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Role of Neoadjuvant Chemotherapy Followed by Interval Cyto-Reductive Surgery in Reducing Progression and Recurrence of Patients with Advanced Endometrial Cancer

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ABSTRACT

Background: Cytoreductive surgery (CRS) roles in advanced EC are not fully defined and there are few published data about role of neoadjuvant chemotherapy followed by cytoreductive surgery in advanced endometrioid endometrial adenocarcinoma which is the commonest histopathological subtype of EC**.**

Objective: The aim of the study was to evaluate the roles of neoadjuvant chemotherapy followed by interval cyto-reductive surgery in reducing progression improving survival and prognosis of patients who were initially diagnosed with advanced stage EC. **Patients and Methods:** we collected 50 patients of advanced endometrial carcinoma stage III and divided them into 2 groups the first group included 36 (72%) patients who underwent cytoreductive surgery after neoadjuvant chemotherapy and remaining patients who have not undergone surgery.

Results: Patients who underwent interval cytoreductive surgery after neoadjuvant chemotherapy had longer progression-free survival rate (12.53 vs. 5 months, p = 0.001) and longer overall survival rate (25 vs. 8 months, p = 0.002) in comparison with patients who have not undergone surgery.

Conclusions: Using neo-adjuvant chemotherapeutic agents followed by cyto-reductive surgery in cases of advanced endometrial carcinoma reduces rates of disease recurrences and improving patients' survival rates.

Keywords: Neo-adjuvant chemotherapy, Cyto-reductive surgery, Recurrence, Endometrial cancer.

INTRODUCTION

Endometrial cancer (EC) is considered the commonest gynecological cancer in developed countries, which has a relatively good prognosis. Advanced EC has a poor prognosis and a high incidence of progression with the 5-year OS of stage III EC about 36%–57% **(1).** About 13% of female patients with EC were found to have stage III or IV disease **(2),** at initial diagnosis and have a dismal outcome **(3, 4).**

Management of those patients includes many combined lines of therapy, which includes chemo-radiotherapy in addition to surgery **(5).** Cytoreductive surgery (CRS) roles in advanced EC are not fully defined **(6)**. In the past adjuvant chemotherapy (CT) was found to reduce incidence of distant recurrence but CT could not prevent occurrence of local or pelvic recurrence, which happens in about 18% of cases presented with advanced EC **(7).**

It was found that using multimodality treatment, which include neoadjuvant chemotherapy followed by cytoreductive surgery could improve prognosis, decrease morbidity and mortality in ovarian carcinoma patients **(8).** This approach was suggested to be beneficial in uterine papillary serous carcinomas **(9)** due to its histopathological similarity to papillary serous ovarian carcinoma **(10).** But there are few published data about roles of neoadjuvant chemotherapy followed by cytoreductive surgery in endometrioid endometrial adenocarcinoma, which is the commonest histopathological subtype of EC **(11, 12).**

The aim of the study was to evaluate the roles of neoadjuvant chemotherapy followed by interval cyto-reductive surgery in reducing progression improving survival and prognosis of patients who initially diagnosed with advanced stage EC.

PATIENTS AND METHODS

We collected all cases with EC who admitted to Gynecology and Obstetrics Department and General Surgery Departments, Faculty of Medicine, Zagazig University in the period from May 2015 to May 2020. All specimens were sent to the Pathology Department, where they processed for routine H & E staining, and immunohistochemistry for diagnoses of EC, classification into subtypes and grading.

Histopathological study:

For initial carcinoma diagnosis most patients underwent endometrial biopsy or a paracentesis for cytology. All patients underwent comprehensive imaging after initial diagnosis and all patients were confirmed to

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have endometrial cancer initially. The specimens were fixed in 4% formalin and embedded in paraffin then cut into 5µm thick sections and stained with hematoxylin and eosin (H & E) for examination of histopathological changes [13-15]

Immunohistochemical study:

Representative samples from all specimens were immunohistochemically stained with the PAX8, CK7, p16, p53, HNF-1B and, Napsin A antibodies. The immunohistochemistry technique was performed as fellow; initially, heating was used to extract antigens from tissue sections [16-18]. The sections were treated and chilled overnight with PAX8, CK7, p16, p53, HNF-1B and Napsin A rabbit monoclonal primary antibodies. The sections were then rinsed with phosphate-buffered saline and treated with the matching secondary antibody for 2 hours [19-21]. For 20 minutes, the avidin-biotin complex was applied to the sections [22-24]. The sections were then washed again, and the immunoreactivity was identified using (3,3′-Diaminobenzidine) DAB staining and hematoxylin counterstaining. Positive immunoreactivity was shown by brown staining [25-28].

Inclusion criteria: Cases initially diagnosed with stage III EC, patients who were diagnosed with endometrioid EC, clear cell EC and serous EC were included in our study.

Exclusion criteria: Cases diagnosed with other EC stages, cases presented with distant metastases, cases with incomplete data, cases with lost follow-up or cases who refused to be included in the study.

After application of the inclusion criteria of the study 50 patients were included. We collected clinical findings as age, diagnosis date, any performed surgery, adjuvant treatment, relapse, and patients' outcome from patients' files. Tumor grade, stage and subtypes were assessed by expert pathologist, where staging was done using the classification of international Federation of Gynecology and Obstetrics (FIGO) [29]**.** Multiagent neoadjuvant therapy with carboplatin and paclitaxel was administered (paclitaxel was infused at a dose of 60 mg/mq intravenously once weekly) [5]**.**

We followed all patients with pelvic examination every three months during the first two years, then every six months after ending therapy. We performed computed tomography scans annually for chest–abdomen and pelvis. We collected data about plans of neo-adjuvant treatment as type and cycles of chemotherapy, response to neoadjuvant treatment using clinical and radiographic reports and we classified response to therapy as progressive disease, stable disease, partial response and complete response.

Performed surgeries were done in Gynecology and Obstetrics Department and General Surgery Department in the form of cyto-reductive surgery, total hysterectomy with bilateral salpingo-oophorectomy and lymphadenectomy. We recorded all surgical variables as operative method, time, blood loss, surgical complication and degree of optimal cytoreduction and we classified it into; no residual visible disease = optimal, <1 cm residual visible disease = suboptimal and >1 cm residual visible disease = unresectable.

We determined the last date of follow-up, date and site of disease recurrence if present and subsequent treatment. We recorded the date of cancer related patient death if the patient died during the follow-up period from cancer.

Ethical approval:

Approval was obtained from Zagazig University's Faculty of Medicine's Institutional Review Board (IRB), Egypt, (no. ZU-IRB#10141) to collect data and samples from relevant departments. The research was carried out in compliance with the declaration of Helsinki of the World Medical Association. Before participating in the study, all patients or their legal representatives signed informed permission forms.

Statistics:

We used descriptive statistics for comparing baseline patient characteristics and described continuous variables as means ± standard deviations, while we described ranges and categorical variables as percentages. We used Kaplan Meier survival curves for describing progression free survival and overall survival rates and compared curves using the log-rank test with a $p \leq 0.05$ considered statistically significant.

RESULTS

Patient data

Fifty patients treated with neoadjuvant chemotherapy for management of advanced endometrial carcinoma between 2015 and 2020 were included.

Baseline, clinical and operative patients' details were found in **tables (1) and (2)**. The patient median age was 56.5 years (range 44–71). 90% of included patients had Ca-125 levels above the upper normal limits (≤ 35 U/ml). We consider all patients ineligible for primary cytoreductive surgery due to unresectable disease or due to severe comorbidities. We have given neoadjuvant chemotherapy for all patients with most patients (91%) were given intravenous carboplatin and paclitaxel and remaining patients (9%) were given other regimens as carboplatin and docetaxel, paclitaxel, cisplatin, and adriamycin, and weekly carboplatin single-agent. FIGO stages were as follows: stage IIIA, 8 (15%); stage IIIB, 10 (20%) and Stage IIIC, 32 (65%) (**Table 1).**

The mean number of chemotherapy cycles was 4 (ranged from 1–7), and most patients received 3 cycles before surgery (**Table 2).**

We performed restaging imaging after the neo-adjuvant therapy and we found that 10% of included patients had progressive disease, 75% had partial response and 4% had complete response to treatment. 36 (72%) of patients who underwent successive cyto-reductive surgery received adjuvant chemotherapy. At the end of surgery, there was a residual tumor larger than 1 centimeter in 4 patients (11.1%); all other patients have no macroscopically residual tumor. Majority of patients who received post-operative chemotherapy have received 3 additional cycles of chemotherapy. Patients that have not undergone surgery received hormonal treatment with letrozole [(30)]. 39 (78%) of patient presented with either local or distant recurrence, 50% of patients with disease recurrences were diagnosed by imaging remaining patients with recurrences were diagnosed by a combination of imaging and Ca-125 levels. 80% of recurred patients received chemotherapy and 20% received radiation with or without chemotherapy. The median period of follow-up was 11.6 months (range 3.1–20 months). Patients who underwent interval cytoreductive surgery after neoadjuvant chemotherapy had longer progression-free survival rate (12.53 vs. 5 months, p = 0.001) and longer overall survival rate (25 vs. 8 months, p = 0.002) in comparison with patients who have not undergone surgery.

There was a statistically association between overall survival and all of histology (p=0.005), presumed FIGO, location, neoadjuvant chemotherapy, response to chemotherapy, degree of cytoreduction, hepatosplenomegaly, omentectomy, lymphadenectomy, upper abdominal debulking, bowel resection (p<0.001), operative time (p=0.028), intraoperative complications and blood loss (p=0.031)**.**

On doing univariate analysis, non-endometrioid type, neoadjuvant chemotherapy>3, hysterectomy, without omentectomy, upper abdominal debulking, bowel resection, operative time ≥180 minutes, and blood loss > 200 cc significantly increased risk by 3.12, 3.26, 20.83, 20.83, 18.62, 20.83, 2.52 and 2.86 folds respectively. Suboptimal resection, unresectable tumors, carcinomatosis, bone and lung affection significantly increase risk by 6.61, 33.04, 8.5, 32.09 and 46.75 folds respectively. There was statistically association between recurrence free survival and all of histology, presumed FIGO, location, neoadjuvant chemotherapy, response to chemotherapy, degree of cytoreduction, hepatosplenomegaly, type of hysterectomy, omentectomy, lymphadenectomy, upper abdominal debulking (p<0.001), bowel resection, operative time, intraoperative complications and blood loss (p= 0.012, p=0.025). On doing univariate analysis, non-endometrioid type, neoadjuvant chemotherapy > 3, HSM only, omentectomy not done, upper abdominal debulking, bowel resection, operative time ≥ 180 minutes, and blood loss > 200 cc significantly increased risk by 3.9, 3.07, 33.08, 33.08, 31.4, 33.82, 2.81 and 2.65 folds respectively. Suboptimal resection, unresectable tumors, carcinomatosis, distant nodes, bone and lung affection significantly increased risk by 24.56, 113.1, 10.02, 11.89, 66.97 and 60.14 folds respectively (Tables 3 & 4 and figures 1, 2, 3 and 4).

Table (1): Distribution of the studied patients according to baseline data

	N=	%
Marital status:		
Unmarried	12	24
Married	38	76
Gravity:		
Median (range)	2 (0 – 5)	
Nulligravida	5	10%
Parity:		
Median (range)	2 (0 – 5)	
Infertility	11	28.9%
CRS	36	72%
Histology:		
Endometroid	20	40%
Non-endometroid	30	60%
Presumed FIGO:		
IIIA	8	15
IIIB	10	20
IIIC	32	65
Distant location at diagnosis:	6	12
Bone	19	38
Carcinomatosis	10	20
Distant nodes	6	12
Lung	9	12
Upper abdomen		
Cycles of neoadjuvant chemotherapy: Median (range)	3 (1 – 6)	
Response:		
NOR	6	12
CR	4	8
PR	22	44
PD	9	18
SD	9	18
Recurrence:		
No	11	22
Yes	39	78
Death:		
No	17	34
Yes	33	66

Table (2): Operative data of patients underwent operations

	N=36	**%**
Cyto-reduction:		
No visible residual	18	50
Optimal resection	10	27.8
Suboptimal resection	4	11.1
Unresectable	4	11.1
Mode of operation:		
Laparoscopy	7	19.4%
Laparotomy	29	80.6%
Hysterectomy:		
Only	5	13.9%
+BSO	31	86.1%
Omentectomy:		
Absent	5	13.9%
Present	31	86.1%
Lymphadenectomy:		
Absent	32	88.9%
Present	4	11.1%
Upper abdominal debulking:		
Absent	33	91.7%
Present	3	8.3%
Bowel resection:		
Absent	31	86.1%
Present	5	13.9%
Intraoperative complications:		
Absent	34	94.4%
Present	2	5.6%

Table (3): univariate analysis of factors associated with overall survival among the studied patients

Parameter	N =50	Events =33	Censored =17	Mean ± st er	p	AHR (95% CI)	p
Age group:							
≤60 years	21	15	6 (28.6%)	14.74±0.94	0.56		
>60 years	29	18	11(37.9%)	13.52±1.2		1.21 (0.61 – 2.42)	0.582
Histology:							
Endometroid	20	9	11 (55%)	17.16±1.25	0.002*		
Non-endometroid	30	24	6 (20%)	11.94±0.82		3.12 (1.41 – 6.9)	0.005*
Presumed FIGO:							
IIIA	8	15	4 (100%)			1 (reference)	0.001*
IIIB	10	20	7 (77.8%)	NA	<0.001*	6378.2(0 – $1.8*10^{91}$)	0.932
IIIC	32	35	6 (24%)			37134.6(0 – $1.1*10^{95}$)	0.918
location of Distant recurrence							
Upper abdomen	9	1	8 (88.9%)	20.22±1.68		1 (reference)	<0.001*
Carcinomatosis	19	14	5 (26.3%)	14.32±1.06	<0.001*	8.5 (1.11 – 65.34)	0.04*
Distant nodes	10	6	4 (40%)	13.54±0.87		7.64 (0.89 – 65.88)	0.064
Bone	6	6	0 (0%)	9.33±1.09		32.09(3.62-284.43)	0.002*
Lung	6	6	0 (0%)	8.83±0.4		46.75 (5 – 436.76)	<0.001***
neoadjuvant chemotherapy:							
≤3	22	9	13 (59.1%)	17.27±1.21			
>3	28	24	4 (14.3%)	11.82±0.83	0.001*	3.26 (1.48 – 7.17)	0.003*
Response:							
NOR	6	6	0 (0%)			1 (reference)	0.01*
CR	4	0	4 (100%)		0.001*	0 (0 – 0)	0.977
PR	22	13	9 (40.9%)			0.13 (0.04 – 0.42)	<0.001*
PD	9	6	3 (33.3%)			0.24 (0.07 – 0.81)	0.022*
SD	9	8	1 (11.1%)			0.44 (0.14 – 1.37)	0.158
Cyto-reduction:							
No visible residual	18	9	9 (50%)	17.69±1.04		1 (reference)	<0.001*
Optimal resection	10	6	4 (40%)	16.46±1.21	<0.001*	1.54 (0.54 – 4.29)	0.418
Suboptimal resection	4	4	0 (0%)	11.5±0.96		6.61 ((1.85 – 23.65)	0.004*
Unresectable	4	4	0 (0%)	9 ± 0.58		33.04 (6.2 – 175.8)	<0.001*
Mode of operation:							
Laparoscopy	7	4	3 (42.9%)	16.19±1.63	0.584		
Laparotomy	29	19	10 (34.5%)	15.55±0.91		1.33 (0.45 – 3.9)	0.609
Hystrectomy:							
Only	5	5	0 (0%)	9.2±0.49	<0.001*	20.83 (4.1 – 105.4)	<0.001*
+BSO	31	18	13 (41.9%)	16.81±0.8			
Omentectomy:							
Absent	5	5	0 (0%)	9.2±0.49	<0.001*	20.83 (4.1 – 105.4)	<0.001*
Present	31	18	13 (41.9%)	16.81±0.8			
Lymphadenectomy:							
Absent	32	23	9 (28.1%)		0.027*	26.5 (0.193 – 3640.1)	0.193
Present	4	0	4 (100%)				
Upper abdominal debulking:							
Absent	33	20	13 (39.4%)	16.4±0.8			
Present	3	3	0 (0%)	8.67±0.67	<0.001*	18.62(3.99 – 86.83)	<0.001*
Bowel resection:							
Absent	31	18	13 (41.9%)	16.81 ±0.8	<0.001*		
Present	5	5	0 (0%)	9.2 ±0.49		20.83(4.12 – 105.4)	<0.001*
Intraoperative complications:							
Absent	34	21	13 (38.2%)	16.21±0.8			
Present	2	2	0 (0%)	8.0 ± 0	<0.001*	1 (0.002 - 424.3)	>0.999
Operative time:							
≤180 min	19	10	9 (47.4%)	17.49±1.04	0.021*		
>180 min	17	13	4 (23.5%)	13.28±0.88		2.52 (1.06 – 6)	0.038*
Blood loss:							
≤200 cc	15	6	9 (60%)	17.96±1.28	0.016*		
>200 cc	21	17	4 (19%)	14.04±0.87		2.86(1.11 – 7.4)	0.021*

*p<0.05 is statistically significant

Table (4): univariate analysis of factors associated with disease free survival among the studied patients

Parameter	N =50	Events =39	Censored =11	Mean ± st er	p	AHR (95% CI)	p
Age group:							
≤60 years	21	18	3 (14.3%)	10.84 ± 0.81	0.464		
>60 years	29	21	8 (27.6%)	9.45 ± 1.13		1.25 (0.66 – 2.36)	0.492
Histology:							
Endometroid	20	9	11 (55%)	13.85±1.26	<0.001*		
Non-endometroid	30	30	0 (0%)	7.77±0.67		3.9 (1.83 – 8.3)	<0.001*
Presumed FIGO:							
IIIA	4	0	4 (100%)			1 (reference)	0.001*
IIIB	9	2	7 (77.8%)	NA	<0.001*	0 (0 – $1.8*10^{91}$)	0.932
IIIC	25	25	0 (24%)			1.15 (0 – $7.6*10^{23}$)	0.996
IVA	6	6	0 (0%)			7.47 (0-$5*10^{24}$)	0.943
IVB	6	6	0 (0%)			41.36 (0-$2.8*10^{25}$)	0.894
Distant location							
Upper abdomen	9	1	8 (88.9%)	17.33±1.57		1 (reference)	<0.001*
Carcinomatosis	19	16	3 (15.8%)	10.05±1.12	<0.001*	10.02 (1.32 – 75.83)	0.026*
Distant nodes	10	10	0 (0%)	10.1 ±0.71		11.89 (1.5 – 94.16)	0.019*
Bone	6	6	0 (0%)	5.33±0.92		66.97 (7.2-622.03)	0.001*
Lung	6	6	0 (0%)	5.83±0.48		60.14 (6.38 – 567.01)	<0.001*
neoadjuvant chemotherapy:							
≤3	22	11	11 (50%)	13.0±1.28			
>3	28	28	0 (0%)	8.0 ±0.69	0.001*	3.07 (1.52 – 6.22)	0.002*
Response:							
NOR	6	6	0 (0%)			1 (reference)	0.003*
CR	4	0	4 (100%)		0.001*	0 (0 – 0)	0.974
PR	22	15	7 (31.8%)			0.13 (0.04 – 0.406)	<0.001*
PD	9	9	0 (0%)			0.26 (0.081 – 0.861)	0.027*
SD	9	9	0 (0%)			0.65 (0.22– 1.92)	0.435
Cyto-reduction:							
No visible residual	18	9	9 (50%)	14.31±1.08		1 (reference)	<0.001*
Optimal resection	10	10	0 (0%)	11.5±0.82	<0.001*	2.35 (0.95 – 5.83)	0.065
Suboptimal resection	4	4	0 (0%)	7.75±0.48		24.56 (5.31 – 113.26)	<0.001*
Unresectable	4	4	0 (0%)	6.5 ± 0.29		113.1 (14.4 – 885.7)	<0.001*
Mode of operation:							
Laparoscopy	7	4	3 (42.9%)	12.71±1.59	0.369		
Laparotomy	29	23	10 (34.5%)	11.52±0.79		1.57 (0.54 – 4.55)	0.406
HSM:							
Only	5	5	0 (0%)	6.6 ± 0.25	<0.001*	33.8 (4.67 – 245.2)	<0.001*
+BSO	31	22	9 (29%)	12.66 ±0.74			
Omentectomy:							
Absent	5	5	0 (0%)	6.6 ± 0.25	<0.001*	33.8 (4.67 – 245.2)	<0.001*
Present	31	22	9 (29%)	12.66 ±0.74			
Lymphadenectomy:							
Absent	32	27	5 (15.6%)		0.013*	27.16 (0.3 – 2431.01)	0.15
Present	4	0	4 (100%)				
Upper abdominal debulking:							
Absent	33	24	7 (27.3%)	12.32±0.74	<0.001*	31.4(5.93 – 166.2)	
Present	3	3	0 (0%)	6.33±0.33			<0.001*
Bowel resection:							
Absent	31	22	5 (29%)	12.66 ±0.74	<0.001*	33.82(4.67 – 245.19)	
Present	5	5	0 (0%)	6.6 ±0.25			<0.001*
Intraoperative complications:							
Absent	34	25	9 (26.5%)	12.16±0.73	<0.001*	1 (0.002 - 424.27)	
Present	2	2	0 (0%)	6.0 ± 0			>0.999
Operative time:							
≤180 min	19	11	8 (42.1%)	13.89±1.05	0.005*		
>180 min	17	16	1 (5.9%)	9.53±0.61		2.81 (1.26 – 6.26)	0.012*
Blood loss:							
≤200 cc	15	8	7 (46.7%)	13.97±1.22	0.013*		
>200 cc	21	19	2 (9.5%)	10.27±0.74		2.65 (1.13 – 6.2)	0.025*

*p<0.05 is statistically significant

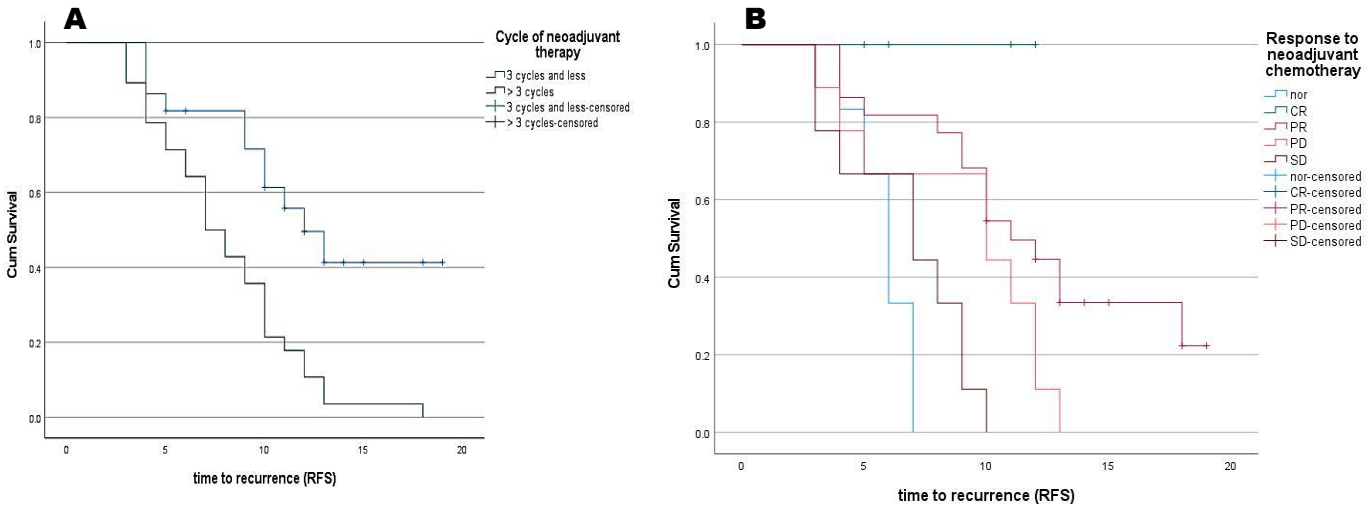
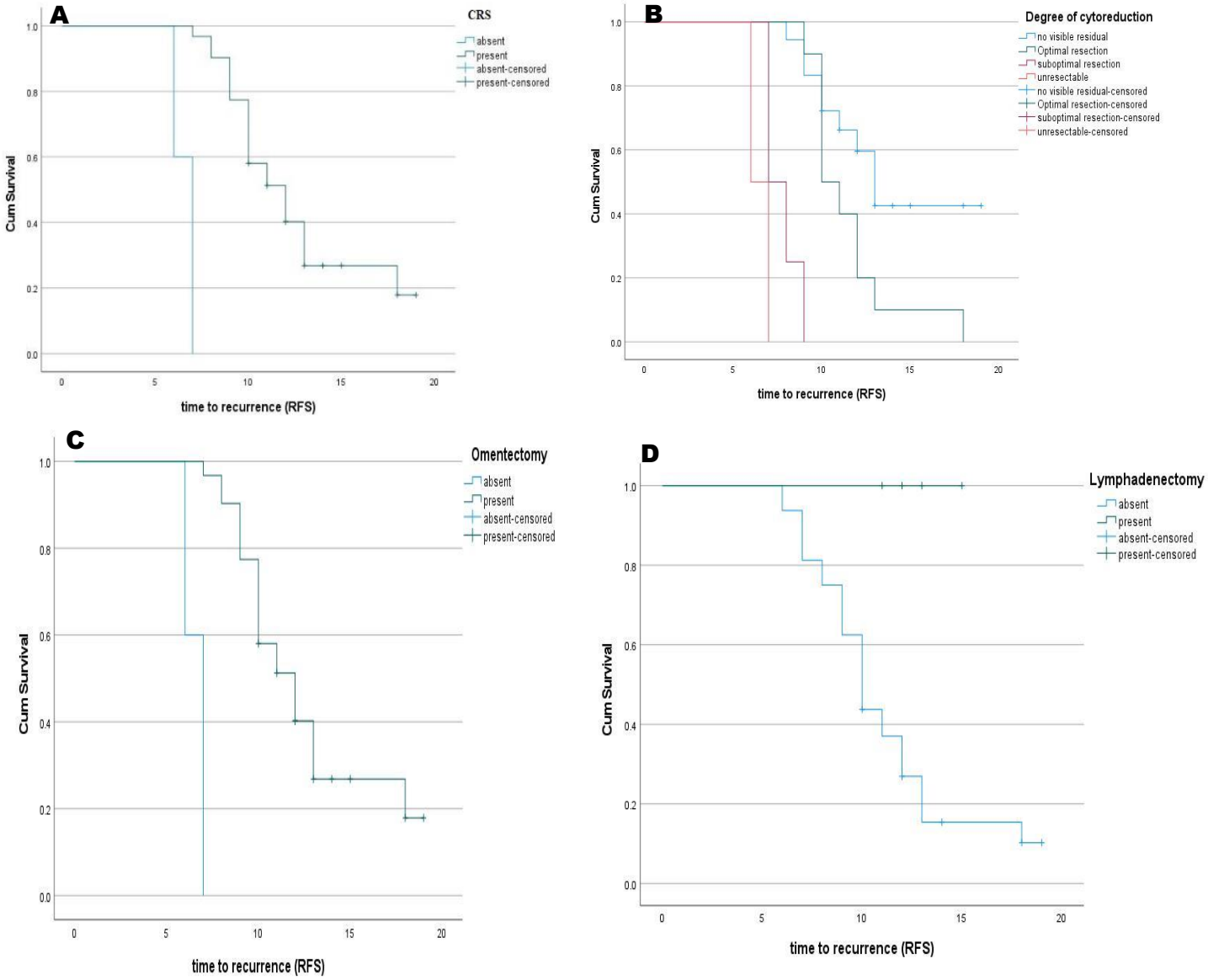


Figure (1): Kaplan Meier survival curves demonstrated associations between recurrence free survival rate (RFS) and number of cycles of neo-adjuvant chemotherapy intake (A) and response to chemotherapy (B).



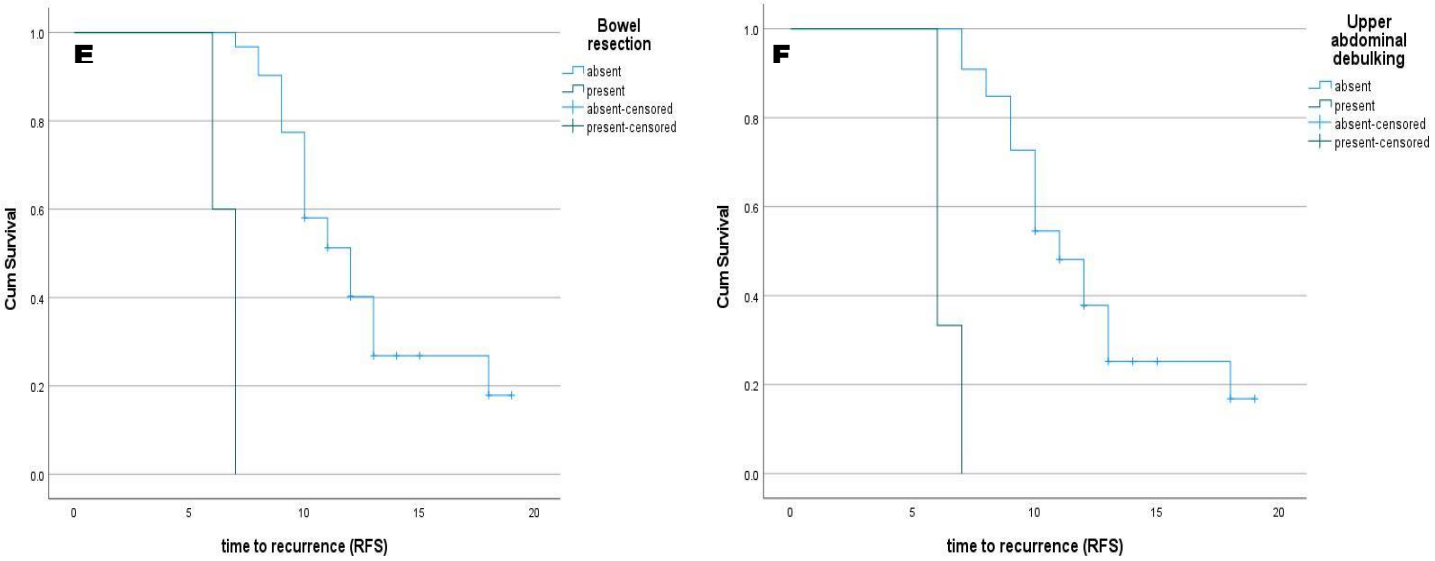


Figure (2): Kaplan Meier survival curves demonstrated associations between recurrence free survival rate (RFS) and (A) performing cytoreduction surgery (CRS) (B) Degree of cytoreduction (C) performing omentectomy (D) performing lymphadenectomy (E) performing bowel resection (F) performing upper abdominal debulking.

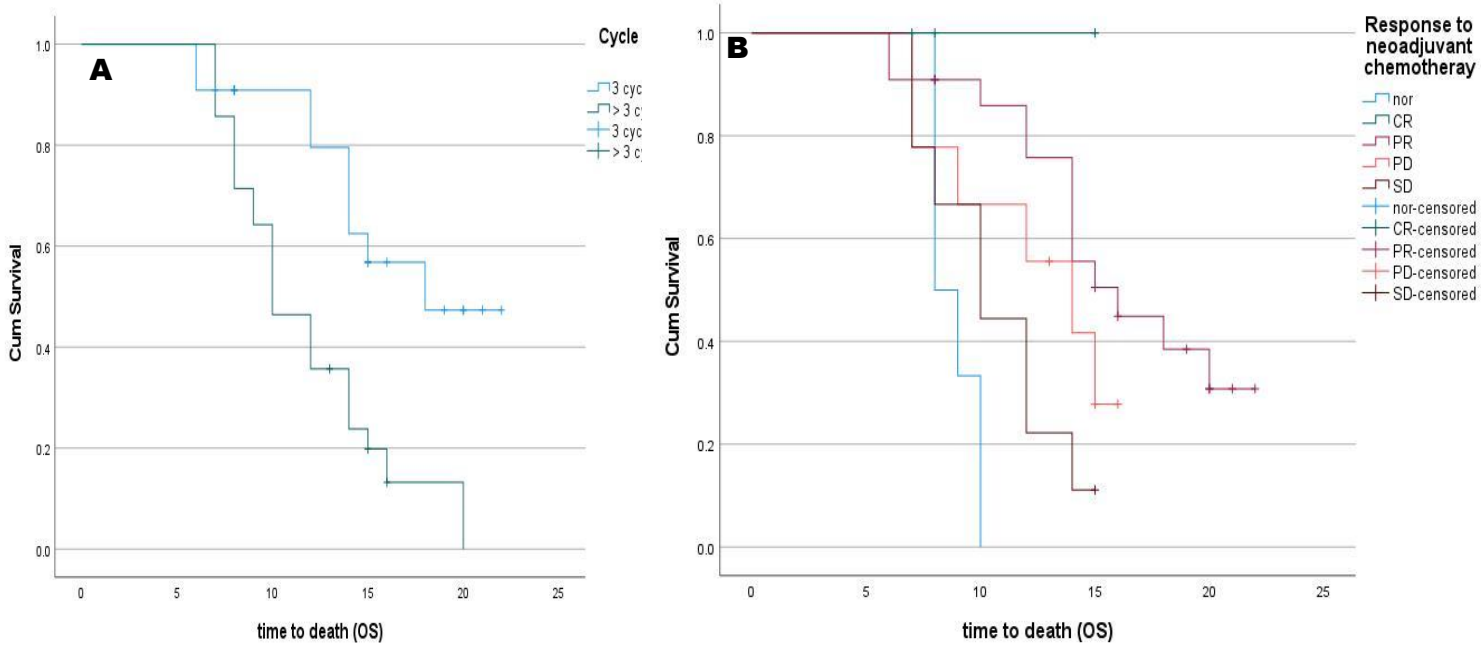


Figure (3): Kaplan Meier survival curves demonstrated associations between overall survival rate (OS) and number of cycles of neo-adjuvant chemotherapy intake (A) and response to chemotherapy (B).

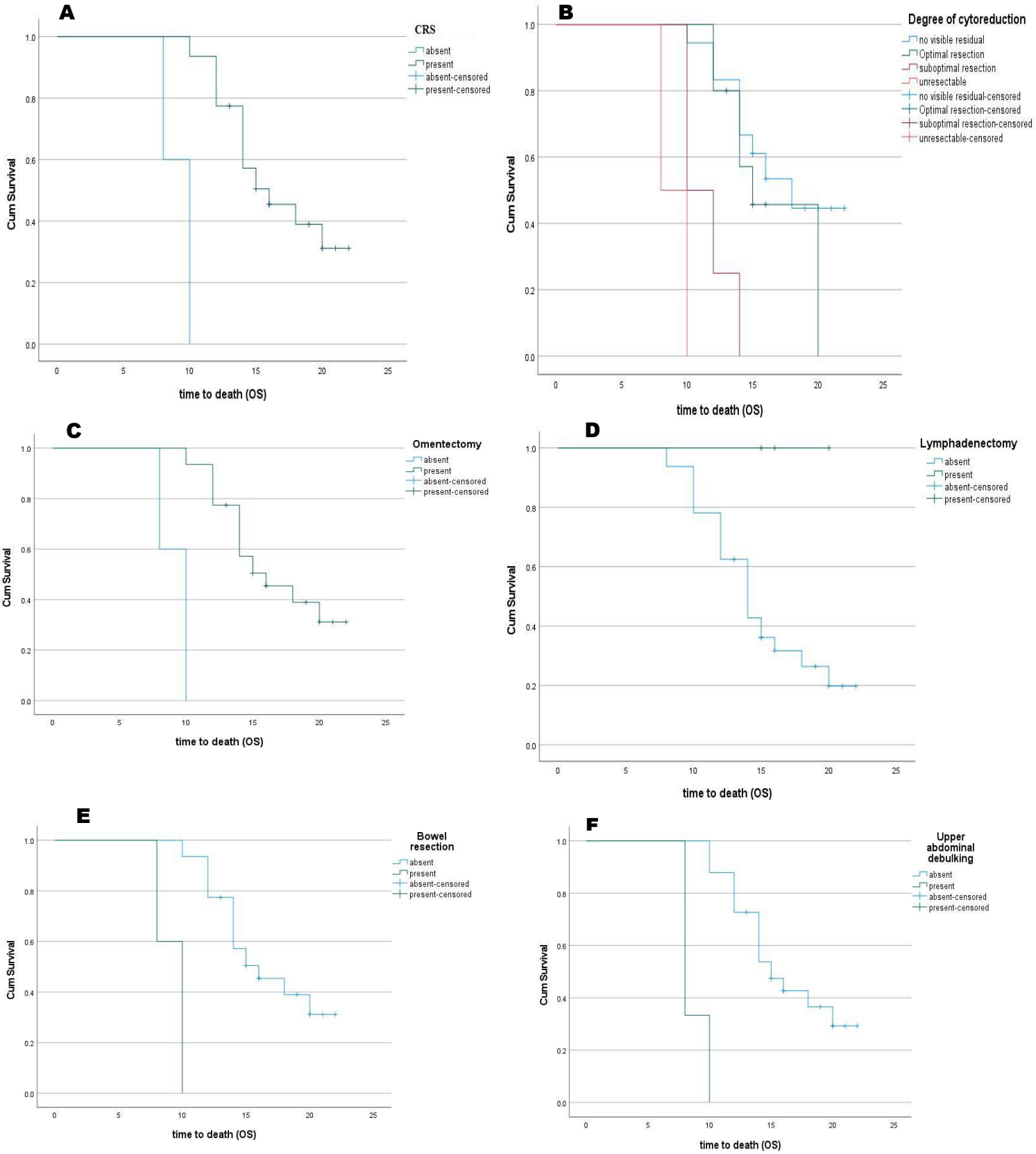


Figure (4): Kaplan Meier survival curves demonstrated associations between overall survival rate (OS) and (A) Performing cytoreduction surgery (CRS) (B) Degree of cytoreduction (C) Performing omentectomy (D) Performing lymphadenectomy (E) Performing bowel resection (F) Performing upper abdominal debulking.

DISCUSSION

Number of patients who initially presented with locally advanced endometrial carcinoma is relatively low and about 10%–15% of all new endometrial carcinoma cases spread outside the uterus with markedly low survival rates [31]**.** The standard management strategy of endometrial carcinoma is total hysterectomy, bilateral salpingo-oophorectomy in addition to peritoneal lavage, assessment and surgical staging of pelvic and para-aortic lymph nodes. Management of advanced endometrial carcinoma is still controversial; the role of cytoreductive surgery (CRS) is not clearly defined in advanced EC [31]**.**

Multimodal approaches were suggested for those patients as cyto-reductive surgery, CT, and RT.

In the present study about role of cyto-reductive surgery in management of advanced endometrial carcinoma (stage III), we proved the benefits of optimal cytoreduction. Our results are similar to results of **Verrengia *et al.*** [5] and **Bristow *et al.*** [31]**.**

Also our results are in line with **Verrengia *et al.*** [5] who studied a group of patients with advanced endometrial cancer who were treated with neoadjuvant chemotherapy and cytoreductive surgery, and they found that cytoreductive surgery, with no visible residual disease was achieved in 52% and it was associated with relative improvement in survival rates. The advantages of such surgical management are that it was done without needing complex procedures as resection of bowel or abdominal debulking. Our results are in line with many previously performed studies which assessed the advantages of optimal cytoreductive surgery in advanced endometrial carcinoma patients in improving survival rates and patients outcome [32-35]**. Eto *et al.*** [36] in their large cohort reported the value of neoadjuvant chemotherapy and interval cytoreduction surgery**. Barlin *et al.*** [37] meta-analysis which include 14 retrospective studies concluded that reported women with complete cyto-reduction have longer survival rates and favorable outcomes**.** The advantages of cyto-reductive surgery in endometrial carcinoma could be proved by similar mechanisms to that in ovarian cancer as reducing viable malignant tissue mass, poorly vascularized tumor cells removal, which reduced resistance to the chemotherapeutic agents in addition to enhancing the immune response through removing large part of the tumor [34]**.** Although performing optimal cyto-reductive surgeries have many therapeutic benefits but patients with distant metastases still have high risks of local and distant recurrences so they will benefit from taking adjuvant treatments**.**

CONCLUSIONS

In the present study we demonstrated the value of using neo-adjuvant chemotherapeutic agents followed by cyto-reductive surgery in cases of advanced endometrial carcinoma in improving local and systemic symptoms, reducing rates of local and distant recurrences in addition to improving patients' survival rates.

Points of strength of the study: We included a relatively large number of patients with advanced endometrial carcinoma who had similar demographic data and were managed at a single institution. All slides from D & C samples before neo-adjuvant chemotherapy and after cyto-reductive surgeries were reviewed by an experienced pathologist, and finally the prospective nature of the study with the availability and completeness of follow-up data made results more accurate.,

Recommendations due to few studies, which assessed the values of neo-adjuvant chemotherapy in advanced endometrial carcinoma**, f**urther studies are needed for confirmation of our findings, evaluating molecular risk factors and tumor characteristics of patients who will get benefit from neoadjuvant chemotherapy.

DECLARATIONS

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