

# Could Surgery Improve Survival in Patients with Advanced Endometrial Cancer?

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## Abstract

**Background:** Patients with endometrial cancer are mostly diagnosed at an early stage. But unfortunately 10% to 15% of endometrial cancer patients will present with advanced-stage disease, and hence poorer prognosis. When disease is primarily intraperitoneal, cytoreduction to <2 cm has also been correlated with better survival, with the maximum benefit in patients who can be reduced to no visible disease remaining. **Aim:** Of the work is to detect the survival rate benefits of primary surgery in patients with advanced endometrial cancer at gynecologic oncology unit in El Shatby Maternity University Hospital. **Methods and Materials:** Retrospective study was conducted on 102 patients diagnosed to have advanced endometrial cancer FIGO (stage III/IV) in a duration of 4 years between 2016 and 2020 and had undergone cytoreductive surgery. The patients were further subdivided into two groups: group 1 who underwent optimal cytoreduction with residual disease less than or equal 1 cm visible lesion, and group 2 who had residual disease more than 1 cm visible lesion and they were followed to check the survival benefits. **Results:** The mean of disease free survival in group: 1) patients was 2 years which was significantly longer than those in group; 2) those who had residual disease > 1 cm,  $p < 0.001$ . Also cases with type I endometrial cancer had significantly longer (DFS) than those diagnosed to have type II endometrial cancer,  $p = 0.046$ . **Conclusion:** Primary complete cytoreductive (upfront) surgery when possible has a favorable impact on overall survival in patients with advanced endometrial cancer.

## Keywords

Endometrial Cancer, Chemotherapy, Survival, Upfront Surgery, Radiotherapy

## 1. Introduction

Early endometrial cancer (EC) has a good prognosis when timely diagnosed and properly managed with achievement of 5 years survival rate exceeding 80% [1]. Unfortunately 10% - 15% of patients of endometrial cancer are diagnosed in advanced stage [2] [3]. Subdivision of endometrial cancer into two types is well recognized. This subdivision was based on the biological behavior and spread of the disease [4], but other new classifications are proposed based on molecular and genetics characterization [5] [6]. Type II endometrial cancer is managed similarly to high grade serous ovarian cancer [7]. Lines of treatment of advanced endometrial cancer are not solidified, the choice differs from one institution to another. Whether neoadjuvant chemotherapy then secondary cytoreductive surgery or primary cytoreductive (upfront) surgery [8].

Neoadjuvant chemotherapy followed by secondary cytoreductive surgery is usually considered in patients who have poor performance status and fairly tolerate major surgery [9]. This line of treatment was postulated to have the advantage of reduced incidence of morbidity and increase the possibility of secondary complete debulking surgery [10].

Large studies of advanced ovarian cancer management concluded that primary complete cytoreductive surgery that achieved no residual visible lesions or residual visible lesions less than 1 cm improved survival rate of patients [11] [12] [13]. The possibility to apply this concept in patients with advanced endometrial cancer to achieve better survival has been tested [14] [15].

The aim of this study is to test the impact of optimal primary upfront surgery on the survival rate in patients of advanced stage endometrial cancer.

## 2. Methods and Patients

This retrospective analytic study which included patients with advanced endometrial cancer who presented between 2016 and 2020 to the gynecological-oncology unit of Shatby University hospital was approved by the faculty of medicine ethical committee number: 0305240. The study was conducted in accordance with the ethical standards established in the Declaration of Helsinki of 1946.

The study included records of 102 patients with stage III/IV endometrial who underwent upfront primary surgery with intention to optimal cytoreductive surgery. The data were analyzed and patients were further subdivided in to two groups; group (1) who had under gone optimal cytoreduction with residual disease less than or equal to 1 cm visible lesions. And group (2) who had residual disease more than 1 cm visible lesion. The patients who had received neoadjuvant or had major comorbidity—which may impact on survival—were excluded from the study.

Demographic data such as age, parity, menopausal state, body mass index (BMI) and other medical problems were analyzed. Also data about site and distribution of metastatic disease either pelvic or extra pelvic disease or the type of surgical

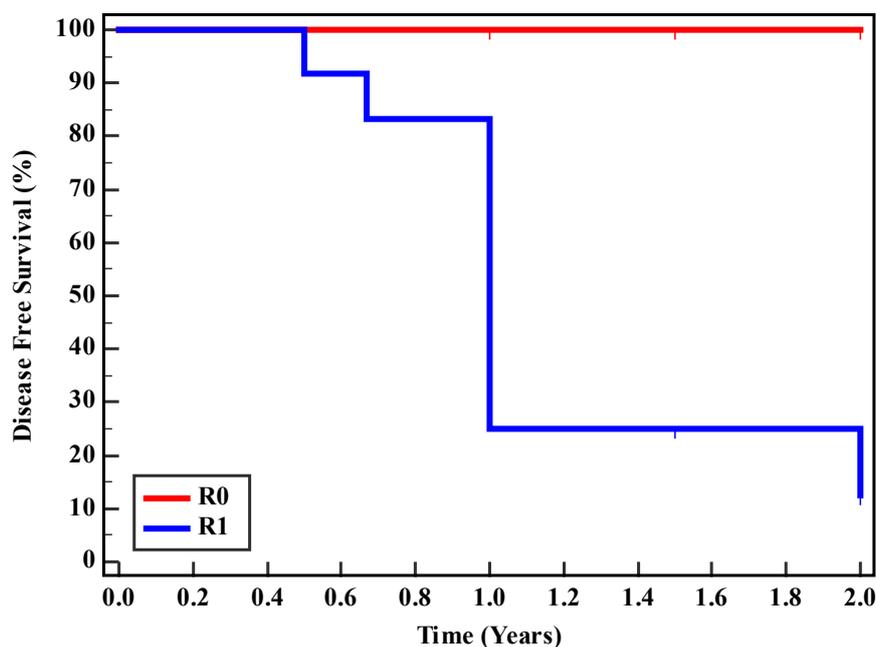
procedure done, were also collected and analyzed. Post-operative surveys and follow up data as regards the histopathological evaluation of the surgical specimens. Data about post-operative adjuvant therapy and disease free survival duration were also collected and analyzed.

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, and standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level. Survival curves were plotted by Kaplan Meier method and median survival estimates were compared using log rank test.

### 3. Results

The median age of the patients in this study group was 64 yrs old. The median BMI was 36.2 kg/m<sup>2</sup>. 83 patients had controlled uncomplicated medical problems, as shown in **Table 1**. As regards surgical staging, 45.1% of patients were stage IIIA while 31.6% were stage IIIC. 61 patients had undergone Total abdominal hysterectomy & bilateral salpingo-oophorectomy (TAH & BSO) and pelvic lymphadenectomy while 4 patients underwent (TAH & BSO) + pelvic & paraaortic lymphadenectomy. Staging laparotomy as primary cytoreductive surgery was performed in 37 patients. Complete cytoreduction was achieved in 58 patients while residual lesions more than 1 cm were left in 44 patients, as shown in **Table 2**. Analysis of data showed that disease free survival (DFS) differed according to different biological nature of the disease. Tumour grade had not a significant impact on (DFS) as there was not a statistically significant difference between low, moderate and high grade tumours. The (DFS) was 2 years in the 4 patients who had low grade disease. While the mean (DFS) was 1.64 and 1.63 years in patients with moderate and high grade disease respectively  $p = 0.789$ . There were 66 patients who had endometrioid (type I) endometrial cancer who had (DFS) of 1.81 years while the 36 patients who had type II had a mean (DFS) of 1.37 years. There was a significant survival advantage in patient who had type I endometrial cancer  $p = 0.046$  as shown in **Table 3**. The mean of disease free survival in group (1) patients was 2 years which was significantly longer than those in group (2) who had residual disease > 1 cm,  $p < 0.001$  as shown in **Figure 1**. Also cases with type I endometrial cancer had significantly longer (DFS) than those diagnosed to have type II endometrial cancer,  $p = 0.046$  as shown in **Figure 2**. Poor performance status impact on survival couldn't be tested because patients who had serious or complicated medical disease that might have affected the survival were excluded from the study. Analysis of data shown in **Table 4** showed that the mean was 1.61 years in patients with low grade disease. The mean (OS) was 1.69 & 1.62 years in patients with moderate and high grade disease respectively. There was not statistically significant difference between the (OS) in the patient with different tumour grades  $p = 0.782$ . The 66 patients with

type I endometrioid carcinoma had mean (OS) of 1.92 years which was statistically better than that of the 36 patients with type II non endometrioid endometrial cancer  $p = 0.047$  as shown in **Table 4**. The mean overall survival (OS) was significantly improved when R0 was achieved  $p = 0.007$  as shown in **Figure 3**. Type I endometrial cancer was also associated with better (OS),  $p = 0.047$  as shown in **Figure 4**.

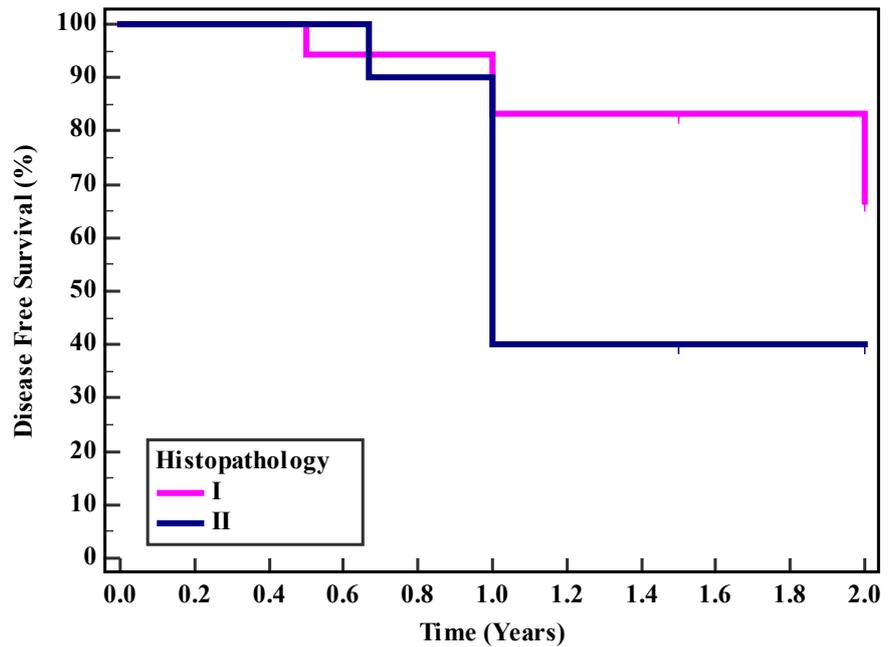


**Figure 1.** Kaplan-Meier curve for disease free survival with R0/R1.

**Table 1.** Distribution of the studied cases according to personal data (n = 102).

Personal data	
<b>Age at diagnosis</b>	
Min. - Max.	39.0 - 76.0
Mean $\pm$ SD.	61.54 $\pm$ 8.55
Median (IQR)	64.0 (58.4 - 68.50)
<b>BMI</b>	
Min. - Max.	24.0 - 45.0
Mean $\pm$ SD.	36.18 $\pm$ 4.80
Median (IQR)	36.20 (30.90 - 45.0)
<b>Medical History</b>	<b>No. (%)</b>
No	19 (18.9%)
Yes	83 (81.1%)

IQR: Inter Quartile Range; SD: Standard Deviation.

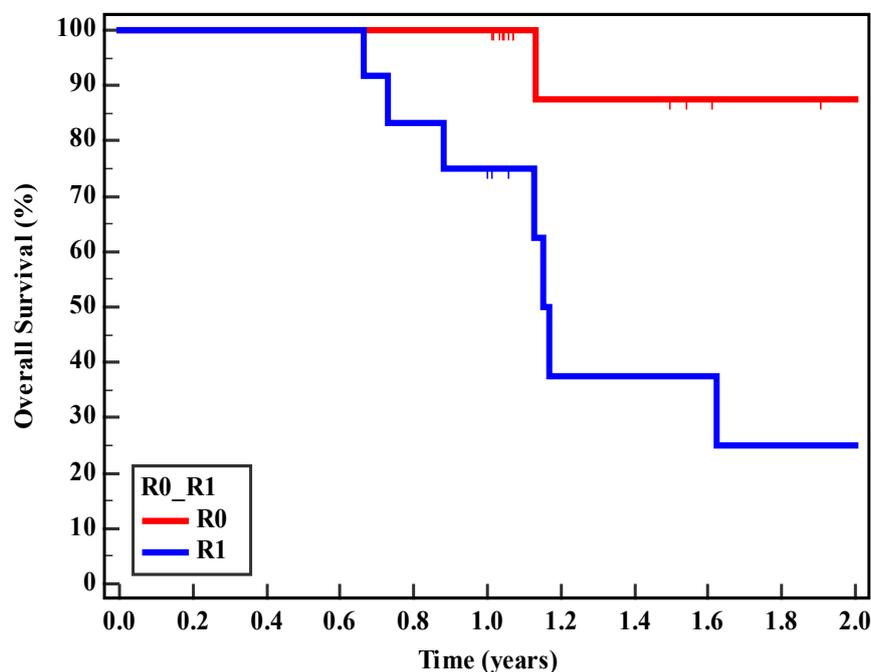


**Figure 2.** Kaplan-Meier curve for disease free survival with histopathology.

**Table 2.** Distribution of the studied cases according to surgical characteristics (n = 102).

Surgical characteristics	No.	%
<b>Staging</b>		
IIIA	46	45.1
IIIB	5	4.8
IIIC	32	31.6
IVA	11	10.3
IVB	8	8.2
III	83	81.5
IV	19	18.5
<b>Type of procedure</b>		
(TAH & BSO) + pelvic lymphadenectomy	61	51.0
(TAH & BSO) + pelvic & paraaortic lymphadenectomy	4	3.7
Staging laparotomy (primary cytoreductive surgery)	37	45.3
<b>R0/R1</b>		
R0	58	56.8
R1	44	43.2

(TAH & BSO): total abdominal hysterectomy & bilateral salpingo-oophorectomy. R0: complete cytoreduction with residual disease less than or equal to 1 cm visible lesions; R1: residual disease more than 1 cm visible lesion.

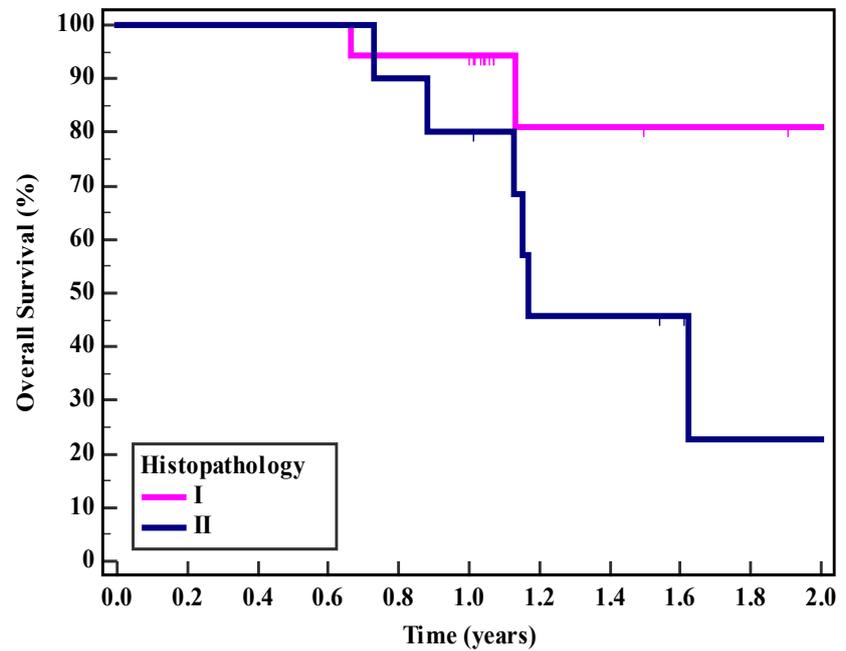


**Figure 3.** Kaplan-Meier curve for overall survival with R0/R1.

**Table 3.** Relation between diseases free survival and different parameters (n = 102).

	N	Diseases Free Survival		SE	Log rank	p value
		Mean (95% CI)	LL - UL			
<b>Grading</b>						
Low	4	2.0 (2.0 - 2.0)		0.0		
Moderate	66	1.64 (1.378 - 1.899)		0.13	0.475	0.789
High	32	1.63 (1.282 - 1.977)		0.18		
<b>R0/R1</b>						
R0	58	2.0 (2.0 - 2.0)		0.0	19.149	<0.001*
R1	44	1.18 (0.884 - 1.477)		0.15		
<b>Histopathology</b>						
I -endometrioid	66	1.81 (1.568 - 2.043)		0.12		
II-sarcoma	23	1.28 (0.858 - 1.697)		0.21	5.481	0.140
II-serous	11	1.33 (1.067 - 1.60)		0.14		
II-clear cell	2	1.0 (1.0 - 1.0)		0.0		
I	66	1.81 (1.568 - 2.043)		0.12	3.986	0.046*
II	36	1.37 (1.041 - 1.693)		0.17		

SE: Standard Error; C.I: Confidence Interval; LL: Lower Limit; UL: Upper Limit; \*: Statistically significant at  $p \leq 0.05$ .



**Figure 4.** Kaplan-Meier curve for overall survival with histology.

**Table 4.** Relation between overall survival and different parameters (n = 102).

	N	Overall Survival		Log rank	p value
		Mean (95% CI) LL - UL	SE		
<b>Grading</b>					
Low	4	1.61 (1.611 - 1.611)	0.0		
Moderate	66	1.69 (1.319 - 2.062)	0.19	0.492	0.782
High	32	1.62 (1.261 - 1.968)	0.18		
<b>R0/R1</b>					
R0	58	2.02 (1.784 - 2.248)	0.12	7.338	0.007*
R1	44	1.36 (1.026 - 1.692)	0.17		
<b>Histopathology</b>					
I-endometrioid	66	1.92 (1.639 - 2.209)	0.15	5.636	0.131
II-sarcoma	23	1.36 (0.910 - 1.801)	0.23		
II-serous	11	1.63 (1.625 - 1.625)	0.0		
II-clear cell	2	1.15 (1.153 - 1.153)	0.0		
I	66	1.92 (1.639 - 2.209)	0.15	3.928	0.047*
II	36	1.41 (1.087 - 1.733)	0.17		

SE: Standard Error; C.I: Confidence Interval; LL: Lower Limit; UL: Upper Limit; \*: Statistically significant at  $p \leq 0.05$ .

## 4. Discussion

Management of Stage III and IV endometrial cancer patients is usually individualized and could include different modalities such as a cytoreductive surgery (CRS), radiotherapy, chemotherapy or combination of them according to risk assessment stratification. In this study we tested the performance of optimal primary cytoreductive on patients of advanced stage endometrial cancer.

The analysis of results showed that 102 patients under went upfront surgery with the aim of complete cytoreduction that was planned according to the preoperative data, the complete cytoreduction could be achieved in only 58/102 (52.6%) patient which matches with what was observed by Benjamin B Albright *et al.* who reviewed and did a meta-analysis of results of 34 studies, which tested the extent of residual disease after primary cytoreductive surgery, they found that 52.1% of cases reached no gross residual disease status among cases of advanced stage endometrial cancer underwent primary cytoreductive surgery, a significant proportion of patients are left with residual disease, which was associated with worse survival outcomes [14].

Our results showed significant favorable DFS and OS in patients who underwent complete cytoreduction. This improved survival was also observed by Savithri Raj Kumar *et al.* who stated that suboptimal cytoreduction ( $p = 0.006$ ) was a significance predictor of poor survival on multivariate analyses [16].

R E Bristow *et al.* showed similar results to our results. They studied a cohort of 65 patients of stage IVB endometrial carcinoma whom optimal cytoreductive surgery (residual tumor  $\leq 1$  cm in maximal diameter) was achieved in only 55.4% of patients. The median survival rate of them was 34.3 months, which was statistically better compared to patients with  $>1$  cm residual tumor (11.0 months,  $p = 0.0001$ ) [17].

Lisa M Landrum did a case control study to test the application of an ovarian cancer treatment paradigm in a cohort of 55 patients with stage IVB endometrial cancer; they concluded that optimal CRS was associated with a survival advantage over suboptimal for EC patients with a hazard ratio of 2.4 [18].

Several points of strengths' are present in this study the first of them was the inclusion of a relatively large number of patients who fulfilled the selection criteria, this could be achieved because the gynecology unit in Shatby university hospital is considered a tertiary referral center for many nearby cities. Another point of strength was the exclusion of poor performance status patients who had complicated comorbidity which nullified the confounder effect on survival.

One of the Limitations of this study was lack of randomization of patients which could not be achieved due to retrospective nature of the study and non-homogeneity of the studied severity of the disease as we included both stages III & IV, this could be achieved by further subdivision of patients when the number is sufficient for analysis.

## 5. Conclusion

Primary complete cytoreductive (upfront) surgery when possible has a favorable

impact on overall survival in patients with advanced endometrial cancer.

### Recommendation

Further prospective comparative studies are needed to increase the evidence and prove the benefit of value of primary complete cytoreductive surgery in patients with advanced endometrial cancer.

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### Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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