



ORIGINAL ARTICLE

Oncological Outcomes and Safety of Ovarian Preservation in Early-Stage Carcinoma of the Cervix

Mohammad Samir Badr¹, Amr Abd Almohsen Alnemr¹, Ahmed Z. Alattar², Mohamed Ali Alabiad³, Gamal Osman⁴, Ahmed K. El-TaHER⁴

¹Department of Gynecology and Obstetrics, Zagazig University Faculty of Medicine, Zagazig, Egypt

²Department of Clinical Oncology and Nuclear Medicine, Zagazig University Faculty of Medicine, Zagazig, Egypt

³Department of Pathology, Zagazig University Faculty of Medicine, Zagazig, Egypt

⁴Department of General surgery, Faculty of Medicine, Zagazig University Zagazig, Egypt

Corresponding author:

Submit Date 2020-08-07
Revise Date 2020-09-27
Accept Date 2020-09-15

ABSTRACT

Background: Conservative ovarian management plans for young patients having cervical cancer is now widely accepted, especially in management of squamous cell carcinoma (SCC) of the cervix. Preservation of one or both ovaries in patients with cervical adenocarcinoma is still a controversial issue as such subtype has a more liability of spread to the ovaries than SCC which ranges from 0 to 10.2%. Even if we consider the risks of ovarian metastasis, but preservation of the ovaries in patients with certain criteria might be considered more important to those patients having cancer cervix who were diagnosed in the early stage. So it is important to establish the selection criteria of cervical cancer patients who will be eligible for preservation of ovarian function.

Our study aimed to identify suitable cervical cancer patients who will benefit from preservation of their ovaries and to detect the survival benefits and patients' outcome.

Methods: Performing the current prospective cohort study was done in the period from September 2014 to October 2019. We included 60 females with cancer cervix stage (I-II), we divided patients into two groups the first group included 30 females underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and the second group included 30 patients and underwent total abdominal hysterectomy with preservation of the ovaries. We followed the patients for 5 years.

Results: we showed that patients with preserved ovaries were younger, with lower T stage, earlier FIGO stage (IA-B), lower histological grades. Five-year cancer specific survival rate was higher in the ovarian conservation group than in the oophorectomy group, OS rate was higher in the ovarian conservation group than in the oophorectomy group.

Conclusions: Our study showed that preservation of ovaries in in young female patients who diagnosed with early stage cervical carcinoma (FIGO I-II) is associated with a favorable outcome due to avoiding induction of premature surgical menopause without increasing risks of ovarian metastases or increasing cervical cancer related death risks.

Keywords: Cervical cancer; ovarian preservation; staging



INTRODUCTION

Cervical carcinoma is considered the 2nd commonest cause of cancer related females' mortality in women aged from twenty to forty years old [1]. The incidence of such cancer has been decreased due to establishing successful screening programs for its early diagnosis and adequate management. But there was elevation in the number of young women who have been diagnosed with cervical cancer in the early stage, particularly

adenocarcinoma [2]. The management guidelines of patients having cancer cervix in the early stage included: total hysterectomy, pelvic lymphadenectomy in addition to performing para-aortic lymphadenectomy in certain cases, but performing bilateral oophorectomy was not established as a part of the cervical cancer standard surgical management strategies. Preserving the ovaries; particularly in young women has been found to be important to physiological, psychological and

sexual females' life in the premenopausal period, which is affected by cervical cancer [3]. Conservative ovarian management plans for young patients having cervical cancer is now widely accepted, especially in management of squamous cell carcinoma (SCC) of the cervix [4]. Although SCC is the considered commonest histo-pathological subtype of cervical cancers, but recently the incidence of adenocarcinoma of the cervix has been increased [5]. Preservation of one or both ovaries in patients with cervical adenocarcinoma is still a controversial issue as such subtype has a more liability of spread to the ovaries than SCC which ranges from 0 to 10.2% [6]. Even if we consider the risks of ovarian metastasis, but preservation of the ovaries in patients with certain criteria might be considered more important to those patients having cancer cervix who were diagnosed in the early stage. So, it is important to establish the selection criteria of cervical cancer patients who will be eligible for preservation of ovarian function. The aim of our study was to identify suitable cervical cancer patients who will benefit from preservation of their ovaries and to detect the survival benefits and patients' outcome.

METHODS

Performing the current prospective cohort study was done after having a local ethical committee approval and an informed consent from all included patients in the period from September 2014 to October 2019 in Zagazig University Hospitals. Most included cases were operated in Gynecology and Obstetrics Department, Oncology Unit. There were some cases with accidental diagnosis of cervical cancer in females underwent other surgical intervention in General Surgery department and we included them in the study when they have met the inclusion criteria. We included 60 females with cancer cervix stage (I-II) who were histo-pathologically diagnosed with SCC, adenocarcinoma and adeno-squamous carcinoma in Pathology Department, Faculty of Medicine, Zagazig University. We followed the patients for median time of 30 months (range from 15-60 months) to detect recurrence free survival, overall survival rates, liability and occurrence of ovarian metastases in the second group. Follow-up was performed in Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Zagazig University. The current study has been performed according to the guidelines of the World Medical Association for studies on human patients (Declaration of Helsinki).

Inclusion criteria: Cervical cancer patients aged 45 or younger, early-stage cervical cancer (FIGO stage I- II), cervical cancer patients who were managed initially by surgery taking no pre-operative chemotherapy or radiotherapy and cervical cancer patients with no history of ovarian malignant tumors were included in the study.

Exclusion criteria: Cervical cancer patients older than 45 years, cervical cancer patients with advanced stages (FIGO stages III, IV), cervical cancer patients with suspicious spread to lymph nodes, corpus uteri or with abnormal appearing ovaries, patients having another cancer at other location and cases with loss of follow-up or incomplete data were excluded from the study.

After selection of patients who were eligible for the study, we randomly divided patients into two groups the first group included 30 females underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and the second group included 30 patients and underwent total abdominal hysterectomy with preservation of the ovaries by computerized randomization.

We performed pre-operative CT and MRI for evaluation of the tumor size. We evaluated and recorded the following parameters: age and marital status of patients, tumor size, grade, histopathological morphology, invasion of corpus uteri, invasion of the lympho-vascular and perineural spaces, invasion of the para-metrial tissues, invasion of the endometrium, invasion of the vagina, invasion of the fallopian tubes, invasion of the pelvic and or para-aortic lymph nodes. Staging of patients was performed according to FIGO staging system. We have recorded all patients' follow-up and outcome data as; recurrence free survival rate, cervical cancer-related mortalities and overall survival rate.

STATISTICAL ANALYSIS

We have performed the statistical analysis of the collected data using SPSS 19.0 statistical program. We have analyzed continuous variables as mean \pm standard deviation. We have used the *t* test to perform intergroup comparison. We have used the Fisher's exact test to perform comparison between intergroup rates. We have used the Kaplan Meir curves to assess and represent the survival rates. We have considered the *p* value of <0.05 as being statistically significant.

RESULTS

Patients' demographic and clinical characteristics Table 1: The included sixty cervical cancer patients who were diagnosed in the early stages and who were

eligible to be included in the current study were identified and their basic demographic and clinical characteristics were shown in Table 1.

We showed that patients with preservation of ovaries were younger in age, having a lower T stage, earlier FIGO stages, more differentiated architecture and lower histo-pathological grades than patients with oophorectomy (all $p < 0.05$). Figure 1

Patients who were histopathologically diagnosed as adenocarcinoma of the cervix have less liability of performing ovarian conservation than patients diagnosed with SCC of the cervix ($p=0.021$).

Survival and follow-up data analysis Table2, Figures; 2 and 3: carcinoma specific survival and five-year overall survival rates were better in the group of patients who underwent ovarian conservation than in the group of patients who underwent oophorectomy.

Moreover, we showed that there are more causes for mortalities in the group of patients who underwent oophorectomy than in the group of patients who underwent ovarian conservation as chronic heart disease, hypertension, atherosclerosis and ischemic heart diseases due to premature reduction in estrogen levels.

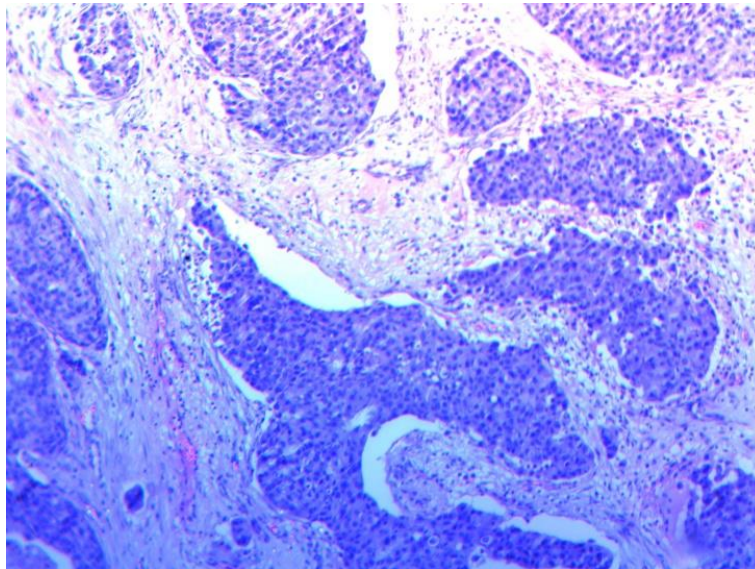


Figure 1 A

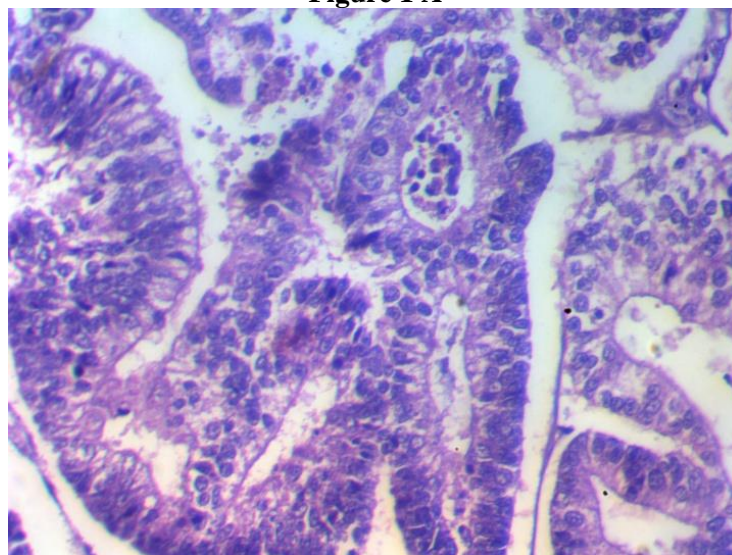


Figure 1 B

Figure1: Histopathological appearance of cervical carcinoma grade II (A) poorly differentiated invasive keratinizing squamous cell carcinoma of the cervix Grade IIIx200 (B) moderately differentiated adenocarcinoma of the cervix Grade II x400

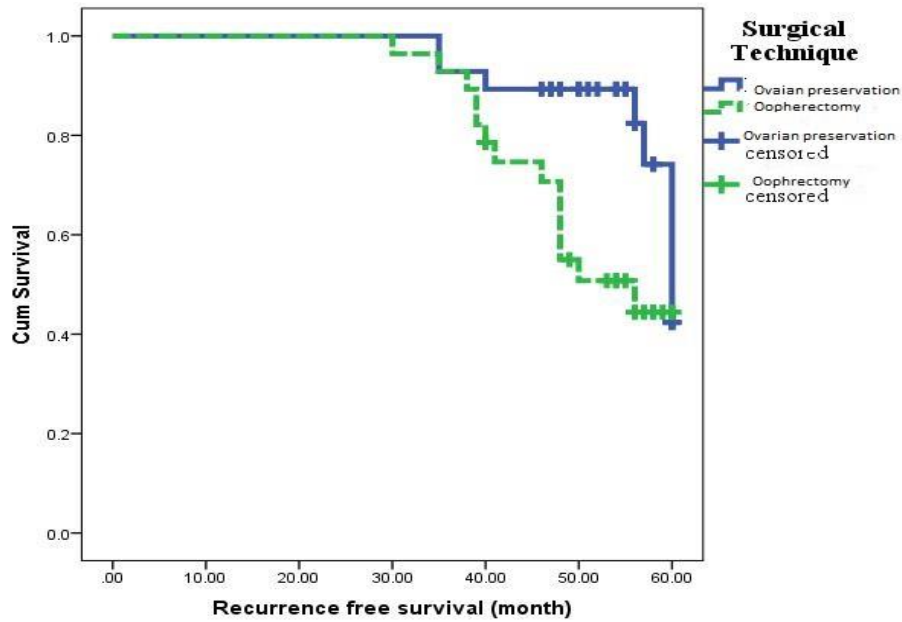


Figure2: Kaplan Meier plot showing disease free survival (time to recurrence) among patients underwent different management techniques

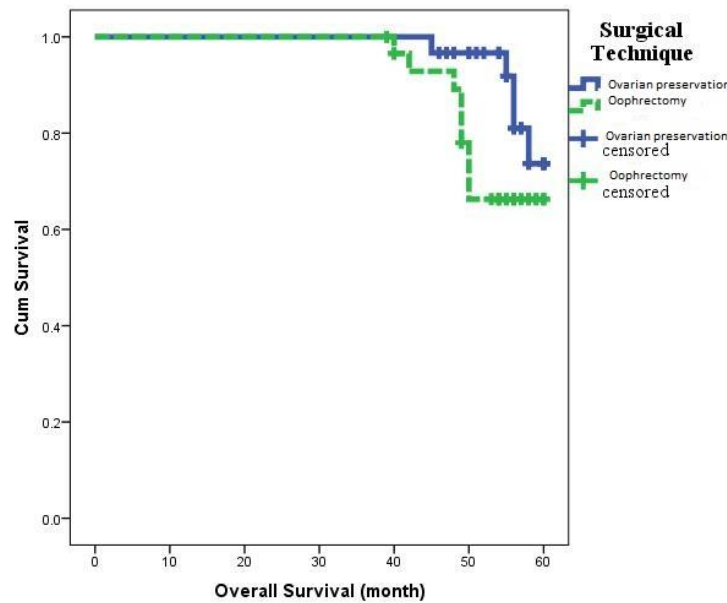


Figure3: Kaplan Meier plot showing overall survival (time to death) among patients underwent different management techniques.

Table1: Comparison between the studied surgical techniques regarding demographic, pathological, operative, postoperative data

Variables	Total N=60 (%)	Management techniques		p
		Ovarian preservation N=30 (%)	oophorectomy N=30 (%)	
Age (years): Mean ± SD	37.93 ± 10.57	32.43 ± 11.2	40.33 ± 5.29	0.047
Range	25 - 45	25 - 30	25 - 45	

Variables	Total N=60 (%)	Management techniques		p
		Ovarian preservation N=30 (%)	oophorectomy N=30 (%)	
Tumor size ≤4 >4	30 (50) 30 (50)	20 (66.6) 10 (33.4)	10 (33.3) 20 (66.7)	0.006
Deep stromal invasion Superficial Deep	30 (50) 30 (50)	20 (66.7) 10 (33.3)	10 (33.3) 20 (66.7)	0.006
Tumor Morphology Exophytic Endophytic	35 (55) 25 (45)	20 (66.6) 10 (33.4)	15 (50) 15 (50)	0.003
Histopathological type: Squamous cell carcinoma Adenocarcinoma adenosquamous carcinoma	30 (50) 20 (33.3) 10 (16.7)	20 (66.6) 8 (26.7) 2 (7)	10 (33.3) 12 (40) 8 (26.7)	0.005
Grade: High grade Low grade	12 (20) 48 (80)	3 (10) 27 (90)	9 (30) 21 (70)	0.019
FIGO stage: IA IB IIA IIB	15 (25) 20 (30) 15 (25) 10 (16.7)	11 (36.7) 11 (36.7) 5 (16.6) 3 (10)	4 (13.3) 9 (30) 10 (33.3) 7 (23.3)	0.004

Table2: Comparison between the studied surgical techniques regarding patient outcome (relapse and death):

Variables	Total N=60 (%)	Management techniques		Test	
		Ovarian preservation N=30 (%)	oophorectomy N=30 (%)	X ² /t/Z	p
Postoperative complications:					
Absent				3.068 [∞]	0.08
present	44 (73.3) 16 (26.7)	25 (83.3) 5 (16.7)	19 (63.3) 11 (36.7)		
Relapse (n=56):					
Absent	34 (60.7)	20 (66.7)	14 (48)	2.695 [∞]	0.101
Present	22 (39.3)	8 (26.4)	14 (48)		
Death					
No	46 (76.7)	25 (83.3)	21 (70)	1.491 [∞]	0.222
Yes	14 (23.3)	5 (16.7)	9 (30)		
Recurrence free survival:					
Mean ± SD	50.7 ± 8.15	52.86 ± 7.28	38.54 ± 8.52	2.04 [∅]	0.046*
Range	30 - 60	34 - 60	20 - 50		
Overall survival:					
Median	53.79±5.71	55.23±4.66	51.97 ± 6.52	2.234 [∅]	0.03*
Range	39 - 60	45 - 60	39 - 60		

DISCUSSION

Removal of both ovaries during the radical management of cervical cancer patients were previously performed, but recent studies showed that

preservation of ovaries could be able to maintain a better physical, psychological and sexual lifestyle in young premenopausal women [7]. Premature menopause induction by surgical removal of both

ovaries leads to occurrence of; hot flashes, atrophy of the vagina, diseases of the cardiovascular system, osteoporosis, hip fracture, emotional instability and Alzheimer's disease [8]. To reverse the drawbacks of premature menopause, the patients need hormonal replacement therapy for a long time which was found to be of poor compliance and higher expenses [9], another essential problem in the issue of ovarian preservation is patients' safety from malignant invasion of the ovaries and later risks of ovarian metastases that was showed to be extremely low [7]. Our present study showed that ovarian preservation is related to a better life style, favorable survival rates in young females in the premenopausal period who were diagnosed with cancer cervix in the early stage (FIGO stages I-II), of different histopathological subtypes whether SCC or adenocarcinoma or adeno-squamous carcinoma, so results of the current study provided recent selection criteria for patients who were eligible for ovarian conservation in cervical carcinoma patients aiming at increasing their lifestyle and safety. Additionally, we showed that avoiding induction of surgical premature menopause would reduce the occurrence of cardiovascular diseases, without increasing the occurrence of ovarian metastases or cervical cancer related mortality.

Our study results were in line with recent studies that demonstrated the association of oophorectomy in patients with early stages cervical cancer with unfavorable outcomes and increased mortality [2, 6, 7].

Matsuo et al., [7], showed that preservation of ovarian functions was associated with a better overall survival rate in addition to reducing incidence of mortality from cardiovascular diseases without increasing cancer cervix related mortalities particularly in young women having early-stage cervical cancer.

We showed that ovarian preservation is beneficial in improving lifestyle without increasing risks of ovarian metastases in all cancer cervix patients regardless that histopathological subtype, Jiao et al., and Macdonald and Tidy [10, 11], showed results like us that ovarian preservation in SCC of the cervix is beneficial with a neglected risk of ovarian metastasis.

Additionally, Matsuo et al., [12], showed the increased risks of many diseases which is related to premature surgical menopause as; cardiac and atherosclerotic vascular changes and nonalcoholic fatty liver disease in case of cervical cancer patients who underwent oophorectomy without increasing

risks of cancer cervix related mortality or occurrence of metastases in the preserved ovaries later on. Ovarian conservation was found to have no adverse prognostic parameters in patients with early-stage carcinoma of the cervix [13]. Moreover, results of Cheng, et al., [2] supported our results by showing that the ovarian metastases incidence in patients diagnosed with early-stage cancer cervix (FIGO I-II) is extremely low.

Results of Landoni et al., [14], were slightly different from us that occurrence of ovarian metastases were more evident in adenocarcinoma than in SCC of the cervix, but results of other studies showed that cervical cancer patients diagnosed with either adenocarcinoma or SCC underwent hysterectomy with preservation of both ovaries for management of early-stage cervical cancer have a similar prognosis and spread regardless their histopathological subtype. Additionally, preservation of both ovaries in cervical carcinoma patients in the early stage is safe and more beneficial to young patients due to very low incidence of ovarian metastases and avoidance of surgical premature menopause [13, 15, 16].

Similar to our results recent studies showed that the following selection criteria could be applied for cervical carcinoma patients who will be eligible for performing ovarian preservation; young patients aged less than 45 years old, cancer size less than 4 cm, FIGO stage not more than II, clinical, radiological and histopathological evidences of negative lymph nodes and distant metastases, no evidence of invasion of the lymphovascular space, para-metrium or corpus uteri that were showed by CT scan, MRI, or PET-scan [13, 16, 17].

CONCLUSIONS

Our study showed that preservation of ovaries in in young female patients who diagnosed with early-stage cervical carcinoma (FIGO I-II) is associated with a favorable survival rate, favorable outcome, better physical, psychological and sexual lifestyle due to avoiding induction of premature surgical menopause without increasing risks of ovarian metastases or increasing cervical cancer related death risks.

CONFLICTS OF INTEREST: None

FUNDING SOURCES: None

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019; 69:7–34.
2. Cheng H, Huo L, Zong L, Kong Y, Yang J and Xiang Y. Oncological Outcomes and Safety of Ovarian Preservation for Early Stage Adenocarcinoma of

- Cervix: A Systematic Review and Meta-Analysis *Frontiers in Oncology* 2019; 9: 235-242.
3. Zhou J, Chen Y, Zhang P, and Lou H. Ovarian preservation in adenocarcinoma of the uterine cervix *Journal of Ovarian Research*. 2017; 10:48-60.
 4. Plante M. Evolution in fertility-preserving options for early-stage cervical cancer: radical trachelectomy, simple trachelectomy, neoadjuvant chemotherapy. *Int J Gynecol Cancer*. 2013; 23:982–989.
 5. Adegoke O, Kulasingam S, Virnig B. Cervical cancer trends in the United States: a 35-year population-based analysis. *J Womens Health (Larchmt)*. 2012; 21:1031–1037.
 6. Xu HY, Tang X, Ding J, Qiu J, Zhang X, Hua K, Ovarian conservation is associated with better survival in young patients with T1N0M0 cervical adenocarcinoma: a population-based study *Archives of Gynecology and Obstetrics*. 2018; 297:775–784.
 7. Matsuo K, Machida H, Shoupe D, Melamed A, Muderspach L, Roman LD et al. Ovarian conservation and overall survival in young women with early-stage cervical cancer. *Obstet Gynecol*. 2017; 129:139–151.
 8. Rocca WA, Grossardt BR, De AM, Malkasian GD. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *Lancet Oncol*. 2006;7:821–8.
 9. Windbichler GH, Müller-Holzner E, Nicolussi-Leck G, Meisel U, Dapunt O, Marth C. Ovarian preservation in the surgical treatment of cervical carcinoma. *Am J Obstet Gynecol*. 1999; 180:963–9.
 10. Jiao XB, Hu J and Zhu LR. The safety of ovarian preservation in early-stage adenocarcinoma compared with squamous cell carcinoma of uterine cervix: a systematic review and meta-analysis of observational studies. *Int J Gynecol Cancer*. 2016; 2:1510–1514.
 11. Macdonald MC and Tidy JA. Can we be less radical with surgery for early cervical cancer? *Curr Oncol Rep*. 2016; 18:16.
 12. Matsuo K, Gualtieri MR, Cahoon SS, Jung CE, Paulson RJ, Shoupe D, et al. Surgical menopause and increased risk of nonalcoholic fatty liver disease in endometrial cancer. *Menopause*. 2016; 23:189–96.
 13. Chen J, Wang R, Zhang B, Lin X, Wei J, Jia Y, et al. Safety of ovarian preservation in women with stage I and II cervical adenocarcinoma: a retrospective study and meta-analysis. *Am J Obstet Gynecol*. 2016; 215:460.e461–0.e413.
 14. Landoni F, Zanagnolo V, Lovato-Diaz L, Maneo A, Rossi R, Gadducci A, et al. Ovarian metastases in early-stage cervical cancer (IA2-IIA): a multicenter retrospective study of 1965 patients (a Cooperative Task Force study). *Int J Gynecol Cancer*. 2007; 17:623–8.
 15. Zhou J, Chen Y, Zhang P, Lou H. Ovarian preservation in adenocarcinoma of the uterine cervix. *J Ovarian Res*. 2017; 10:48.
 16. Lu H, Li J, Wang L, Zhou H, Liu Y, Wang D, et al. Is ovarian preservation feasible in early-stage adenocarcinoma of the cervix? *Med Sci Monit*. 2016; 22:408–14.
 17. Touhami O, Plante M. Should ovaries be removed or not in (early-stage) adenocarcinoma of the uterine cervix: a review. *Gynecol Oncol*. 2015; 136:384–8.

To Cite:

Badr, M., Elnemr, A., Alattar, A., Alabiad, M., Osman, G., El-Taher, A. Oncological Outcomes and Safety of Ovarian Preservation in Early Stage Carcinoma of the Cervix. *Zagazig University Medical Journal*, 2022; (1009-1015): -. doi: 10.21608/zumj.2020.38315.1915