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Ferhat Çetin
M.D. Osmaniye State Hospital, Department of Gynecology Obstetrics. Osmaniye, Turkey

Mehmet Sait Bakır
M. D. Akdeniz University, Department of Gynecology Obstetrics, Division of Gynecologic Oncology. Antalya, Turkey

Özer Birge
M. D. Akdeniz University, Department of Gynecology Obstetrics, Division of Gynecologic Oncology. Antalya, Turkey

Aliye Nigar Serin
M.D. Karamanoglu Mehmet University, Department of Gynecology Obstetrics. Karaman, Turkey

Ilkan Kayar
M.D. Osmaniye State Hospital, Department of Gynecology Obstetrics. Osmaniye, Turkey

Mehmet Ozeren
M. D. Tepecik Research and Training Hospital, Department of Gynecology Obstetrics. İzmir, Turkey

Corresponding Author:
Ferhat Çetin
M.D. Osmaniye State Hospital, Department of Gynecology Obstetrics. Osmaniye, Turkey

The association between LVSI and lymph involvement in early-stage cervical cancer and its effect on survival

Ferhat Çetin, Mehmet Sait Bakır, Özer Birge, Aliye Nigar Serin, Ilkan Kayar and Mehmet Ozeren

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Abstract
Aim: We aimed to investigate the effect of LVSI and lymph involvement on survival in early stage cervical cancer.
Material and Methods: 223 patients with early stage (stage 1a1-1b2) cervical cancer were enrolled to the study retrospectively between 2000 and 2011. Patients were evaluated according to lymphovascular stromal invasion and lymph node status. In addition, patients were divided into groups according to the number of lymph nodes dissected and malignant lymph nodes, and the effects on survival were analyzed by univariate and multivariate analyzes.
Results: Systemic (lymphadenectomy) LND was performed in 168 patients (75.3%) while bilateral pelvic and paraaortic lymph nodes were sampled in 55 (24.6%) patients. While 67 (30%) patients had lymph node metastasis, 156 (70%) patients did not. While LVSI was not seen in 15 (6.7%) of the patients with lymph node involvement, it was seen in 52 (23.3%) (p: 0.001). Isolated paraaortic lymph was seen in 2 (0.8%) patients. The univariate analysis for PFS showed that the risk is highest in LVSI (HR: 4.11 (95% CI: 1.63-10.36 P: 0.003)) and pelvic lymph involvement (HR: 3.75 (95% CI: 1.66-8.45 p: 0.001)). However, in the univariate analysis for OS, when the number of malignant lymph nodes was above 4, it was found to be the highest risk factor with HR: 13.97 (95% CI: 4.74-41.14 p: 0.001). Lymph node metastasis was found to be an independent prognostic risk factor in the multivariate analysis for OS (HR: 2.52 (95% CI: 1.08-5.86 p: 0.031)).
Conclusion: As a conclusion, it has been demonstrated that LVSI is a prognostic risk factor that significantly affects both short and long-term survival, both indirectly and directly, the lymph involvement is of vital importance in early-stage cervical cancer and is an independent prognostic risk factor. In the surgical treatment of early-stage cervical cancer, maximum effort should be made and a great care taken for the number of lymph nodes to be dissected and it should be taken into consideration that as many lymph nodes should be removed as there is no specific number standard.

Keywords: early-stage cervical cancer, lymphovascular stromal invasion (LVSI), lymph node, survival

Introduction

According to 2018 GLOBOCAN data for cervical cancer, 569,847 new cases and 311,365 new deaths have been reported worldwide. It is in the fourth rank among female cancers with both a 6.6% incidence and 7.5% mortality rate [1]. With increasingly widespread screening programs worldwide, the rate of diagnosis of early-stage cervical cancer is increasing. The standard treatment in early stage cervical cancer is radical hysterectomy and lymphadenectomy or primary radiotherapy, and in patients who have a desire to have children, radical trachectomy and lymphadenectomy [2]. Patients with lymph node metastasis, lymphovascular area invasion, tumor diameter greater than 2 cm, deep stromal invasion, positive surgical margin, and parametrial involvement, known as pathological risk factors, have a higher risk of recurrence than those who are without [3, 4]. Therefore NCCN (National Comprehensive Cancer Network) guidelines recommend post-surgery adjuvant chemoradiotherapy to patients with high risk factors [5].

In patients with intermediate risk factors, treatment is planned according to Sedlis criteria [6]. Lymphovascular space invasion is defined as the identification of viable tumour cells within confined spaces lined by endothelial cells. The prognostic significance of LVSI (lymphovascular stromal invasion) in early-stage cervical cancer and its place in adjuvant treatment decision has been frequently emphasized in recent years. In many studies, LVSI has been accepted as an independent risk factor affecting prognosis and LN involvement has been associated with local

and distant metastasis [7, 8].

However, there are also studies stating that LVSI alone is not considered as a prognostic risk factor and it predicts lymph node metastasis by taking part in risk scoring modeling [9, 10].

While the risk of pelvic lymph involvement increases in patients with LVSI positive early-stage cervical cancer, 5-year disease-free survival decreases [11]. A very important prognostic risk factor is the lymphatic system involvement, which, as with other gynecological malignancies, indisputably affects treatment and survival. In cervical cancer, paracervical and parametrial nodes are first involved in the lymphatic system, then sequentially the obtrator, internal iliac, external iliac and paraaortic nodes. The lymph node involvement rates were found to be 25-30% in early stage cervical cancer [12]. In patients with lymph involvement, 5-year survival decreases from 90% to 50% (11). Since lymphatic system involvement is a high risk factor, it determines the adjuvant treatment. In addition to the presence of lymphatic spread, the number of nodes with lymphatic spread and the extent of spread also play an important role in determining the prognosis. It has been shown that the prognosis is quite poor when there is involvement in 3 or more pelvic lymph nodes and reduces survival as in paraaortic lymph node positivity. While 5-year survival is 16% in paraaortic node involvement, it is around 20% with positivity in 3 and / or more pelvic nodes without paraaortic involvement [12].

In our study, we aimed to discuss the relationship between two important prognostic risk factors such as LVSI and lymph involvement in early stage cervical cancer and their effects on survival in the light of the literature.

Materials and Methods

The study included 223 cases who applied to Ege Maternity and Gynecology Training and Research Hospital between 2000-2011 and who were treated surgically for early stage cervical cancer or had surgical procedures in external centers and applied to our hospital together with information and pathology reports regarding the procedure. Data for each case were obtained from patient records, surgery and pathology reports. Cases receiving pre-operative neoadjuvant or primary chemoradiotherapy and with a second tumor were excluded. In addition, patients whose follow-up files were missing and who did not have regular follow-up were excluded from the study. All patients were staged by the FIGO 2009 staging system. All cases were evaluated by bimanual gynecological examination before the operation and were subjected to clinical staging. Cases that could not be evaluated adequately were examined under general anesthesia. Pelvic CT and pelvic MR radiological imaging methods were used in cases where parametrial evaluation was insufficient in bimanual examination. Tumor size was recorded during the preoperative staging during the examination. No patients operated on by laparoscopy because of laparoscopic energy modalities are not common and we do not have enough experience. All patients underwent laparotomy. Laparotomy, radical hysterectomy (type II, type III) and bilateral pelvic and para-aortic lymphadenectomy were performed to almost all patients by specialists in gynecological oncology. Retroperitoneal spaces were created following exploration of the abdomen through incisions below and above the umbilicus. Any suspect or bulky lymph node was dissected and sent to pathology for frozen section. Otherwise, the procedure was performed from the circumflex iliac vein to the middle part of the common iliac artery, including the lymph node and surrounding adipose tissues, lymph nodes in the obturator space, whereas in the paraaortic LND, lymph node and surrounding adipose tissues were dissected from the common iliac artery in the cephalic direction to the vena cava inferior and the aortic anterior face below and above the inferior mesenteric artery at the level of left renal vein. The uterine artery, ventral, lateral and dorsal parametrium were dissected based on the radicality and dissected with 1-2 cm of proximal vagina. In this study, we considered the tumor size from pathology reports as a value. Paraffin blocks of tumor tissue were stained with hemotoxylin-eosin and evaluated.

Statistical Package for the Social Sciences (spss) 22 was used to analyze the data. In the analysis of quantitative data, compliance with the normal distribution was examined using kolmogrov simirnov test and the homogeneity by Levene testing; the parametric methods were used in the analysis of data with normal distribution, and non-parametric methods were used in the analysis of variables that did not show normal distribution. Quantitative data are expressed as mean, std (standart deviation), median, minimum-maxium values in the tables. Categorical data are expressed in n (count) and percentages (%). Among the parametric methods, independent t test was used in binary comparison of independent groups. Among the non-parametric methods, mann whitney u test was used in binary comparison of independent groups. Pearson chi-square, chi-square, continuity correction and fisher exact tests were used to compare categorical data. Linearity between numerical data was evaluated based on a pearson or spearman correlation according to the normal distribution. Kaplan-meier (product limit method) and life table -Log Rank (Mantel-Cox) analysis were used to examine the effects of factors on life span. Univariate or multivariate cox proportional hazards model was used to analyze the effects of various prognostic factors, alone or combined, on survival. The data were analyzed at a 95% confidence level, and a p value less than 0.05 was considered significant.

Results

Descriptive Findings

The median age of enrolled patients was 46 (min. 29 - max. 76). The median age of patients in the non-LVSI group was 45 (min: 29 - max: 76), while the median age of those with involvement was 48 (min: 34 - max: 76) (p: 0.005). Systemic LND was performed in 168 patients (75.3%) while bilateral pelvic and paraaortic lymph nodes were sampled in 55 (24.6%) patients. The median follow-up time of the patients was 80 months (min: 9-max: 138). During this period, 24 patients had relapses (10.8%) and 29 patients died (13%). Regarding the complications, ureteral injuries were the most common with 12 patients (5.4%), followed by a neurogenic bladder with 3.1%. There were 10 (4.5%) patients in stage 1A1, 18 (8.1%) in 1A2, 133 (59.6%) in 1B1, and 62 (27.8%) in 1B2. While there was no patient with LVSI in stage 1A1, LVSI involvement was found to be 22.4% in stage 1B1, and it was observed that LVSI involvement increased as the stage increased (p: 0.001) The clinical and pathological characteristics of the patients are shown in table-1. The incidence of LVSI was 7.2% when the tumor size was $\leq$ 2cm and 36.8% with tumors >2 cm in diameter (p: 0.001). Recurrence occurred in 6 (6.7%) and death in 8 (3.1%) of LVSI negative patients, whereas 18 (8.1%) relapses and 21 (9.4%) deaths occurred in LVSI positive patients (respectively. p: 0.001, p: 0.001). While 67 (30%) patients had lymph node metastasis, 156 (70%) patients did not. While LVSI was not seen in 15 (6.7%) of the patients with lymph node involvement, it was seen in 52 (23.3%) (p: 0.001). LVSI positivity increased the rate of pelvic lymph involvement from 5.8% to 23.3% (p: 0.001).

Considering the paraaortic lymph involvement, 7 were LVSI negative and 4 were LVSI positive (p: 0.603). Isolated paraaortic lymph was seen in 2 (0.8%) patients. When dissected lymph nodes were divided into 3 groups between 1-20, 21-40 and> 40, there was no significant relationship with LVSI (p: 0.294). However, when the number of dissected malignant lymph nodes was examined, 1-4 lymph nodes were observed in 4.9% in the non-LVSI group, while it was 20.6% in the LVSI group (p: 0.001). There was a weak to moderate but significant correlation between the number of pelvic lymph nodes and the number of paraaortic lymph nodes (spearman p: 0.345 p: 0.001).

Survey Analysis

When patients were divided into two groups, over and under 50, there was a significant relationship in both PFS and OS (p: 0.003, p: 0.001, respectively). While the mean PFS and OS was 131 months in patients without LVSI, it was 114 months in patients with LVSI (p: 0.001, p: 0.001, respectively) (table-2). While the mean PFS was 130 months in the group without lymph node metastasis, it was 111 months in the group with metastasis (p: 0.001) (figure 1(A, B, C, D)). The situation was similar for OS in terms of lymph node involvement (p: 0.001). No significant relationship was detected in PFS in terms of stage and tumor diameter (p: 0.960, p: 0.140, respectively). While detecting pelvic lymph metastasis contributed badly to both PFS and OS (p: 0.001, p: 0.001, respectively), paraaortic lymph node involvement was found to be significant only in OS (p: 0.024). As the number of dissected malignant lymph nodes increased, both PFS and OS decreased (p: 0.001, p: 0.001, respectively). Age was found to be an independent prognostic risk factor in univariate and multivariate analyzes for both PFS and OS (HR: 2.35 (1.02-5.43 p: 0.044, HR: 2.48 (1.6-5.31) p: 0.019, respectively). The univariate analysis for PFS showed that the risk is highest in LVSI (HR: 4.11 (95% CI: 1.63-10.36 P: 0.003)) and pelvic lymph involvement (HR: 3.75 (95% CI: 1.66-8.45 p: 0.001)). However, in the univariate analysis for OS, when the number of malignant lymph nodes was above 4, it was found to be the highest risk factor with HR: 13.97 (95% CI: 4.74-41.14 p: 0.001). The examination by univariate analysis between LVSI and OS showed a HR of 3.52 (95% CI: 1.55-7.96 p: 0.002), but LVSI was not found to be significant in multivariate analysis. Due to multicolinearity, pelvic and paraaortic lymph node metastasis were not included in the multivariate analysis. Lymph node metastasis was found to be an independent prognostic risk factor in the multivariate analysis for OS (HR: 2.52 (95% CI: 1.08-5.86 p: 0.05) (Table 3).

Discussion

The occurrence of tumor recurrence and metastasis is mainly due to the proliferative tumoral cells invading the lymphatic ducts and capillaries, and tumor cells migrating into these vessels cause metastasis by creating a thrombus [13]. Therefore, LVSI is a process that should occur in cervical cancer metastasis. Although it has a critical role, there are opposing results in the literature about LVSI being a prognostic risk factor. For example; Singh *et al*. [14] stated that LVSI is an independent risk factor affecting both PFS and OS, but Wang *et al*. [15] stated that although LVSI is a risk factor, there is no direct evidence of LVSI being a prognostic risk factor. Because it can be thought that LVSI cannot act independently from lymph involvement. Despite this controversial situation, postoperative LVSI is within the Sedlis criteria [6] and adjuvant treatment is planned accordingly. It is known that the occurrence of LVSI increases as the tumor volume increases [16]. In our study, when the tumor was below 2 cm, the LVSI rate was 7.2%, when it was above 2 cm, it was statistically significant with 36.8%.

In addition, in our study the occurrence of LVSI increased significantly as the stage increased. In a review by Enrica *et al*., LVSI was a cornerstone in the treatment plan of patients with early stage ≥2 cm cervical cancer who want to have a child, and they emphasized that, after determining the lymph node status in patients with negative lVSI, simple trachelectomy or conization can be performed with both low recurrence and low positive surgical margin rates [17]. There is a significant correlation between lymph involvement and LVSI. In a study performed by Sakuragi *et al*., 4.2% of patients without LVSI had lymph node involvement, while 43.3% of those with LVSI had lymph involvement [18]. The distance between LVSI and primary tumor area has also been investigated in the literature and the appearance of LVSI at least 10 mm from the tumor is called satellite LVSI. In the study by Herr *et al*., it was shown that the occurrence of LVSI at least 10 mm from the tumor is a more important prognostic risk factor than being within the tumor and that satellite LVSI is associated with lower PFS and OS [2]. In another study, all patients with lymph node metastases were found to have satellite LVSI [19]. It may also be beneficial for the pathologist to inform the clinician about this issue while looking at LVSI. In our study, lymph involvement was seen in 15 (6.7%) patients without LVSI, while 52 (23.3%) patients with LVSI had lymph involvement (p: 0.001). There was a significant increase in pelvic lymph node involvement in particular. In our own study, we found that the presence of LVSI is also effective in the number of malignant lymph nodes. In a recent retrospective cohort study, 80 of 1523 patients with early-stage cervical cancer experienced recurrence, and a significant reduction in survival was observed in those with LVSI [20]. With an increase in lymph node involvement, it was observed that our relapse rates were approximately 3 times higher in the LVSI group (2.7%, 8.1% p: 0.001, respectively). While the mean PFS was 131.9 months in the group without LVSI, it was 114.8 months in the LVSI group (p: 0.001). Considering its effect on OS, it was 131.2 months in the group without LVSI, while it was 114.1 months in the LVSI group (p: 0.001). In our univariate analysis, LVSI was found to be an important prognostic factor for PFS (HR: 4.11 (95% CI: 1.63-10.3, p: 0.003)), while it was found to be an independent risk factor at borderline significance level (p: 0.060) in the multivariate analysis. We found that LVSI is not an independent prognostic risk factor for overall survival, but it negatively affects survival (HR: 3.52 (95% CI: 1.55-7.96 p: 0.002)).

The presence of tumor at the surgical margin, the presence of parametrial invasion, and the presence of metastasis in the pelvic-paraaortic lymph node after the surgical treatment of early-stage cervical cancer were defined as high risk factors [21]. In the presence of these, NCCN recommends adjuvant chemoradiotherapy. Based on the indisputable importance of lymph status, FIGO (International Federation of Gynecology and Obstetrics) revised the cervical ca staging in 2018, adding pelvic and paraaortic lymph involvement. This new staging also suggested the radiological (eg PET, CT, MRI) or histologic detection of lymph status [22].

In the literature, PET-CT (Positron Emission Tomography) reveals lymph nodes above 10 mm better than both MRI (Magnetic Resonance Imaging) and CT (Computerize Tomography) with 4-15% false negativity rate. Since false positivity is observed especially when the incidence of tuberculosis and HIV are high, these conditions should be

considered [23]. In addition, revealing lymph status surgically by either laparoscopy or laparotomy has a better prognosis than radiological exclusion and is accepted as the gold standard [24]. In the literature, pelvic lymph involvement is seen in about 20-30% of early-stage cervical cancer [25], and paraaortic lymph involvement occurs between 1.6% and 24% [26]. The results of our study show that 29.1% of pelvic lymph involvement and 4.9% of paraaortic lymph node involvement were compatible with the literature.

At the same time, 80% of those with pelvic lymph node involvement in our data had LVSI positive. In our two patients, we have detected isolated paraaortic lymph involvement (0.8%) and this finding is consistent with the 1-4% reported in previous studies [26, 27].

As mentioned before, 5-year survival in patients with lymph involvement decreases from 90% to 50% [11]. In our study, while the mean PFS was 130 months in the group without lymph involvement, it was 124 months in the group with involvement (p: 0.001). For OS, the average survival was 129 months in patients without lymph node involvement and 108 months in patients with involvement (p: 0.001). Both pelvic lymph node involvement and paraaortic lymph node involvement were found to have a significantly negative impact on long-term survival (p: 0.001, p: 0.024, respectively). In our univariate analysis, we found that lymph node involvement was a prognostic factor that had a negative effect on PFS (HR: 3.23 (95% CI: 1.54-6.78)). Again in the evaluation of OS, lymph node involvement was found to have an adverse effect (HR: 4.01 (95% CI: 1.89-8.49). In addition, the multivariate analysis for overall survival revealed that lymph status was an independent prognostic risk factor (HR: 2.52 (95% CI: 1.08-5.86). While the net effect of lymph node metastasis on survival is obvious, the contribution of the number of dissected lymph nodes or the number of malignant lymph nodes to survival is controversial. Pieterse *et al*. [28] stated that removing high numbers of lymph nodes in patients with lymph node metastasis would contribute positively to survival. In another publication, it was emphasized that in patients without lymph node involvement, dissection of a large number of lymph nodes with the necessary care has been contributed to survival [29]. In another study, it was emphasized that as the number of dissected metastatic lymph nodes increased, PFS and OS decreased but the number of dissected lymph nodes was not associated with survival [30]. In another study, they stated that the survival was better in patients who had more than 40 lymph nodes dissected than those with less than 40 [31].

If the number of dissected malignant lymph nodes is one, it has been reported to be the survival is the same as that of the patient without lymph node metastasis [32]. Because the lymph node involvement is sequential in cervical cancer, if there is only one lymph node involvement, it is assumed that the tumor remains stable there. Therefore the systemic lymphadenectomy should be performed with great care. In our study, no significant correlation was found between LVSI and the number of dissected lymph nodes (p: 0.294). However, there was a significant correlation between LVSI positivity and the number of malignant lymph nodes (p: 0.001). In our examination, we found that as the number of dissected lymph nodes increased, it had a significant effect on both PFS and OS (p: 0.004, p: 0.001, respectively). PFS was 116 months on average when the number of malignant lymph node detected was 1-4, and 24 months on average when the number was more than 4 (p: 0.001). In addition, when the number of dissected malignant lymph node was 1 to 4, the mean OS was 115 months, and when the number was more than 4, the OS was 45 months (p: 0.001). In the univariate analysis, dissection of more than 4 lymph nodes posed a 9.46 times greater risk in PFS and 13.97 times in OS (p: 0.001, p: 0.001, respectively) which were statistically significant.

Regarding the limitations of our study, due to its retrospective design, naturally, bias can be seen in the selection of patients. The number of patients could be higher for paraaortic lymph node evaluation. Standardization among the surgeries was not known since all patients were not operated at a single center.

As a conclusion, it has been demonstrated that LVSI is a prognostic risk factor that significantly affects both short and long-term survival, both indirectly and directly, but not an independent prognostic risk factor, the lymph involvement is of vital importance in early-stage cervical cancer and is an independent prognostic risk factor.

Table 1: Clinical and pathological characteristics of cases

		LVSI + n: 98	**LVSI - n: 125**	**Total n: 223**	***p value***
Age	≤50 >50	56 (25.1%) 42 (18.8%)	96 (43%) 29 (13%)	152 (68.2%) 71 (31.8%)	0,002
Stage	Stage 1A1 Stage 1A2 Stage 1B1 Stage 1B2	0 2 (0.9%) 50 (22.4%) 46 (20.6%)	10 (4.5%) 16 (7.2%) 83 (37.2%) 16 (7.2%)	10 (4.5%) 18 (8.1%) 133 (59.6%) 62 (27.8%)	0.001
Tumour diameter	≤2cm >2cm	16 (7.2%) 82 (36.8%)	59 (26.5%) 66 (29.6%)	75 (33.6%) 148 (66.4%)	0.001
Death	Yes No	21 (9.4%) 77 (34.5%)	8 (3.4%) 117 (52.5%)	29 (13%) 194 (87%)	0.001
Lymph status	Yes No	52 (23.3%) 46 (20.6%)	15 (6.7%) 110 (49.3%)	67 (30%) 156 (70%)	0.001
Recurrence status	Yes No	18 (8.1%) 80 (35.9%)	6 (2.7%) 119 (53.4%)	24 (10.8%) 199 (89.2%)	0.001
Pelvic Lymph Node status	Yes No	52 (23.3%) 46 (20.6%)	13 (5.8%) 112 (50.2%)	65 (29.1%) 158 (70.9%)	0,001
Paraortic Lymph status	Yes No	4 (1.8%) 94 (42.2%)	7 (3.1%) 118 (52.9%)	11 (4.9%) 212 (95.1%)	0,603
Number of lymph nodes	1-20 21-40 >40	10 (4.5%) 52 (23.3%) 36 (16.1%)	22 (9.9%) 61 (27.4%) 42 (18.8%)	32 (14.3%) 113 (50.7%) 78 (35%)	0.294
Number of malignant lymph nodes	0	46 (20.6%)	110 (49.3%)	156 (70%)	0.001

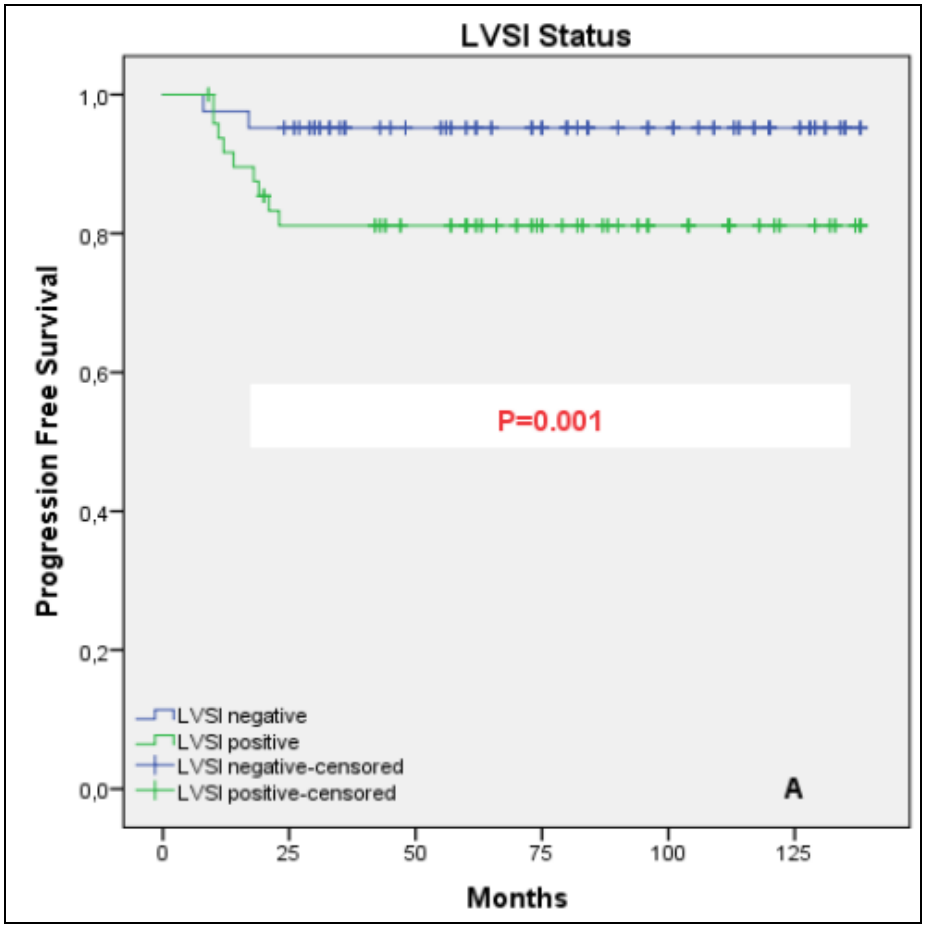
	1-4 >4	46 (20.6%) 6 (2.7%)	11 (4.9%) 4 (1.8%)	57 (25.6%) 10 (4.5%)	

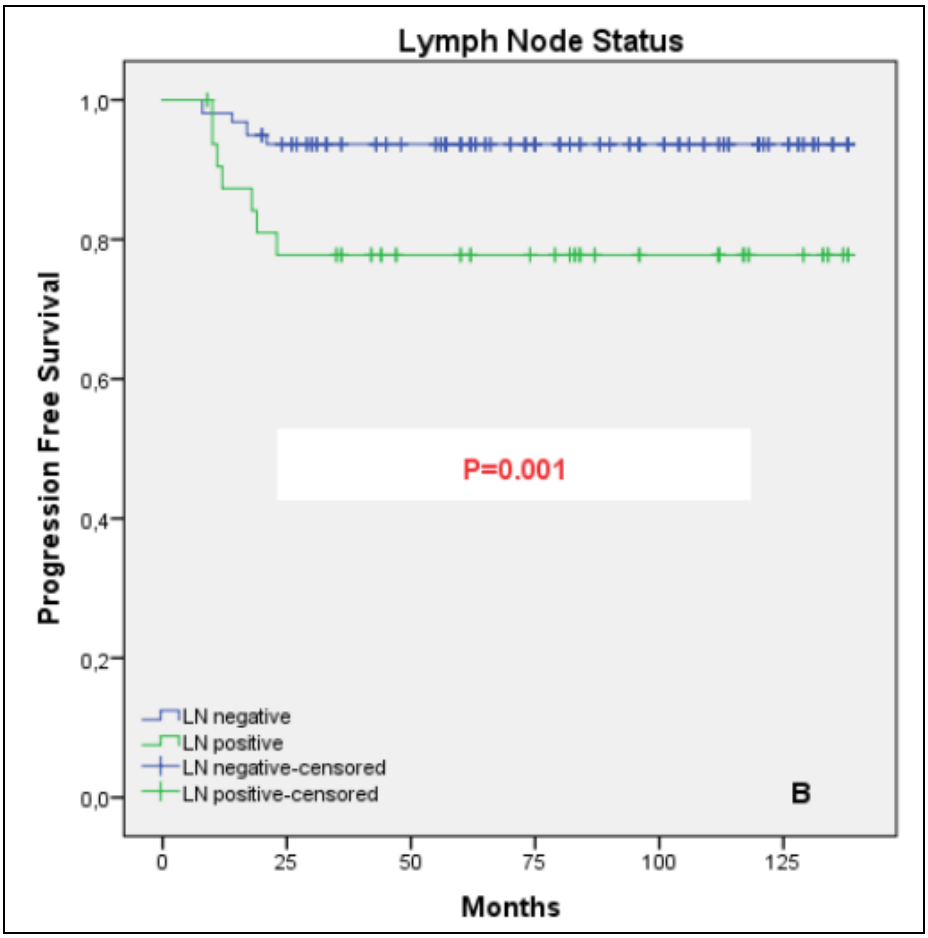
Table 2: Effect of clinical and surgical parameters on overall and progression free survival

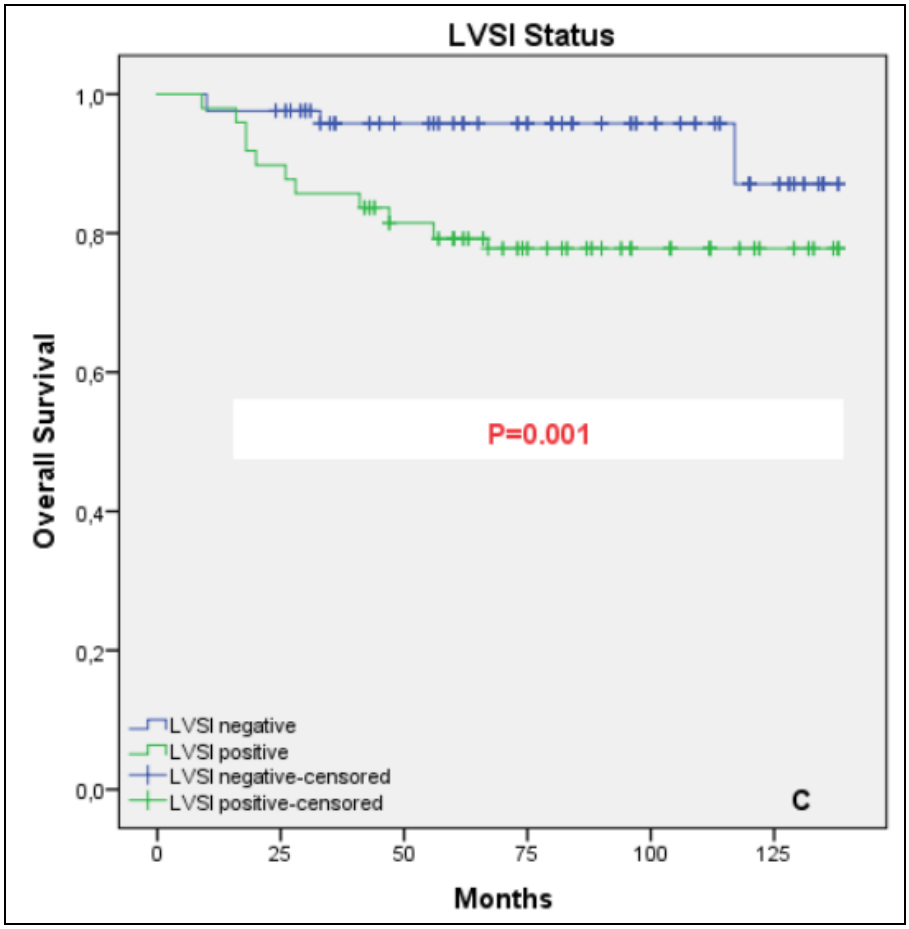
			PFS				OS			
			mo	CI 95%		p	mo	CI 95%		p
		n		Lower	Upper			Lower	Upper	
Age, year	≤50 >50	152 71	129 108	124 97	134 119	0,003	129 106	124 96	134 117	0,001
Stage	1A 1B	28 195	125 124	111 119	138 129	0,960	129 122	117 117	140 127	0,362
Tumour diameter (cm)	≤2 >2	75 148	130 121	123 115	136 128	0,140	131 119	126 112	137 125	0.020
LVSI status	No Yes	125 98	131 114	127 105	136 124	0,001	131 114	126 105	135 123	0.001
Pelvic Lymph status	No Yes	158 65	130 110	125 97	134 123	0,001	129 108	124 97	134 120	0.001
Lymph Node Involvement	No Yes	156 67	130 111	125 99	134 123	0,001	129 109	124 97	134 120	0.001
Number of lymph nodes	1-20 21-40 Over 40	32 113 78	NA	NA	NA	0,004	NA	NA	NA	0,001
Paraortic Lymph status	No Yes	212 11	125 99	119 76	130 121	0,465	124 107	119 86	129 127	0.024
Number of malignant lymph nodes	0 1-4 >4	156 57 10	130 116 24	125 104 17	134 128 32	0,001	129 115 45	124 104 27	134 126 63	0.001

Table 3: Univariate and multivariate analysis of clinical and pathological risk factors of cases

				PFS				OS		
	Number of cases	Univariate		Multivariate		Univariate		Multivariate		
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	
Age	≤50 >50	1 3.226 (1.43-7.26)	0.005	1 2.357 (1.02-5.43)	0.044	1 3.289 (1.56-6.80)	0.002	1 2.486 (1.16-5.31)	0.019	
LVSI status	No Yes	1 4.112 (1.63-10.36)	0.003	1 2.647 (0.95-7.30)	0,060	1 3.524 (1.55-7.96)	0.002			
Lymph involvement	No Yes	1 3.237 (1.54-6.78)	0.002			1 4.013 (1.89-8.49)	0.001	1 2.527 (1.08-5.86)	0.031	
Stage	1A 1B	1 1.03 (0.30-3.45)	0,960			1 1.923 (0.45-8.08)	0,372			
Tumour diameter	≤2cm >2cm	1 2.06 (0.76-5.51)	0,151			1 3.244 (1.12-9.32)	0.029			
Number of positive lymph	0 1-4 4 <	1 2.86 (1.19-6.89) 9.46 (2.95-30.29)	0.018 0.001			1 3.15 (1.41-7.03) 13.97 (4.74-41.14)	0.005 0.001			
Pelvic Lymph Involvement	No Yes	1 3.754 (1.66-8.45)	0.001			1 4.107 (1.93-8.67)	0.001			
Paraaortic Lymph Involvement	No Yes	1 1.702 (0.40-7.23)	0,472			1 3.148 (1.09-9.05)	0.033			


LVSI Status
Progression Free Survival
1,0
0,8
0,6
0,4
0,2
0,0
P=0.001
LVSI negative
LVSI positive
LVSI negative-censored
LVSI positive-censored
A
0
25
50
75
100
125
Months


Lymph Node Status
Progression Free Survival
1,0
0,8
0,6
0,4
0,2
0,0
P=0.001
LN negative
LN positive
LN negative-censored
LN positive-censored
B
0
25
50
75
100
125
Months



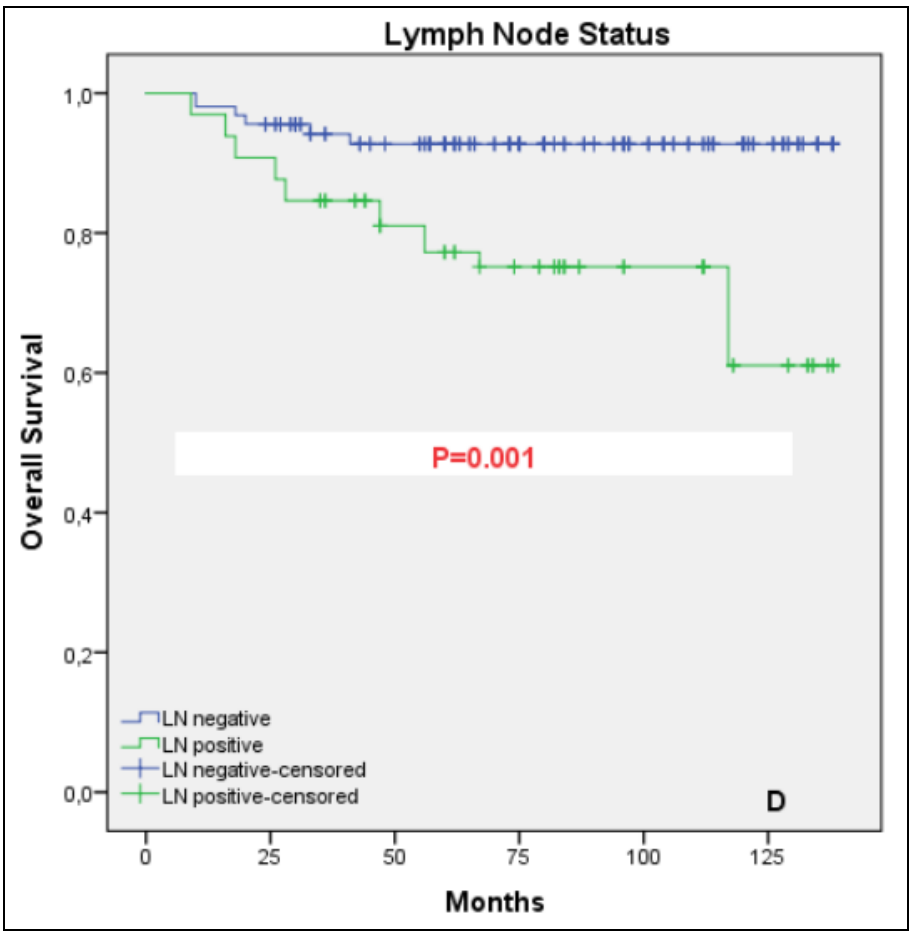


Fig 1: The relationship of lymphovascular stromal invasion and lymph status with PFS and OS.

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