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The struggle against endometrial cancer: ten years of experience of a tertiary center

Short title: Endometrial cancer and experience

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ABSTRACT

Objectives: We aimed to investigate the clinical and pathological factors of our patients who were diagnosed with endometrial cancer in terms of prognosis. With this study, we present our 10 years of surgical experience in endometrial carcinoma cases.

Material and methods: Four hundred twelve patients with endometrial carcinoma who applied to our center between 2010–2019 and that we followed up were evaluated retrospectively.

Results: Most of the tumors were low-grade endometrioid malignancies. Non-endometrioid types accounted for 12.1% of cases. Lymph node dissection was performed in 395 of 412 patients (95.9%). 66 (16.01%) of the 412 patients died during the follow-up period in the study sample. Higher OS and DFS rates were associated with endometrioid histological types, FIGO stage, absence of lymphovascular space invasion, lower grade and less than 50%

myometrial invasion ($p < 0.05$). 5-year OS at stage 1, 2, 3, 4 was found as 88.9 ± 2.2%, 65.5 ± 10.8%, 49.4 ± 0.79% and 23.7 ± 0.97% respectively. 5-year DFS at stage 1, 2, 3, 4 was found as 84.1 ± 2.6%, 65.5 ± 10.8%, 47.7 ± 0.78% and 23.7 ± 0.97% respectively. In univariate analysis, Age, tumor histology, FIGO stage, histological grade, LVSI, positive peritoneal cytology, cervical involvement, myometrial invasion and not receiving adjuvant therapy were defined as prognostic factors.

Conclusions: Age, grade, FIGO stage, myometrial invasion, histological type, LVSI involvement, cervical involvemet, positive peritoneal cytology and not receiving adjuvant therapy are important prognostic factors for progression-free survival and overall survival in patients diagnosed with endometrial cancer.

Key words: endometrial carcinoma; lymph node; stage; prognostic factors

INTRODUCTION

Endometrium cancer (EC) is the most common gynecological cancer in developed countries and the second most common gynecological cancer worldwide after cervical cancer [1]. Approximately, 3850 new cases are reported annually and around 520 deaths linked to endometrial cancer are seen in Turkey [2]. Most of the patients are diagnosed at an early stage (80% Stage 1) and the average age at the time of diagnosis is reported to be 63 [3]. The incidence of EC is increasing due to various factors such as increased prevalence of obesity, decreased menopausal hormone therapy with progestins, increased prevalence of diabetes and changes in reproductive behavior (increased prevalence of nulliparity, etc.) [4]. Surgery with hysterectomy and salpingo-oophorectomy is the mainstay of EC treatment. Approach to lymph node evaluation in women with EC is a matter of discussion. The application varies according to different institutions and surgeons. In recent years, a more conservative approach has been adopted, and some criteria have been determined and lymph node dissection has been applied in selected patients. Similarly, sentinel lymph node applications have started to be adopted as a popular approach in endometrial cancers [5]. Routine full bilateral pelvic and paraaortic lymphadenectomy provides the most information about the degree of malignancy for planning adjuvant therapy, but the primary concern for its universal use is lymphedema in the lower extremity and the morbidity of associated cellulitis. In this study, we aimed to

present our 10 years of experience in endometrial cancer treatment in our clinic, which is a tertiary center, in terms of surgical, histopathological and prognostic aspects.

MATERIAL AND METHODS

This study was approved by the ethics committee decision of our university numbered 2020/508. Four hundred twelve patients who were operated with the diagnosis of EC in our clinic between January 2010 and December 2019 were included in this study. Age, menopausal status, histological type, stage of the disease, histological grade, myometrial invasion, tumor size, lymph node involvement and adjuvant treatments were evaluated retrospectively from the files of the cases. The staging of the cases was done according to FIGO 2009 staging system. We analyzed the clinical characteristics, demographic profiles, pathological data, treatment methods, adjuvant therapies, complications, recurrence, progression-free survival (DFS) and overall survival (OS) of all patients. All cases were pathologically confirmed as EC. DFS was determined from the date of diagnosis to the date of first recurrence or last follow-up, and OS from the date of diagnosis to the date of death or the last follow-up date.

Statistical analysis

Data are presented as number of observations (n, %), mean ± standard deviation, range. The results of homogeneity (Levene's test) and normality (Shapiro-Wilk test) were used to decide the statistical methods for comparing the study groups. Among normally distributed groups with homogeneous variances, dependent groups were compared using the Student's t-test. According to the test results, parametric test assumptions were not available for some variables; therefore, the independent groups were compared using the Mann Whitney-U test. Categorical data were analyzed using Fischer's exact test and the chi-square test. In cases in which the expected counts for inclusion were not met in less than 20% of the cells, the "Monte Carlo Simulation Method" was used and the values were determined. Cox regression analysis was used to reveal the model of the relationship between independent variables and dependent variables in the study. In addition, the lifetimes were estimated according to the Kaplan meier estimator. While comparing the survival times of the groups, evaluation was made with the Log Rank test. For the significance level of the tests, $p < 0.05$ and $p < 0.01$ values were accepted.

RESULTS

During the 10-year study period, 412 histologically confirmed endometrial cancer cases were treated in our institution with primary surgery. The clinicopathological features of the study cohort are shown in Table 1. Most of the tumors were low-grade endometrioid malignancies. High grade tumors consisted of endometrioid grade 3 and non-endometrioid histological types, only non-endometrioid types accounted for 12.1% of cases. Lymph node dissection was performed in 395 of 412 patients (95.9%), pelvic + paraaortic lymphadenectomy was performed in 349 cases (84.7%), and pelvic lymphadenectomy was performed alone in 46 cases (11.2%). Lymphadenectomy was not performed in 17 cases (4.1%). The mean numbers of positive pelvic and paraaortic lymph nodes were 57 (13.8%) and 34 (8.3%), respectively.

Postoperative 247 patients (60%) received adjuvant therapy. Thirty-one patients (7.5%) received chemotherapy (CT), 19 patients (4.6%) received external radiotherapy (ERT) and 89 patients (21.6%) received brachytherapy (BRT). Recurrence was detected in 80 patients (19.4%) during the follow-up period. Recurrence was observed in the pelvic region in 22 (5.34%) cases, distant metastasis in 16 (3.88%) case, and pelvic + distant metastasis in 42 (10.2%) cases.

Sixty-six (16.01%) of the 412 patients died during the follow-up period in the study sample. OS and DFS for all patients and non-recurrent patients are shown in Figure 1a and 1b. Higher OS and DFS rates were associated with endometrioid histological types (Fig. 2a, 2b), FIGO stage I (Fig. 3a, 3b), absence of lymphovascular space invasion (LVSI) (Fig. 4a, 4b), lower grade (Fig. 5a, 5b) and less than 50% myometrial invasion (Fig. 6a, 6b). There was a statistically significant difference between stages in terms of survival ($p < 0.05$). Five-year OS at stage 1, 2, 3, 4 was found as 88.9 ± 2.2%, 65.5 ± 10.8%, 49.4 ± 0.79% and 23.7 ± 0.97% respectively. Five-year DFS at stage 1, 2, 3, 4 was found as 84.1 ± 2.6%, 65.5 ± 10.8%, 47.7 ± 0.78% and 23.7 ± 0.97% respectively. There is also statistically significant difference between LVSI, grade and histological type, myometrial invasion groups in terms of survival times ($p < 0.05$) (Tab. 3).

In univariate analysis, the following parameters were identified as prognostic factors: increased age, histologically non-endometriod type, increased tumor grade, myometrial invasion, advanced FIGO stage, cervical invasion, positivity peritoneal cytology, and not reciewed adjuvant therapy. In the multivariate analysis, advanced age, higher tumor grade,

higher FIGO stage, and no adjuvant therapy were found to be associated with lower overall survival (Tab. 3).

DISCUSSION

Endometrial cancer is divided into two types considering histopathological and molecular markers. Type 1 endometrial cancer is the most common group with a rate of 80-90% and includes grade 1–2 endometroid type histology. Type 2 endometrial cancer represents the non-endometroid group such as serous, clear cell, undifferentiated carcinomas and carcinosarcomas and is observed at a rate of 10–20% [6]. Tumor histology of our patients is compatible with the general literatüre. It was determined that 362 (87.9 %) patients had endometrioid type histology, 50 (12.1 %) patients had non-endometrioid type histology.

Endometrium cancer most often occurs in the 60–70s. The average age is 60. It has been shown that 75% of the patients are over the age of 50 [7]. Endometrial cancer occurs especially during menopause. Although the prognosis was reported to be better in young patients, there are studies reporting that age is not an independent prognostic factor [8]. In our study, the mean age of our patients was 59.5 ± 10.13. Age factor was seen as an independent prognostic factor in univariate and multivariate analyzes. Advanced age was associated with lower overall survival.

Since most of the cases are detected in the early stage, long five-year survival rates are provided with treatment. However, due to the many prognostic factors affecting the biological behavior of the tumor, the optimal surgical treatment is still controversial. Many retrospective studies have shown a statistically significant DFS and OS survival benefit if optimal cytoreduction is achieved [9, 10]. Seventy-three point eight percent of the patients were in stage I in our study. Pelvic and paraaortic lymph node dissection constitutes an important part of surgical staging in the surgical treatment of endometrial cancer. The role of lymphadenectomy in determining adjuvant treatment as well as staging is obvious. It is important to perform lymph node dissection in sufficient numbers and areas. In this context, Mariani et al. [11], reported that in the case of total pelvic and paraaortic lymphadenectomy, there was no lymph node recurrence in the paraaortic region and lymphadenectomy had therapeutic effect . In a study involving 91 patients diagnosed with stage IIIC, microscopic lymph node involvement was found in 39 patients and macroscopic lymph node involvement in 52 patients [11]. When the 5-year OS durations were examined, it was found that it was 58% in cases with microscopic nodal involvement, 41% in patients with complete resection

with macroscopic involvement, and 22% in patients with incomplete resection [12]. In our study, complete resection was performed in 95.9 % of the cases and the 5-year OS and DFS values were found as 54.118 ± 3,978 month, 54.118 ± 3.978 month in those without lymph node dissection, 50.534 ± 5.116 month, 50.534 ± 5.116 month in those who had only pelvic dissection, 57.435 ± 0.995 month, 56.988 ± 0.997 months in those who had both pelvic and paraaortic lymph dissection, respectively. Lymphatic metastasis in endometrial cancer is associated with tumor histology, grade, depth of myometrial invasion, and LVSI. Therefore, it seems reasonable to apply systemic lymphadenectomy, especially in early stage disease with these risk factors, except for the advanced stage [12–14].

Surgical staging has a very important place in determining prognosis. Most of the endometrial cancers (80.3%) are diagnosed at the early stage (FIGO stage I or II) and the 5-year survival of these varies between 74–91%; this rate is between 57–66% for stage III disease and 20-26% for stage IV disease [15]. Endometrial cancer, approximately 16% at the time of diagnosis, is detected at an advanced stage [16]. According to the surgical-pathological staging, Dane et al. [17], found that The 5-year DFS rate was 90% in stage I, 66% in stage II, 32% in stage III and 60% in stage IV and the 5-year OS rate was 95% in stage I, 89% in stage II. 49% in stage III, and 30% in stage IV . These values show that staging is statistically significant as a prognostic factor. In our study, the 5-year OS rate was at stage 1, 2, 3, 4 was found as 88.9 ± 2.2%, 65.5 ± 10.8%, 49.4 ± 0.79% and 23.7 ± 0.97% respectively. Five-year DFS at stage 1, 2, 3, 4 was found as 84.1 ± 2.6%, 65.5 ± 10.8%, 47.7 ± 0.78% and 23.7 ± 0.97% respectively.

Grade is also an important determinant for myometrial invasion and lymph node involvement, which is another prognostic factor. As the differentiation degree of the tumor decreases, the risk of deep myometrial invasion, cervical involvement, lymph node involvement, local recurrence and distant metastasis increases [18]. In the present study, there is a statistically significant difference between the grade groups in terms of OS and DFS ($p < 0.01$). According to the Kaplan-Meier estimator, The OS was 55,866 ± 0.86 months in the grade 1, 53,213 ± 1,625 months in the grade 2 and 47,087 ± 2,810 months in the grade 3. The DFS was detected as 55,764 ± 0,861 months in grade 1, 52,795 ± 1.7 month in grade 2 and 46,202 ± 2,789 months in grade 3.

In the present study, LVSI positivity was detected in 69 (16.7%) patients. It is reported that LVSI positivity is associated with a high risk of recurrence and poor prognosis [19]. In

this study, The OS was found to be 50.697 ± 2.677 months in LVSI positive cases and 54.074 ± 0.849 months in negative cases. The DFS values are 50.697 ± 2.677 and 53.839 ± 0.854 months in LVSI positive and negative cases, respectively. Generally, cases with cervical involvement were found to be higher-grade and deeply invasive tumors (Fig. 7a, 7b).

Invasion of the myometrium by tumoral tissues increases the possibility of extrauterine spread and recurrence since drainage into the lymphatic system is easier when the depth is above 50% [20]. This is the most important pathological finding that determines whether lymphadenectomy will be added to the surgery during the operation. Myometrial invasion is a criterion for the tumor to behave aggressively. In this study, OS and DFS values in cases with less than 50% myometrial invasion were found to be 60.131 ± 0.993 months and 59.844 ± 0.994 months, respectively. The same values were 48.327 ± 1.725 and 47.952 ± 1,722 months for patients with depth of invasion greater than 50%, respectively. Lymph node involvement is the most important prognostic factor in early stage EC [21]. Patients with positive lymph node metastases are six times more likely to develop recurrence [22]. The involvement of the pelvic lymph nodes is a good indicator for the involvement of the paraaortic lymph nodes. However, approximately 11% of patients with clinical stage I have paraortic lymph node metastasis. In the presence of deep myometrial invasion, pelvic lymph node involvement is 25% while paraortic involvement is 17% [23].

This study has some limitations. The first is a retrospective study and limited to the data in the records, so misclassification bias is possible. Also, to obtain a large sample size, patient data were reviewed over 10 years and treatment patterns/practices may have changed during this time.

CONCLUSIONS

This single-center retrospective analysis confirms that Age, Grade, FIGO stage, myometrial invasion, histological type, positive peritoneal cytology, not receiving adjuvant therapy, LVSI and cervical involvement are important prognostic factors for progression-free survival and overall survival in patients diagnosed with endometrial cancer.

Conflict of interests

The all author declared that there is no conflicts of interest.

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Table 1. Characteristics of the study population

Variable	**N**	$\bar{x} \pm S.D$	**Median**	**Range**
Age		59.51 ± 10.13	59.50	33.0–88.0
Gravida		3.51 ± 2.06	3.0	0.0–15.0
Parity		3.30 ± 1.84	3.0	0.0–11.0
Menopausal status		**%**		
Premenopause (50 <)	70	17.0		
Postmenopause (51 ≤)	342	83.0		
Histological type				
Endometrioid	362	87.9		
Mucinous	4	1.0		

Serous	33	8.0		
Clear cell	2	0.5		
Mixt	11	2.7		
FIGO STAGE (2009)				
Stage I	304	73.8		
Stage II	27	6.6		
Stage III	56	13.6		
Stage IV	25	6.0		
Grade				
I	244	59.2		
II	95	23.1		
III	73	17.7		
Myometrial invasion				
< 1/2	285	69.2		
> ½	127	30.8		
LVSI				
(+)	69	16.7		
(–)	342	83.0		
Tumor size				
≤ 2 cm	77	18.7		
2–4 cm	166	40.3		
> 4 cm	167	40.5		
Peritoneal cytology				
Positive	34	8.3		
Negative	378	91.7		
Lymph node dissection				
None	17	4.1		
Pelvic	46	11.2		
Pelvic + Paraaortic	349	84.7		
Abdominal entry technique				
Phannenstiel	207	50.2		
GAM	35	8.5		
GAM + GUM	92	22.3		
Laparoscopic	78	18.9		
Adjuvant therapy				
Not received	165	40.0		
Chemotherapy (CT)	31	7.5		
External radiotherapy (ERT)	19	4.6		
Brachytherapy (BRT)	89	21.6		
CT + ERT	33	8.0		
CT + BRT	21	5.1		
CT + RT + BRT	41	10.0		
ERT + BRT	13	3.2		
Recurrence				
Pelvic	22	5.34		
Distant	16	3.88		
Pelvic + distant	42	10.2		

Death	66	16.01		

LVSI — lymphovascular space invasion; GAM — sub-umbilical median incision; GUM — median incision above the umbilical; CT — Chemotherapy; ERT — External radiotherapy; BRT — Brachytherapy; RT — radiotherapy

Table 2. Chi-square results and confidence intervals of log-rank test as a result of Kaplan-Meier survival analysis

OS		Estimate	Std. Error	95% CI		x^2	p
				Lower Bound	Upper Bound		
Grade	1	55.866	0.860	54.180	57.551	37.385	< 0.001
	2	53.213	1.625	50.028	56.397		
	3	47.087	2.810	41.580	52.594		
FIGO Stage	I	56.976	0.625	55.750	58.202	125.293	< 0.001
	II	49.358	3.425	42.645	56.071		
	III	47.736	3.167	41.528	53.943		
	IV	28.009	4.362	19.459	36.559		
LVSI	Negative	54.074	0.849	52.410	55.738	13.175	< 0.001
	Positive	50.697	2.677	45.449	55.944		
Myometrial invasion	< 1/2	60.131	0.993	58.186	62.077	17.670	< 0.001
	> 1/2	48.327	1.725	44.947	51.707		
Abdominal entry technique	Phannenstiel	55.210	1,000	53,249	57,170	12.659	0.005
	GAM	50.566	2.567	45.535	55,596		
	GAM + GUM	53.340	2.175	49.078	57,603		
	L/S	52.793	2.354	48.178	57.408		
Lymph node dissection	None	54.118	3.978	46.320	61.915	0.808	0.668
	Pelvic	50.534	5.116	40.507	60.561		
	Pelvic + Paraaortic	57.435	0.995	55.485	59.386		
Tumor size	< 2 cm	54.919	1.669	51.649	58.190	3.008	0.222
	2–4 cm	53.178	1.251	50.725	55.630		
	> 4 cm	55.972	1.581	52.874	59.070		
DFS							

Tumor size	< 2 cm	54.091	1.803	50.557	57.624	1.491	0.475
	2–4 cm	53.178	1.274	50.682	55.674		
	> 4 cm	55.745	1.577	52.654	58.837		
Grade	1	55.764	0.861	54.077	57.452	35.566	<0.001
	2	52.795	1.700	49.463	56.128		
	3	46.202	2.789	40.735	51.669		
FIGO Stage	I	56.835	0.641	55.580	58.091	111.772	0.001
	II	49.358	3.425	42.645	56.071		
	III	47.059	3.157	40.871	53.247		
	IV	28.009	4.362	19.459	36.559		
LVSI	Negative	53.839	0.854	52.166	55.513	9.800	0.002
	Positive	50.697	2.677	45.449	55.944		
Myometrial invasion	< 1/2	59.844	0.994	57.895	61.792	18.687	< 0.001
	> 1/2	47.952	1.722	44.577	51.328		
Abdominal entry technique	Phannenstiel	54.951	1.008	52.974	56.927	9.333	0.025
	GAM	50.566	2.567	45.535	55.596		
	GAM + GUM	53.177	2.164	48.935	57.418		
	L/S	52.114	2.393	47.425	56.804		
Lymph node dissection	None	54.118	3.978	46.320	61.915	1.336	0.513
	Pelvic	50.534	5.116	40.507	60.561		
	Pelvic + Paraaortik	56.988	0.997	55.034	58.942		

OS — overal survival, DFS — diseases-free survival, LVSI — lymphovascular space invasion, GAM — sub-umbilical median incision, GUM — median incision above the umbilical

Table 3. Univariate and multivariate analyses for survival in endometrial cancer patients

	UNIVARIATE			MULTIVARIATE		
	HR	**95% CI**	**P**	HR	95% CI	P
Age (years)	1.082	1.057–1.107	**< 0.001**	1.081	1.054–1.110	**< 0.001**
Hystologic type						
Endometrioid	Reference					
Nonendometriod	2.976	1.771–5.001	**< 0.001**	0.520	0.232–1.168	0.113
Tumor grade						
1	Reference					
2	1.845	0.984–3.456	0.056	1.398	0.712–2.741	0.330
3	4.612	2.697–7.886	**< 0.001**	3.569	1.572–8.100	**0.002**
LVSI						
Negative	Reference					
Positive	2.466	1.488–4.088	**< 0.001**	0.752	0.381–1.485	0.412
Tumor diameter						
< 2 cm	Reference					
2–4 cm	1.376	0.647–2.927	0.407			
> 4 cm	1.819	0.872–3.793	0.111			
Myometrial invasion						
Negative	Reference					
Positive	2.629	1.644–4.203	**< 0.001**	1.005	0.578–1.749	0.986
FIGO Stage						
1	Reference					
2	3.647	1.570–8.468	**0.003**	8.158	2.691–24.731	**< 0.001**
3	5.930	3.323–10.584	**< 0.000**	7.027	3.146–15.692	**< 0.001**
4	16.216	8.643–30.426	**< 0.000**	23.488	8.923–61.824	**< 0.001**
Lymph node dissection						
None	Reference					
Pelvic	1.836	0.303–11.143	0.509			
Pelvic + Paraaortic	1.884	0.461–7.700	0.378			
Cervıcal invasion						
Negative	Reference					
Positive	2.674	1.632–4.381	**< 0.001**	0.642	0.311–1.326	0.231
Peritoneal cytology						
Negative	Reference					
Positive	5.632	3.317–9.563	**< 0.001**	1.570	0.750–3.288	0.232
Adjuvan Terapy						
No	Reference					
Yes	1.767	1.043–2.993	**0.034**	0.471	0.242–0.917	**0.027**

Figure 1a. OS for all patients

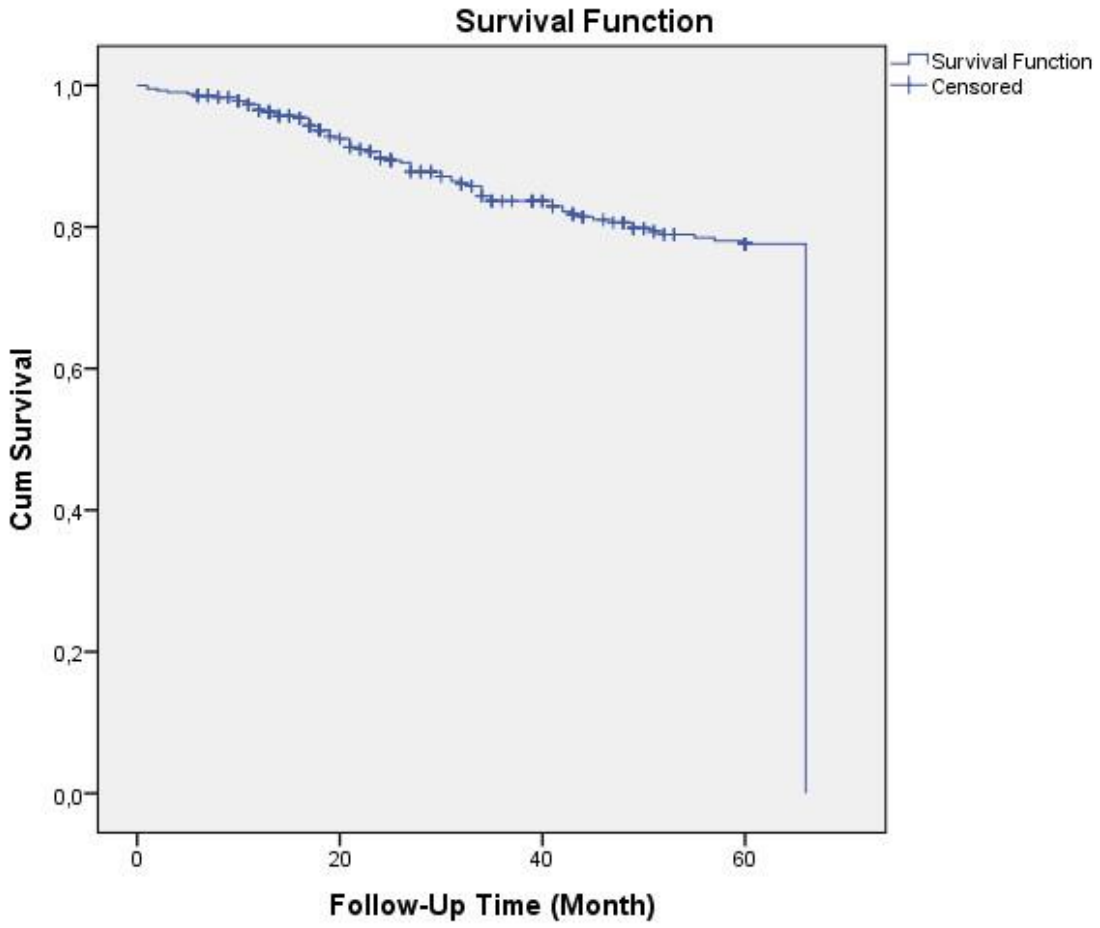


Figure 1b. DFS for patients without relapse

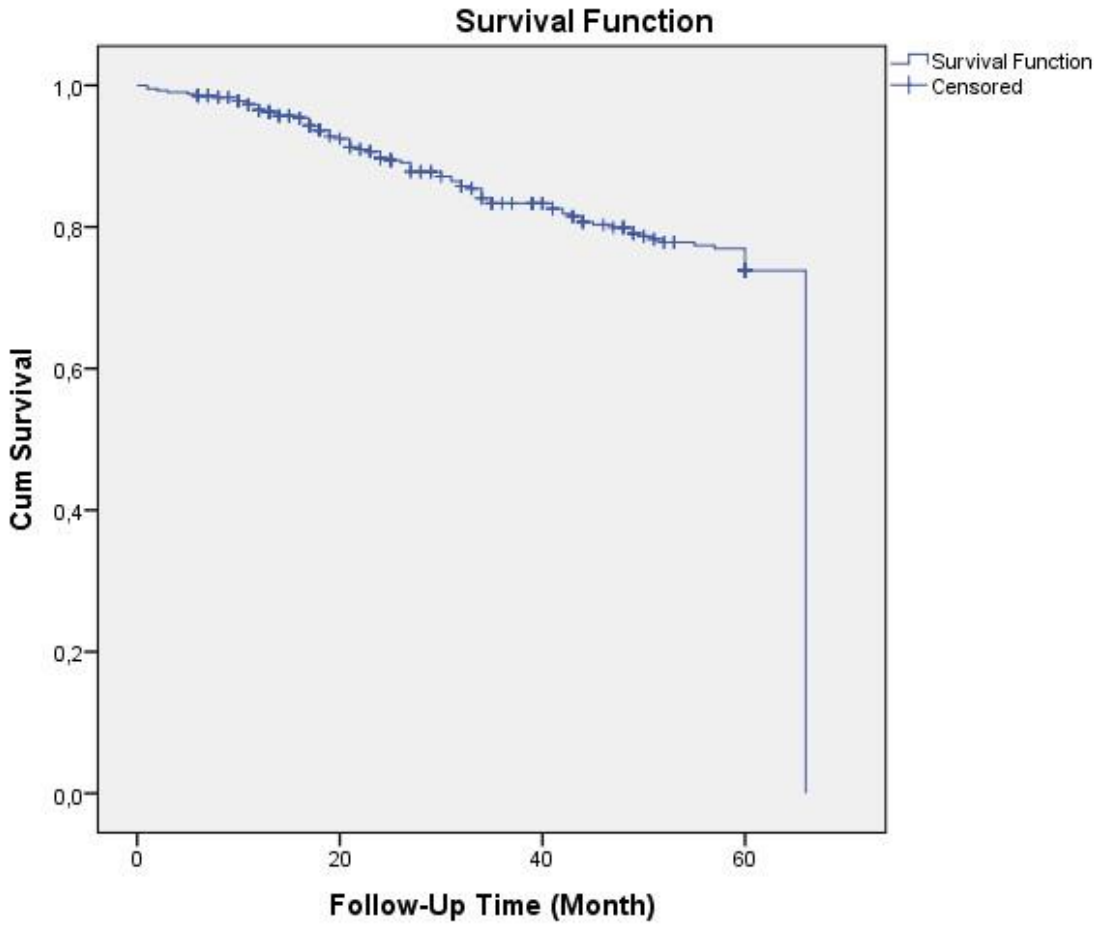


Figure 2a. OS according to histological types

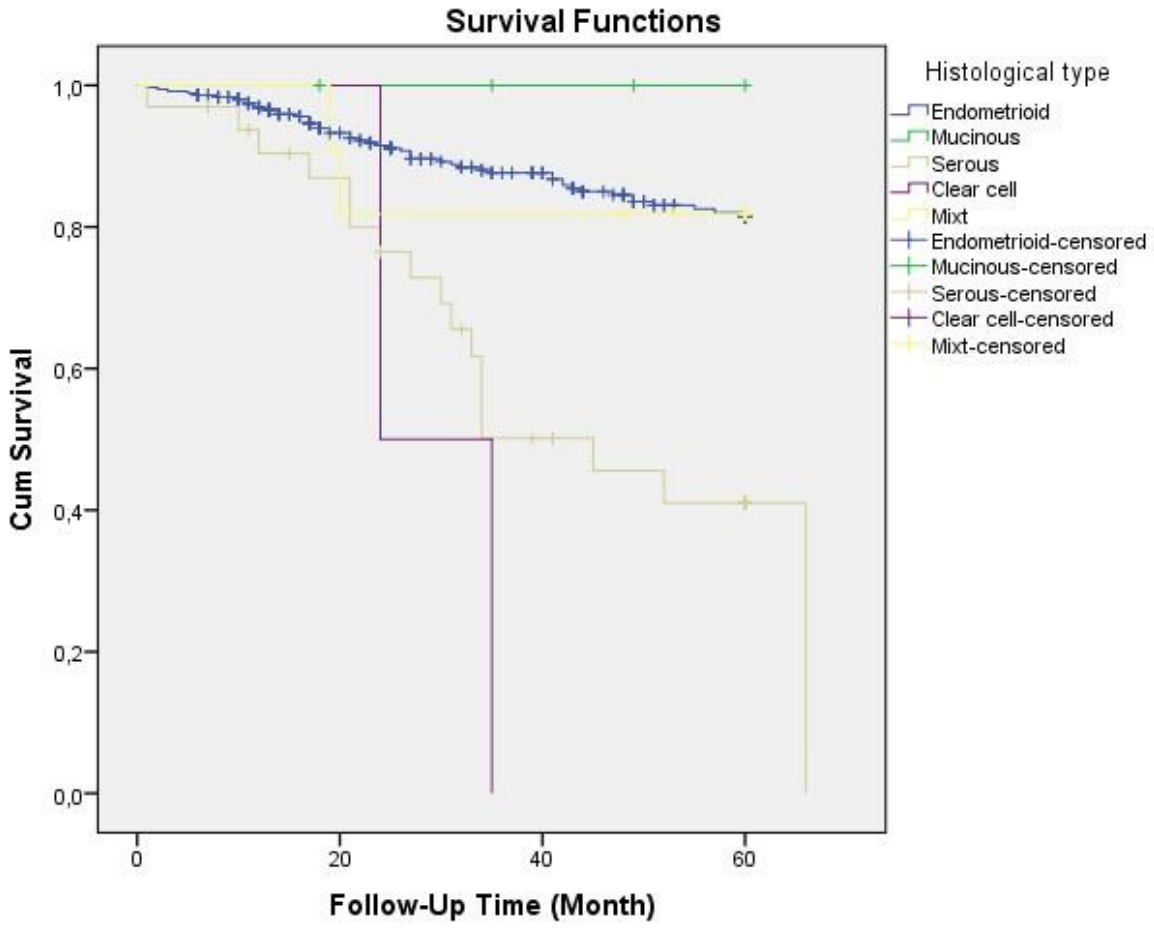


Figure 2b. DFS according to histological types

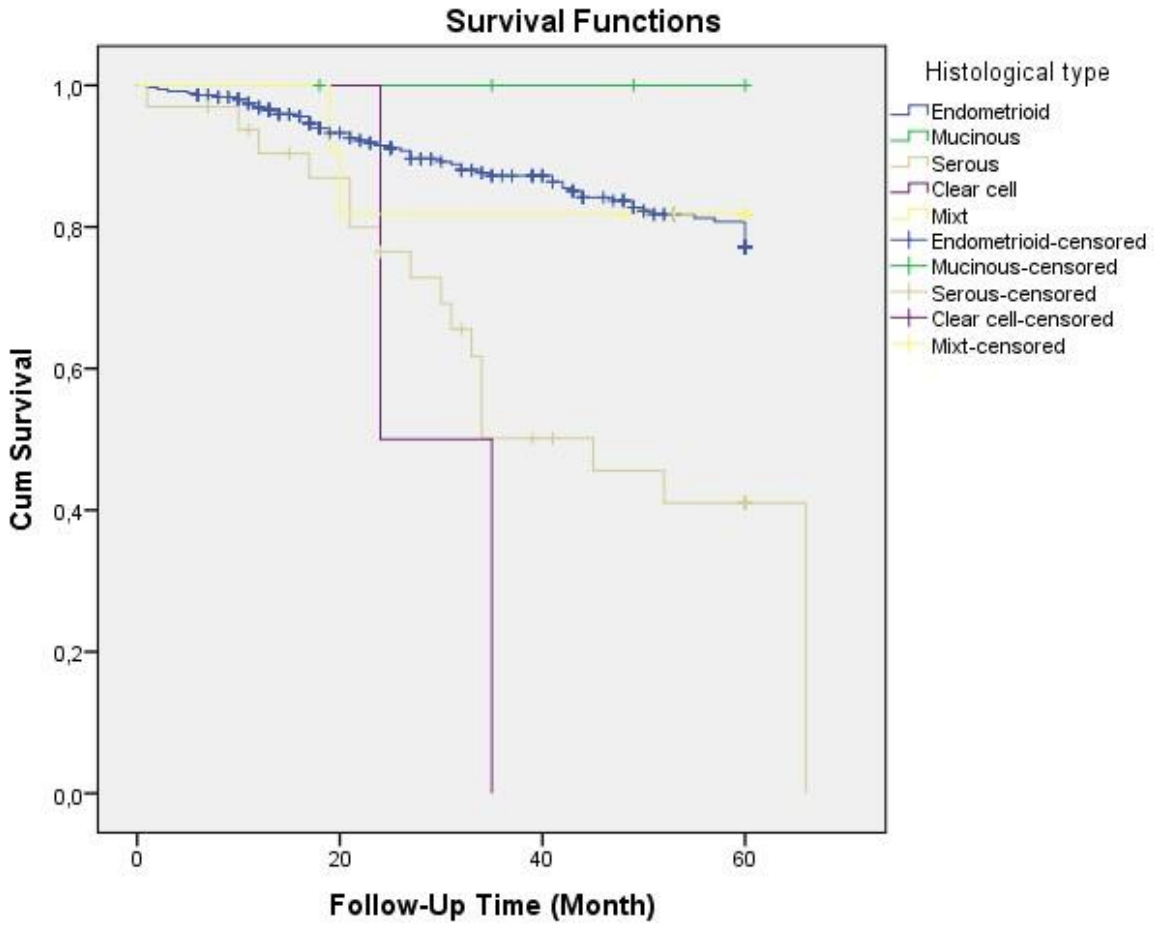


Figure 3a. OS for FIGO stage

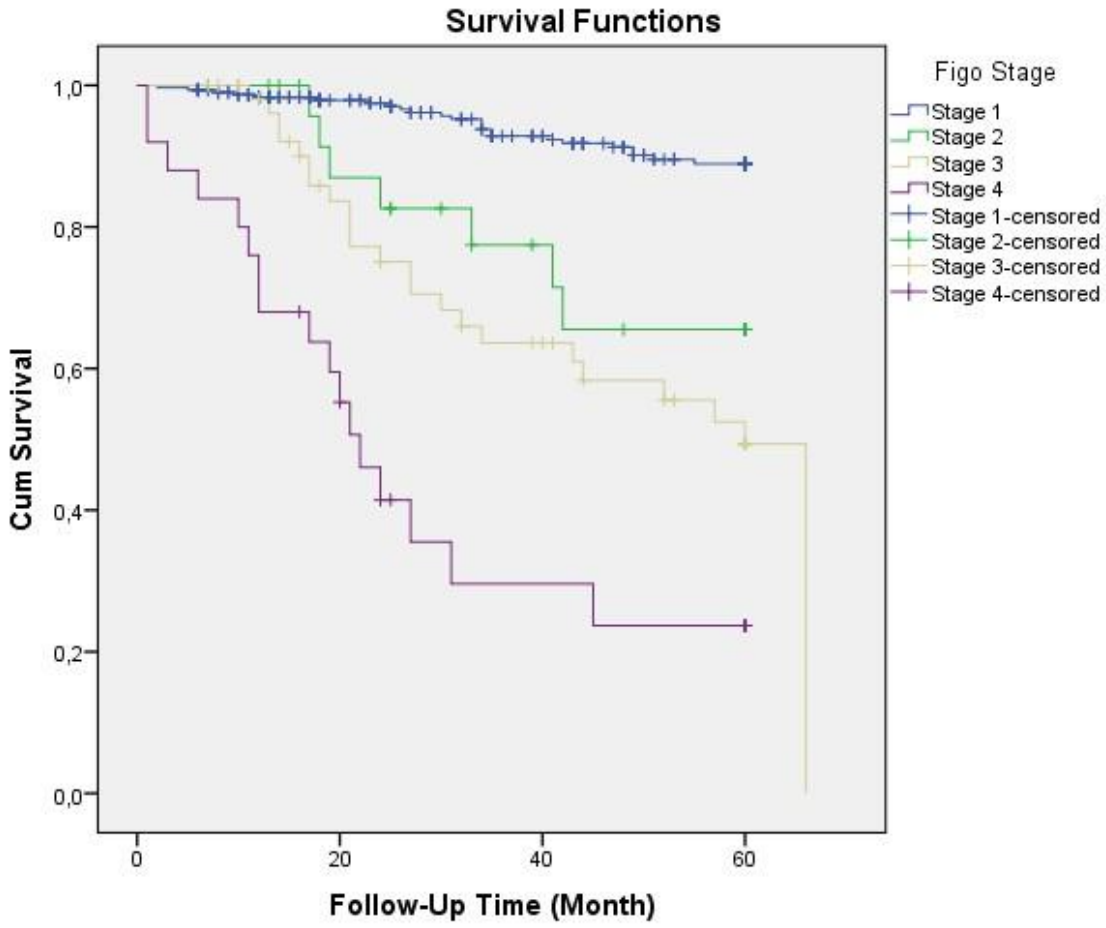


Figure 3b. DFS for FIGO stage

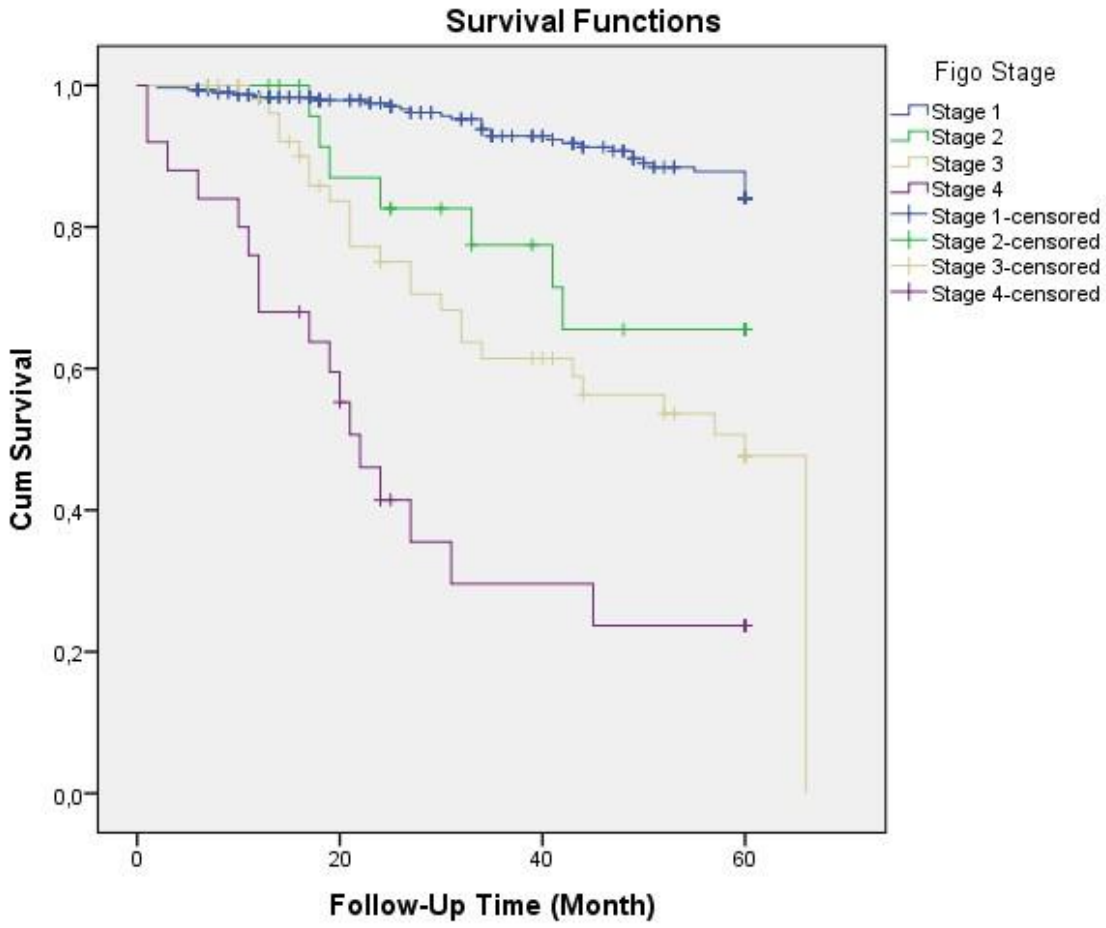


Figure 4a. OS for LVSI involvement

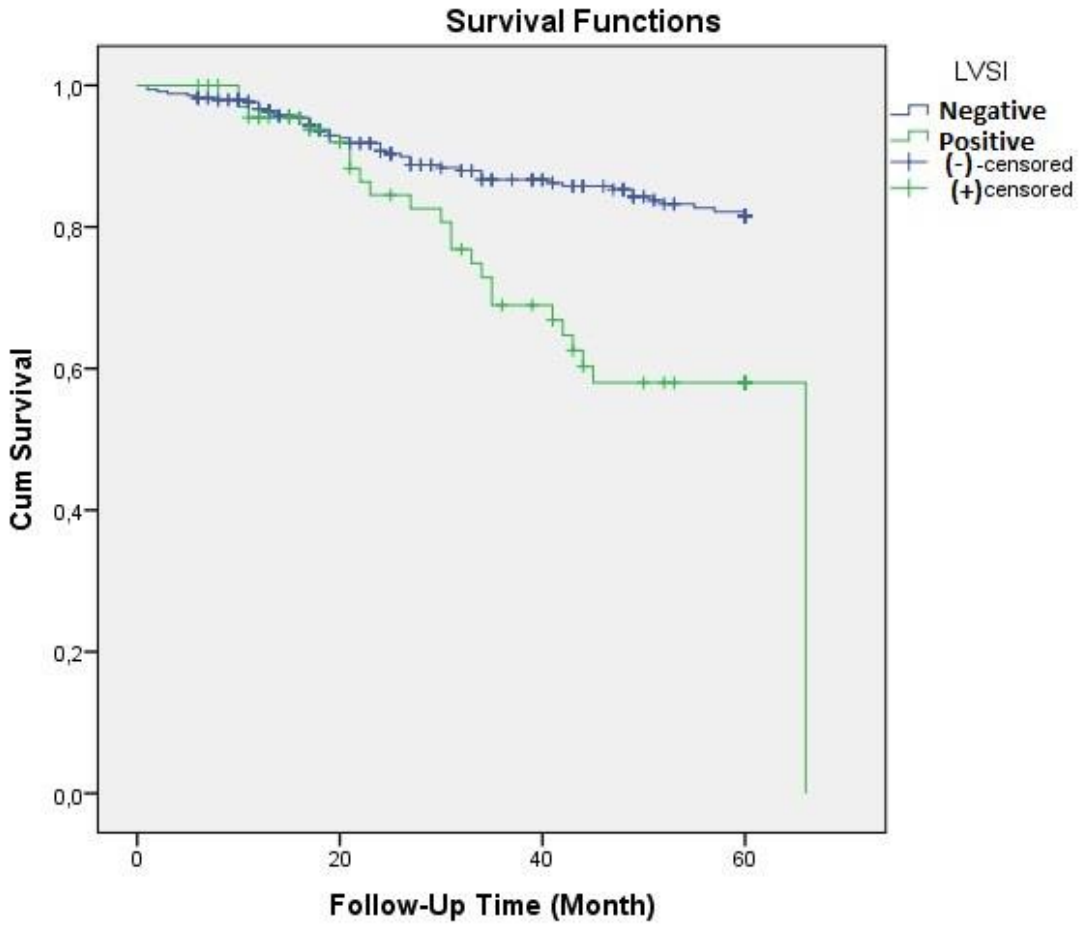


Figure 4b. DFS for LVSI involvement

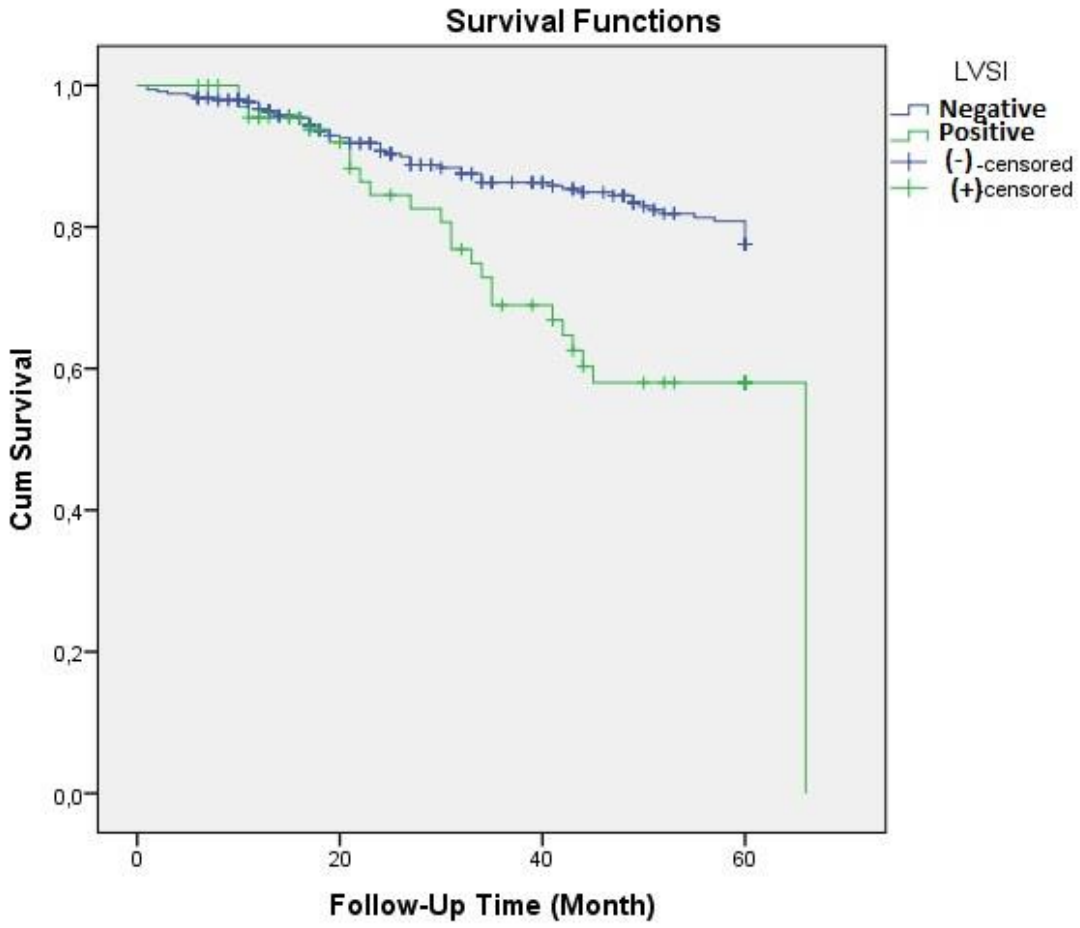


Figure 5a. OS for Grade

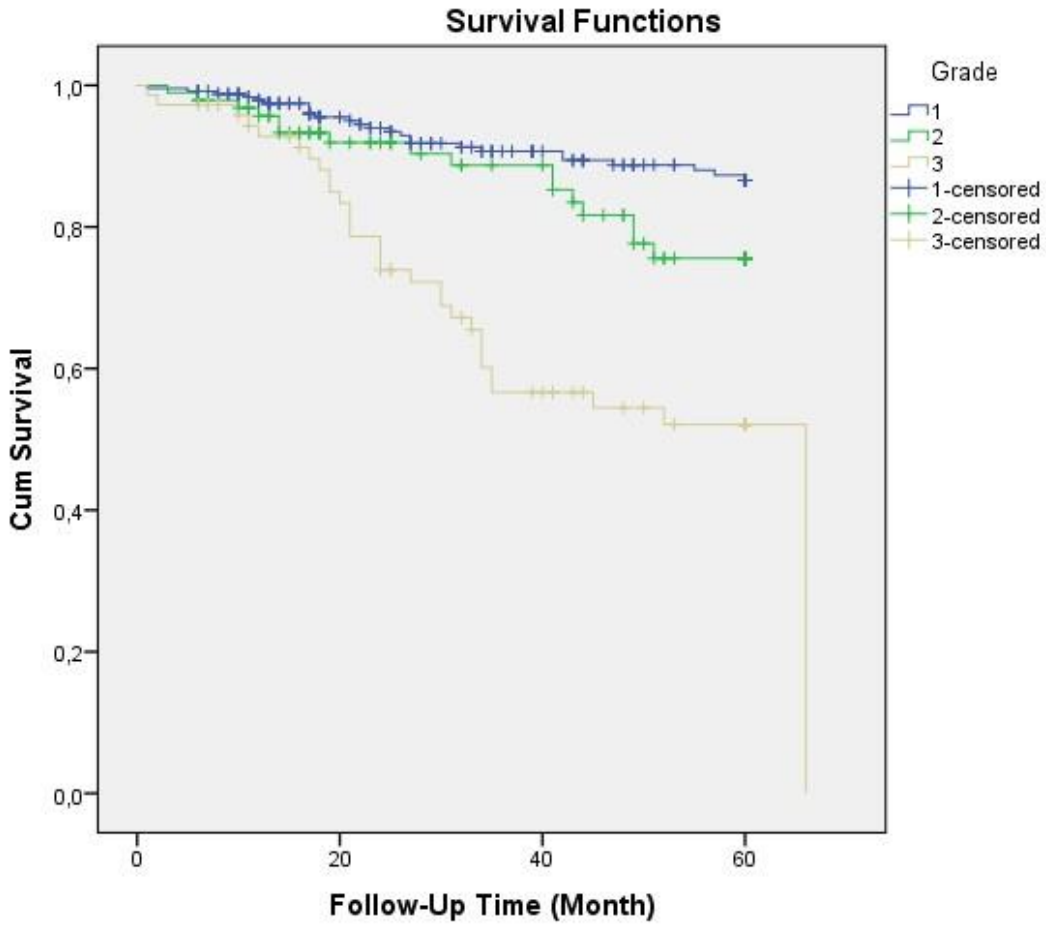


Figure 5b. DFS for Grade

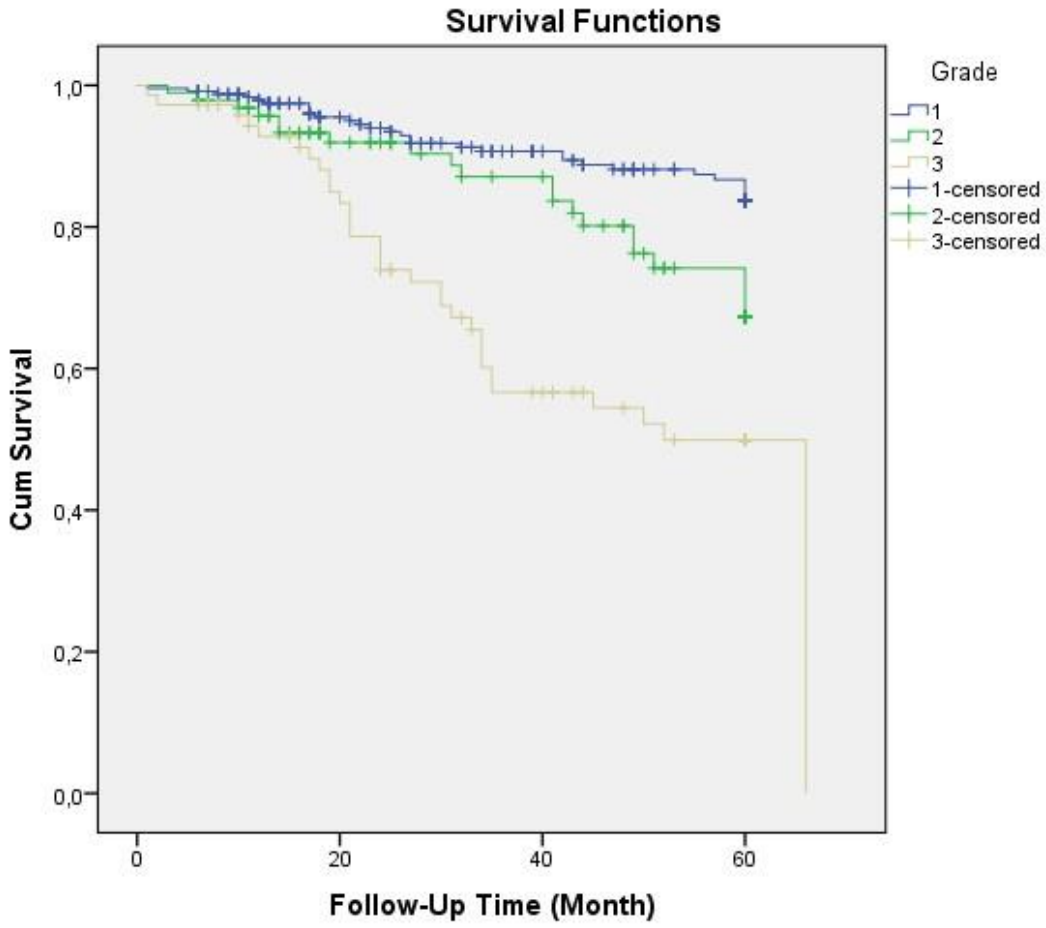


Figure 6a. OS for Myometrial invasion

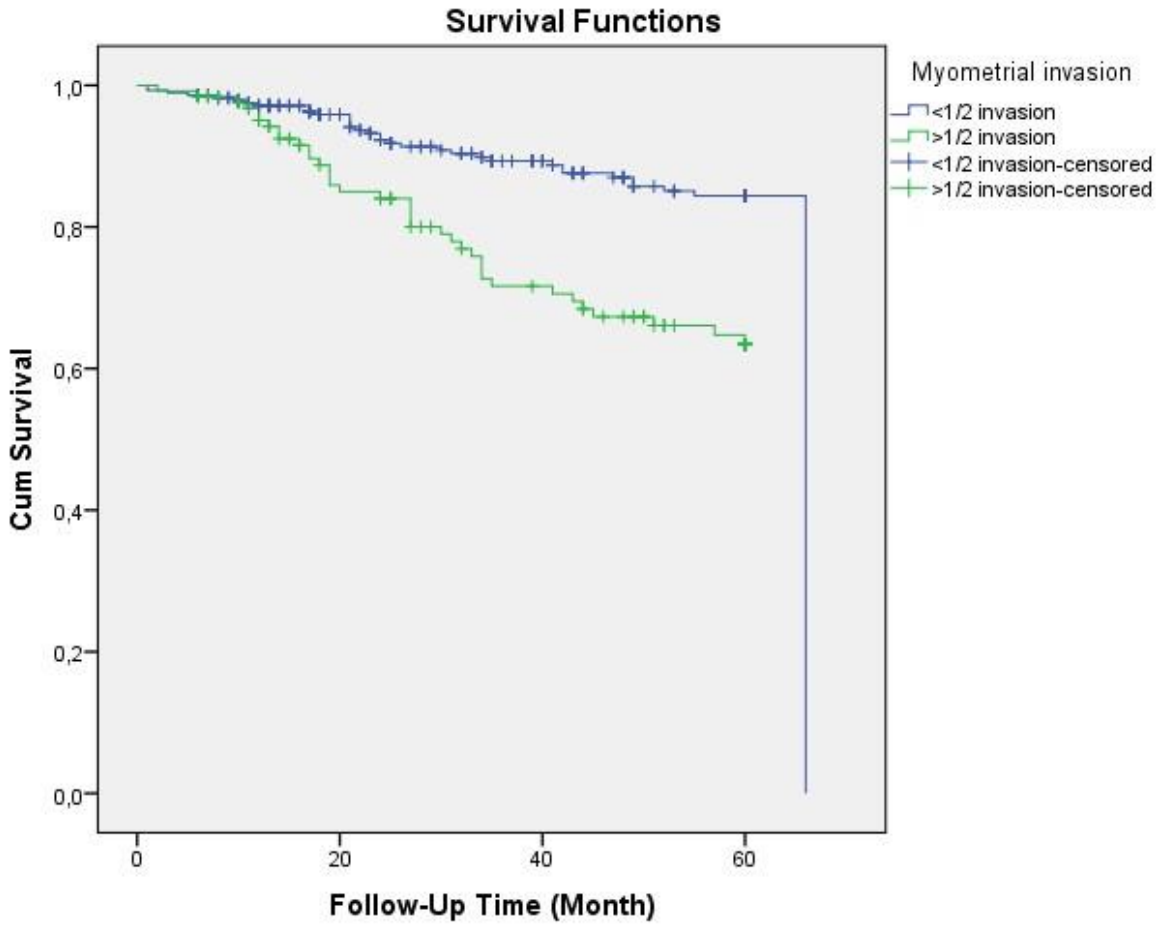


Figure 6b. DFS for Myometrial invasion

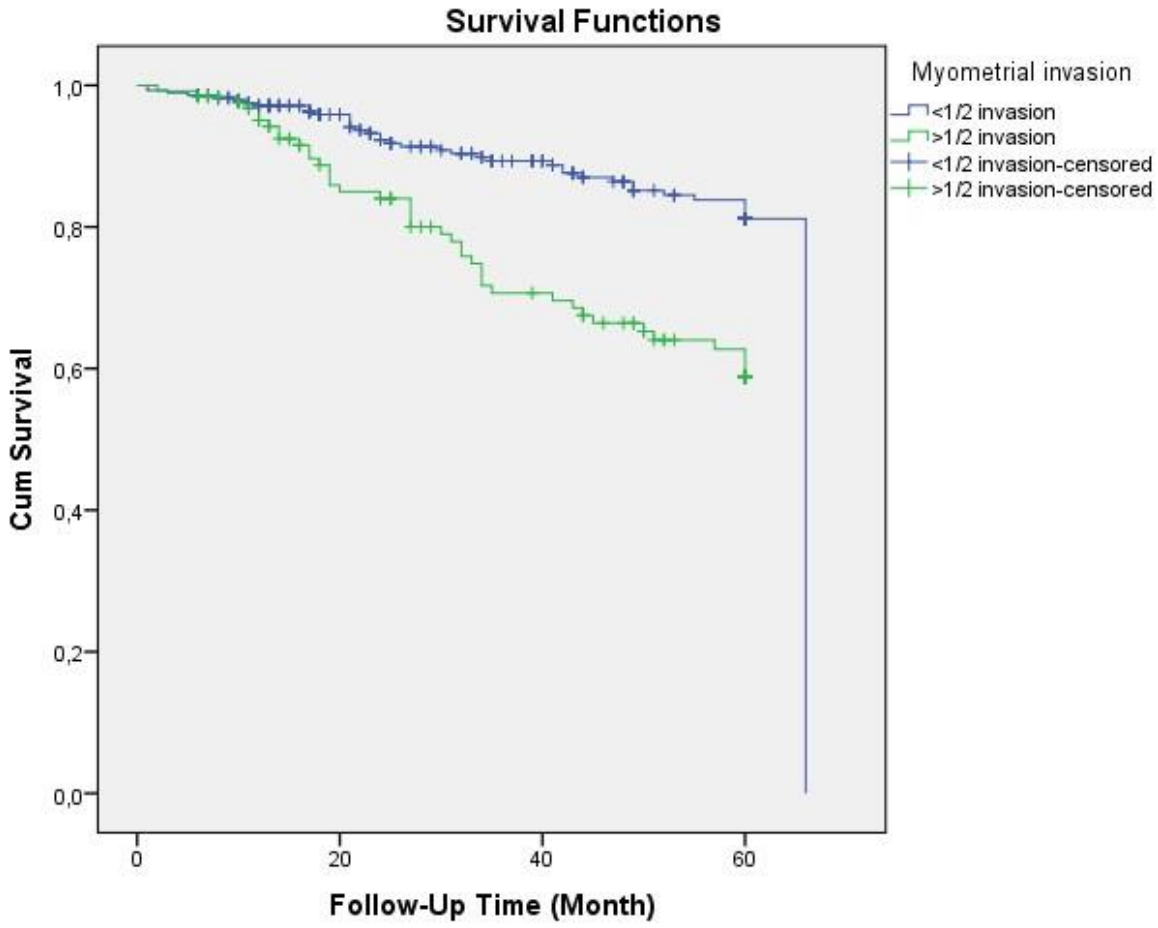


Figure 7a. OS for Cervical involvement

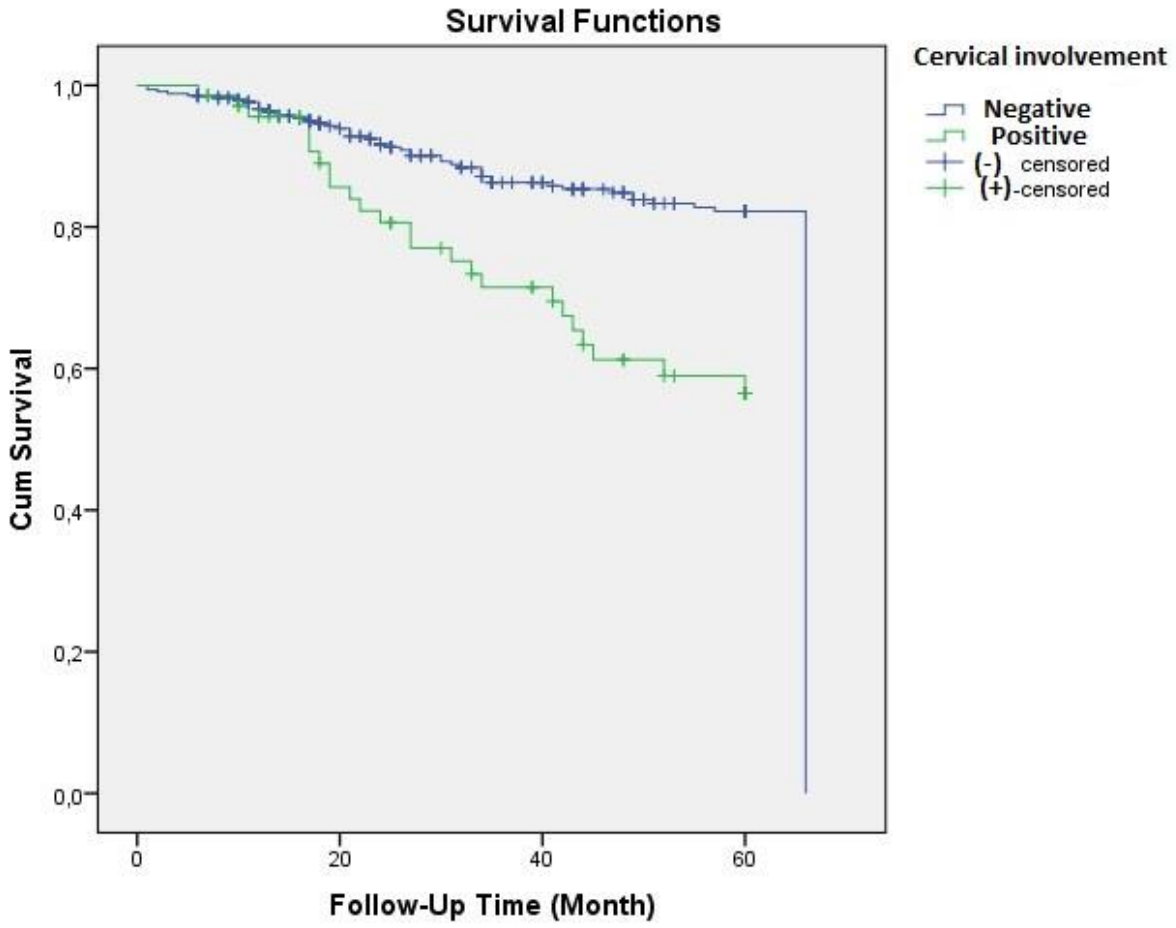
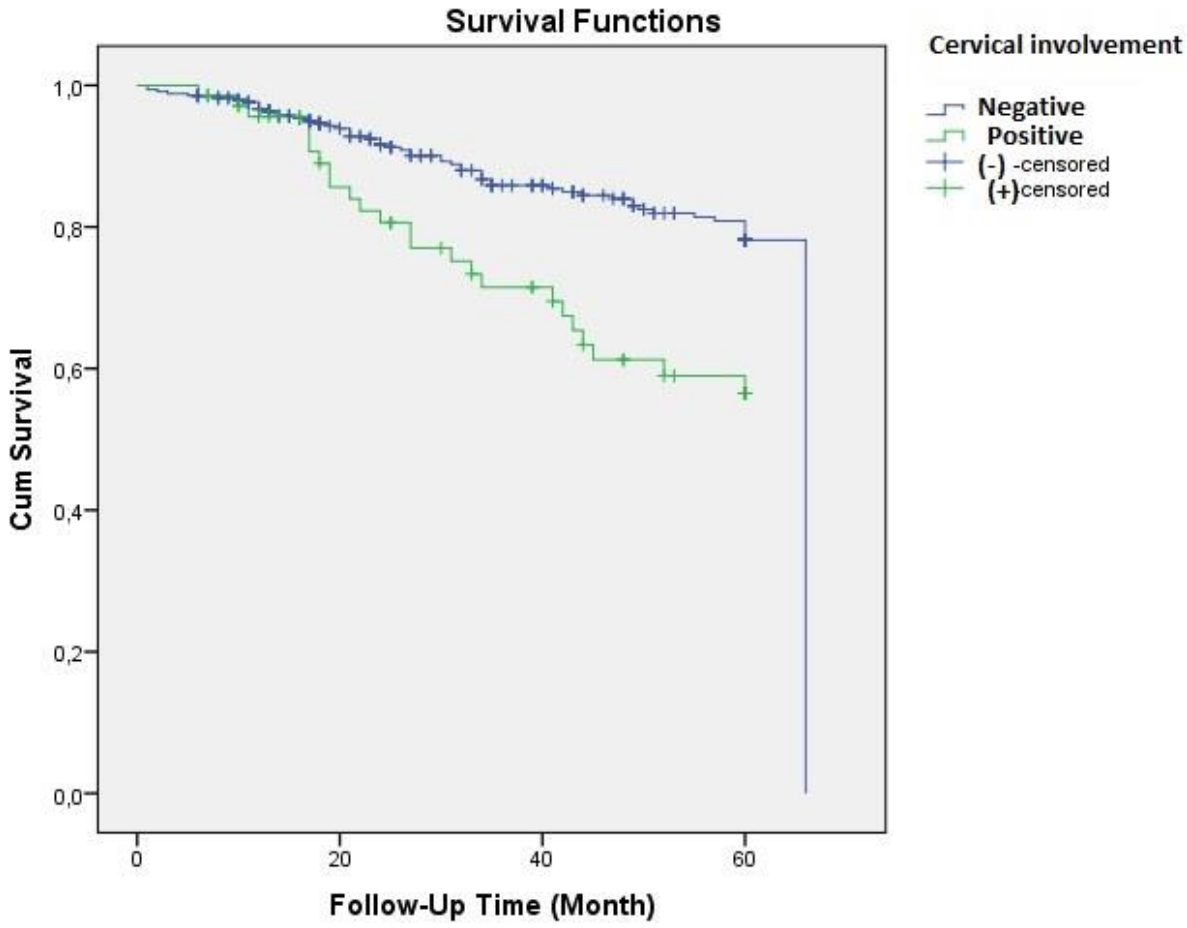


Figure 7b. DFS for Cervical involvement


Survival Functions
Cervical involvement
Negative
Positive
(-) -censored
(+)censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
20
40
60
Follow-Up Time (Month)