencia tumoral o las tasas de supervivencia. De 25 pacientes operadas para preservación de la fertilidad 18 de 25 intentaron quedar embarazadas. Se registraron 15 de 18 embarazos, incluidos 13 nacidos vivos, 1 aborto espontáneo y 1 muerte fetal intrauterina.

CONCLUSIÓN: La cirugía conservadora de la fertilidad podría ser una alternativa adecuada a la cirugía radical para mujeres jóvenes con cáncer epitelial de ovario en estadio I.

PALABRAS CLAVE: Cáncer epitelial de ovario; preservación de la fertilidad; cirugía radical; desenlaces.

INTRODUCTION

Epithelial ovarian cancer mostly encountered in postmenopausal women, but it could be diagnosed at any age.[1,2] The definitive surgical management of epithelial ovarian cancer is total hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, and omentectomy followed by adjuvant chemotherapy.[3] Recently, epithelial ovarian cancer was diagnosed in a big number of premenaupausal young females and about 14% of cases occur in females younger than 40 years and most of those patients were nulliparous and might wish to preserve their fertility.[4] It was found that 7-8% of epithelial ovarian cancer patients stage I were younger than 35 years old.[5] Fertility-preserving surgeries might be beneficial for patient with stage I epithelial ovarian cancer where conservation of the uterus and contralateral ovary was performed.[6]

National Comprehensive Cancer Network (NCCN) recent guidelines stated that epithelial ovarian cancer, patients having unilateral disease stage (IA- IC) could undergo fertility-preserving surgeries, regardless of histopathology or grade of their tumor.[7] European Society of Medical Oncology (ESMO) stated that young females with epithelial ovarian cancer stage IA-C with only non-clear cell carcinoma histology and low grade could underwent fertility-preserving surgeries only after complete surgical staging and lymphadenectomy.[8] However, the safety of fertility-preserving surgeries even in low grade tumors with favorable histology is still controversial.

In the current study, we aimed to compare between radical surgery and fertility saving surgery in females with stage 1A-C epithelial ovarian cancer regarding recurrence rate and patients survival rates in addition to evaluating reproductive and obstetric outcomes for stage I epithelial ovarian cancer females who were managed by fertility saving surgery.

PATIENTS AND METHODS

The study design was approved by local ethics committees of Faculty of Medicine, Zagazig

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University. We prospectively identified patients diagnosed with stage I epithelial ovarian cancer aged ≤ 40 years, who were admitted to Department of Obstetrics and Gynecology of Zagazig University Hospitals in the period between 2012 and 2017. The diagnoses, clinical and histopathological staging were assessed based on the World Health Organization Classification of Female Reproductive Organs Tumors 4th edition and International Federation of Gynecology and Obstetrics (FIGO) staging system (2014).

General inclusion criteria of the study: Females with epithelial ovarian cancer stages 1 A-C serous, mucinous or endometroid histology.

Inclusion criteria for fertility saving surgery: Nulliparous patients in child-bearing age with a strong desire to maintain their fertility and have a sure diagnosis of stage I epithelial ovarian cancer were proposed a fertility-sparing surgery if patients refused to be treated with the conservative approach or they were postmenopausal they underwent radical surgery.

Exclusion criteria: Patients with clear cell carcinoma, borderline epithelial ovarian cancer, squamous cell carcinoma, germ cell tumor, sex cord stromal tumors of the ovary.

Patients with incomplete clinical, pathological and follow-up data

Patients in the fertility-preservation group underwent salpingo-oophorectomy on the side of the affected ovary in addition to incisional biopsy or wedge excision of the ovary on the other side. Patients in the radical surgery group underwent total hysterectomy and bilateral salpingo-oophorectomy.

We performed complete surgical staging for both groups by performing omentectomy, lymphadenectomy, appendectomy, peritoneal washings, and multiple random omental biopsies. Evaluation of all the pathological slides was performed by 2 expert pathologists without previous knowledge of clinical data or patient outcomes. Adjuvant chemotherapy was given after surgery to patients at high risk for recurrence as FIGO stage IC or high grade tumors or tumors with focal clear-cell morphology. Chemotherapy regimen composed of TC (paclitaxel and carboplatin) and PC (cyclophosphamide and cisplatin) cycles number ranged from 3-9 cycles. After finishing primary treatment we followed-up patients monthly for the first six months, every two months for the first year, every six months for 2 years then yearly for 5 years. During followup visit we performed complete clinical examination, pelvic examination, ultrasound scan and evaluation of serum tumor marker CA 125.

Recurrence was proved by histopathological evidence of tumor in recently acquired incisional or fine-needle biopsy, or recently detected lesions during radiological evaluation. Disease-free survival (DFS) rate was calculated from primary surgery time to disease recurrence. Cancer-specific survival (CSS) rate was calculated from primary surgery to cancer specific death or censoring during the last follow-up.

Statistical analysis: The collected data were computerized and statistically analyzed using Statistical Package for Social Sciences (SPSS 24 Inc. Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation). Level of P-value ≤ 0.05 indicates significant, $p < 0.001$ indicates highly significant difference while, $p > 0.05$ indicates non-significant difference.

Survival analysis: Kaplan and Meier method used to estimate overall and event free survival and log rank test compared survival curves. Overall survival (OS): was calculated as the interval between the date of diagnosis till date of death or date of last follow up. Recurrence -free survival (RFS): was calculated from the date of documented CR, till relapse date, or the end date of the study.

RESULTS

The present study included sixty patients; 25 (45%) patients underwent fertility preserving surgery and 35 (55%) patients underwent radical surgery. Patients in the fertility preservation surgery group were significantly younger (30 ± 4 versus 35 ± 5) ($p < 0.001$), their tumor sizes were smaller 3.4 ± 1.3 versus 6.0 ± 2.6 ($p < 0.001$), of lower grade ($p = 0.011$), earlier stage ($p < 0.001$) and has more mucinous histology than patients in the radical surgery group.

All included patients in the fertility preservation surgery group were nulliparous, while most patients in the radical surgery group were multiparous ($p < 0.001$).

Higher number of patients received chemotherapy in the radical surgery group than fertility preservation surgery group.

Correlation between both groups regarding oncologic outcomes. After a median follow-up period of 56 months (range, 25-60 months), 13 (21.7%) patients relapsed, 8 (13.3%) died of the disease from all included patients.

DFS and CSS rates of radical surgery group were and of fertility preservation surgery group were with no statistically significant differences between both groups regarding tumor recurrence or survival rates.

Correlation between both groups regarding pattern of recurrence. In fertility preservation surgery group, 5 (20%) patients underwent recurrence and 3 (12%) cases died from progressive disease most of relapses were limited to the contralateral ovary and only single patient has a disseminated disease with lung metastases. In patients in the radical surgery 8 (22.9%) patients underwent recurrence and 5 (14.3%) cases died from progressive disease most of relapses were multiple and disseminated.

Reproductive outcomes of fertility preservation surgery group of 25 patients underwent fertility preservation surgery, 18/25 (72%) tried to get pregnant. 3/18 (17%) patients were diagnosed with infertility, 15/18 (83%) pregnancies were recorded, including 13 live births, 1 miscarriage, and 1 intrauterine fetal death. Five/25 (20%) patients were unable to get pregnant due to recurrent disease in the preserved ovary.

DISCUSSION

Surgical management of young females with cancer ovary that is primarily limited to the ovary is a challenging issue particularly if the patient was nulliparous and wishes to preserve her fertility.[9] There are few studies regarding comparison between radical surgery and fertility saving surgery and the management strategies were not standardized yet.[10]

Previous studies have considered cases with high grade tumors and tumors with stage IC have a higher relapse and fatality risks and could not be considered for fertility saving.

However, recent studies showed that there are no clear evidences that radical surgery in stage I epithelial ovarian cancer of any grade could improve patients' oncological outcome,[9-14] which support our findings regarding benefits of fertility

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Table 1. Correlations between patients underwent both surgical techniques regarding clinicopathological features and outcome of patients

		Operation				Total n = 60		P
		Conservative surgery n = 25		Radical surgery n =3 5				
		n	%	n	%	n	%	
Clinicopathological								
Age (years)		30±4		35±5		32±8		<0.001
Histopathology	Endometroid	3	12.0%	4	11.4%	7	11.7%	0.582
	Mucinous	7	28.0%	6	17.1%	13	21.7%	
	Serous	15	60.0%	25	71.4%	40	66.7%	
Parity	Nulli	25	100.0%	10	28.6%	35	58.3%	<0.001
	Multi	0	0.0%	25	71.4%	25	41.7%	
Side of tumor	Uni	25	100.0%	24	68.6%	49	81.7%	0.002
	Bilat.	0	0.0%	11	31.4%	11	18.3%	
Size cm		3.4±1.3		6.0±2.6		4.9±2.5		<0.001
FIGO stage	Stage IA	10	40.0%	0	0.0%	10	16.7%	<0.001
	Stage IB	9	36.0%	12	34.3%	21	35.0%	
	Stage IC	2	8.0%	4	11.4%	6	10.0%	
	Stage IIB	0	0.0%	1	2.9%	1	1.7%	
	Stagr IA	2	8.0%	0	0.0%	2	3.3%	
	Stagr IB	1	4.0%	0	0.0%	1	1.7%	
	Stagr IC	1	4.0%	18	51.4%	19	31.7%	
Grade	High grade	6	24.0%	20	57.1%	26	43.3%	0.011
	Low grade	19	76.0%	15	42.9%	34	56.7%	
Number of cth cycles	4	6	24.0%	8	22.9%	14	23.3%	0.918
	6	19	76.0%	27	77.1%	46	76.7%	
Outcome								
Recurrence	0	20	80.0%	27	77.1%	47	78.3%	0.791
	1	5	20.0%	8	22.9%	13	21.7%	
Death	0	22	88.0%	30	85.7%	52	86.7%	0.797
	1	3	12.0%	5	14.3%	8	13.3%	

saving surgeries after application of strict precautions and inclusion criteria of patients. Fruscio et al[10] analysis results confirmed our findings.

Mandelbaumc et al[9] showed that oncologic outcomes after performing fertility sparing surgery were nearly similar to radical surgery in females with epithelial ovarian cancer, stage I, grade 1 and 2 with serous, mucinous or endometrioid histology.

Jiang et al[11] showed cancer specific survival rate in fertility sparing surgery group was better than that in the radical surgery group this is because

Table 2. Correlations between patients underwent both surgical techniques regarding survival analysis rates [OS & RFS] of patients

Operation	Total n	N of Events	Censored		Survival Rate %	Sig.	Survival time in Months		
			n	Percent			Mean		Median
							Estimate ±SE	95% CI	
Overall Survival									
Conservative surgery	25	3	22	88.0%	80.8%	0.848	58.9 ± 0.6	57.7-60.1	NR
Radical surgery	35	5	30	85.7%	70.7%		59.0 ± 0.4	58.1-59.8	NR
Overall	60	8	52	86.7%	74.8%		58.9 ± 0.4	58.2-59.6	NR
Recurrence Free Survival									
Conservative surgery	25	5	20	80.0%	78.2%	0.822	57.1 ± 1.2	54.8-59.4	NR
Radical surgery	35	8	27	77.1%	74.7%		56.6 ± 1.1	54.5-58.7	NR
Overall	60	13	47	78.3%	76.2%		56.8 ± 0.8	55.2-58.4	NR

in their studies most high risk patients with higher grade tumors and clear cell morphology underwent radical surgery.

Similar to our data; previous studies which compared between fertility sparing and radical surgery in stage I epithelial ovarian cancer have not found any adverse effects of fertility sparing surgery on patients survival.[10-14] Most studies showed that stage I epithelial ovarian cancer tumors were usually of low grade, have more mucinous histology, occur in younger females and associated with favorable prognosis which encourage performing fertility sparing in such categories.[10,14]

In the present studies we excluded cases with clear cell morphology from fertility preserving surgery due to its high rate of progression, but in a previous researchers who performed a study on Japanese patients with clear cell carcinoma of the ovary stage I. they found that prognosis of patients with clear cell carcinoma who underwent fertility sparing surgery have-not differed from patients with non-clear morphology or from patients underwent radical surgery.[15]

In recurrent cases in the fertility saving group pattern of recurrence was localized and less disseminated than patients in the radical surgery group which presented with widespread disseminated recurrences which was similar to results of Jiang et al[11] and Bentivegna et al.[16]

This was explained by that recurrence in the preserved ovary has a more liability of saving patients life by surgery and chemotherapy which is not inversely affecting survival of patients underwent fertility sparing surgery.[16]

In the fertility sparing surgery group we reported an accepted pregnancy and live birth rates which was comparable with previously published reports of 80% rate of successful pregnancies after fertility sparing surgery.[10,17]

CONCLUSION

We concluded that fertility sparing surgery could be adequate alternative to radical surgery for young females with stage I epithelial ovarian cancer of serous, mucinous or endometriod morphology. Patients must be informed that their younger age is mostly associated with more liability of low-grade tumors with favorable histology, good prognosis in addition to an accepted high pregnancy rate which might increase liability of choosing the option of fertility-sparing surgery.

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Recommendations

Additional future prospective studies including large number of patients were needed to compare between fertility sparing and radical surgery in epithelial ovarian cancer stage I regarding; endocrinologic, oncologic and reproductive outcomes for proving the success and safety of fertility sparing surgeries.

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