

## An Clinicopathological and Survival Analysis of Non-Squamous Cervical Cancers at Ahpgic

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### Abstract

**Aim and Objective:** An clinicopathological and survival analysis 22 cases cases of no squamous carcinomas of cervix from 2010- 2020

**Primary objective:** is to analyse the extent of microscopic parametrial involvement in early invasive non squamous carcinoma with respect to age, size of lesion, depth of invasion.

To analyse the nodal status in clinically early invasive nonsquamous carcinoma with respect to other variable i.e age, tumor size, depth of invasion, parametrial involvement.

**Secondary Objective:** was to analyse the survival status, of after radical hysterectomy and adjuvant therapy.

**Material and Methods:** The hps confirmed cases of no squamous carcinoma of cervix were included in the study and few cases were ihc confirmed.

**Inclusion Criteria:** Primary non-squamous carcinoma of cervix hps confirmed.

**Exclusion Criteria:** Squamous carcinoma and metastatic carcinoma of cervix

**Methods:** Regression analysis chi square, log rank test. Kaplan Meyers curve was used for survival analysis.

**Results:** On regression analysis with dependent variable as the pelvic node was analysed with age, depth of invasion and size of lesion and parametrium, none of factors were significantly influencing the nodal status. Similarly, the parametrium positivity taken as the dependent variable was analysed with age, size of lesion, depth of invasion. None of the factors could predict the parametrial involvement. Overall 5-year survival probability for the patients is 0.770 i.e 55 months with 95% CI (0.570, 1.000). Here, the 5-year survival probability for the patients with parametrium positive status is 0.917 i.e 48 months 95% CI (0.773, 1.000). The log rank test for change in survival between two parametrium groups i.e., negative and positive patients gives chi-square value 3.59 (d.f.=1, p-value = 0.06), which indicates two groups do not differ in their survival.

Disease free survival of the parametrium -ve/ parametrium +ve (60/24 mths). The log rank test for change in survival between two parametrium groups i.e., negative and positive patients gives chi-square value 2.8 (d.f.=1, p-value = 0.1), which indicates two groups do not differ in their disease free survival.

**Keywords:** Capecitabine, Xeloda, Hypertriglyceridemia, Serum Triglyceride Levels, Drug Adverse Effect

## Introduction

The global incidence of cervical cancer burden is disproportionately high in low and middle income countries, where 83% of all new cases and 855 of cervical cancer death occur [1]. India accounts for nearly one fourth of the world's cervical cancer deaths, with 60,078 death and 96,922 new cases in 2018 [2, 3]. Cervical cancer is the most prominent cause of maternal mortality in Indian women [4].

Adenocarcinoma represent 20-25% of cervical cancers in the industrialized countries.

Most of this is due to relative decrease in incidence of squamous cell carcinoma. In contrast to squamous carcinoma, smoking does not increase the risk adenocarcinoma. Squamous and non-squamous differ in HPV status [5]. HPV 18 accounts for 50% of non-squamous cell cancer (adenocarcinoma) of 15% of squamous cell carcinomas

Management of adenocarcinoma is same as squamous.

When squamous disseminate via lymphatics and adenocarcinoma haematogenous route [6]. This is evident as after lymphatic dissemination adenocarcinoma has poor prognosis compared to squamous cell carcinoma [7].

Other evidence in support of haematogenous spread. The largest series of surgically treated cervical cancers demonstrated a significantly higher rate of ovarian metastasis with adenocarcinoma (5% vs 18% p < .01).

A study of 367 pts of adenocarcinoma from M.D ANDERSON hospital reported a higher rate of distant metastasis for stage II (46% vs 13%) and stage III disease (38% vs 21%) when compared squamous carcinoma.

There are very few studies regarding the prognostic factors i.e. clinical and pathological factors influencing the parametrium positivity and nodal status of non-squamous carcinoma. That is the reason they are overtreated by multimodality i.e. (radical surgery with adjuvant)

Studies done by M.D Anderson on 29 patients of adenosquamous and 97 pts of adenocarcinoma in stage 1b1., with radical hysterectomy. On follow up time to recurrence (7.9 months vs 19 months p = .01)

A STUDY OF 163 adenocarcinoma and adenosquamous carcinoma with stage 1A2 to IIB disease treated by radical hysterectomy with or without adjuvant radiation found no difference in recurrence rate or patterns of recurrences between the two groups, in both low risk, intermediate risk high-risk group [8].

One hundred patients met the inclusion criteria.

The median age was 35 years (range 22–65), and 51% (51/100) had pure high-grade neuroendocrine carcinoma. No patient had a tumor >4 cm or suspected parametrial or nodal disease before surgery. Ten patients (10%) had microscopic parametrial compromise in the final surgical specimens. Ninety-four (94%) patients underwent nodal assessment, and 19 (19%) had positive nodes. Ten patients underwent both sentinel lymph node biopsy and pelvic lymphadenectomy, and none had false-negative findings. Patients with parametrial compromise were more likely to have positive pelvic nodes (80% vs 12%, p < 0.0001), and a positive vaginal margin (20% vs 1%, p = 0.03). All patients with parametrial compromise had lymphovascular space invasion (100% vs 73%, p = 0.10). Of the 100 patients, 95 (95%) were recommended adjuvant therapy and 89 (89%) were known to have received it. Adjuvant pelvic radiotherapy reduced the likelihood of local recurrence by 62%. Gloria Salvo et al [9].

## Descriptive Statistics

A total 22 cases of non-squamous carcinoma were taken for statistical evaluation. The median age incidence is 46 yrs. The youngest age is 28 yrs and maximum age 62 yrs. 9 (40.9) were <46 yrs and no cases more than 46 yrs 13 (59.1). 4 cases i.e. 18.9% cases were multiparous and 4 (18.2) cases were nulliparous. The spectrum of presentation varied from PMB 9 (40.9) cases, watery discharge 9 (22) no cases, AUB were 4 (18.2) and PCB 4 (18.2) TABLE 1

**Table 1: Clinical Statistics**

	Variables	Values
Age (in years)	Mean ± SD	46.04 ± 9.20
	Median	46
	Range (Max, Min)	34 (62, 28)
	< 46, n (%)	09 (40.9)
	≥ 46, n (%)	13 (59.1)
Parity, n (%)	Null parity	04 (18.2)
	Multi parity	18 (81.8)
	Symptoms, n (%)	
	PMB	09 (40.9)
	WD	05 (22.7)
	AUB	04 (18.2)
	PCB	04 (18.2)

Of the total 22 cases all 22 (100) (%) underwent; laparotomy 20 (90.9) cases underwent type 2 radical hysterectomy, and 2 cases underwent type 3 radical hysterectomy. There were intraoperative surgical complications and 22(100) post-operative complications.

There were 4 (18.2) cases with a high residual urine and rest had minor bladder dysfunction 18 (81.8) table -2. The high residual urine post op for the four cases were 200 ml, 90ml, 150ml, 150ml. After adjuvant treatment all four cases required recatheterisation.

**Table 2: Surgical Statistics**

Variables	Values
<b>Surgical Procedure, n (%)</b>	
Laparotomy	22 (100)
Radical Hysterectomy (type-2)	20 (90.9)
Radical Hysterectomy (type-3)	02 (09.1)
Laparoscopy	NIL
<b>Surgical Complications, n (%)</b>	
Intra op	NIL
Post op	22 (100)
Bowel	NIL
Bladder	22 (100)
Bladder Complications (HIGH RESIDUAL URINE)	04 (18.2)
Bladder Complications (MINOR BLADDER DYSFUNCTIONS)	18 (81.8)

**Table 3: Histopathological Statistics**

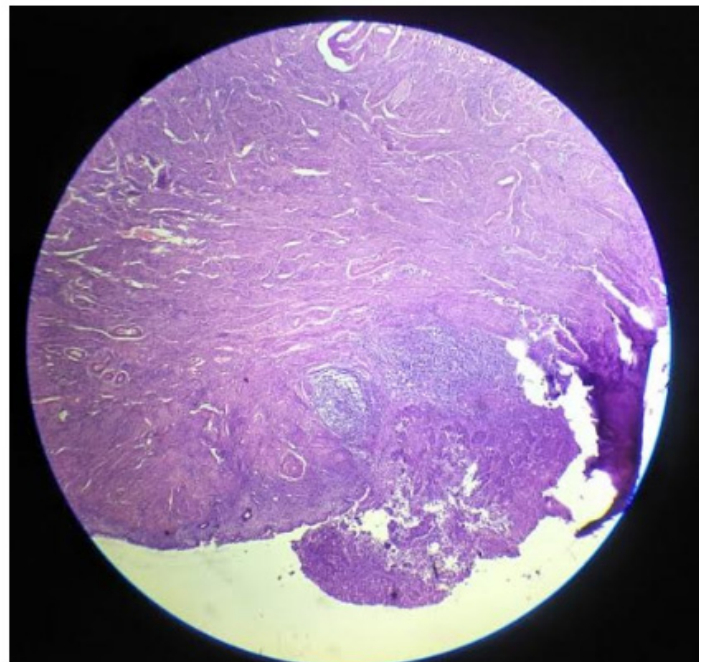
Variables	Histology	Aden squamous	Adenocarcinoma	Basaloid carcinoma	Values	2201
Size of lesion (in cm)	Mean ± SD				3.46 ± 1.5	
	Median				3	
	Range (Max, Min)				5.5 (7, 1.5)	
	< 3, n (%)				07 (33.3)	
	≥ 3, n (%)				15 (66.7)	
<b>Margins, n (%)</b>						
	Positive				10 (45.4)	
	Negative				12 (54.6)	
<b>LVSI, n (%)</b>						
	Positive				07 (33.3)	
	Negative				15 (66.7)	
<b>Grade, n (%)</b>						
	Grade-1				10 (45.4)	
	Grade-2				06 (27.3)	
	Grade-3				06 (27.3)	
<b>Nodal Status, n (%)</b>						
<b>Pelvic</b>						
	Negative				14 (63.6)	
	Positive				08 (36.4)	
	Internal iliac				04	
	Obturator				01	
	Upper External iliac				02	
	Low External iliac				01	

	Common iliac	NIL
	<b>Para aortic</b>	
	Negative	20 (90.9)
	Positive	02 (09.1)
	<b>Depth of stomal invasion, n (%)</b>	
	< 5 mm	07 (31.8)
	≥5 mm	15 (68.2)
	<b>Parametrium, n (%)</b>	
	Positive	05 (22.7)
	Negative	17 (77.3)
	<b>Adnexa, n (%)</b>	
	Positive	NIL
	Negative	22 (100)
	<b>Stage, n (%)</b>	
	Stage-1	17 (77.3)
	A	NIL
	B1	06
	B2	09
	B3	02
	Stage-2	NIL
	Stage-3	05 (22.7)
	C1	04
	C2	01
	Stage-4	NIL

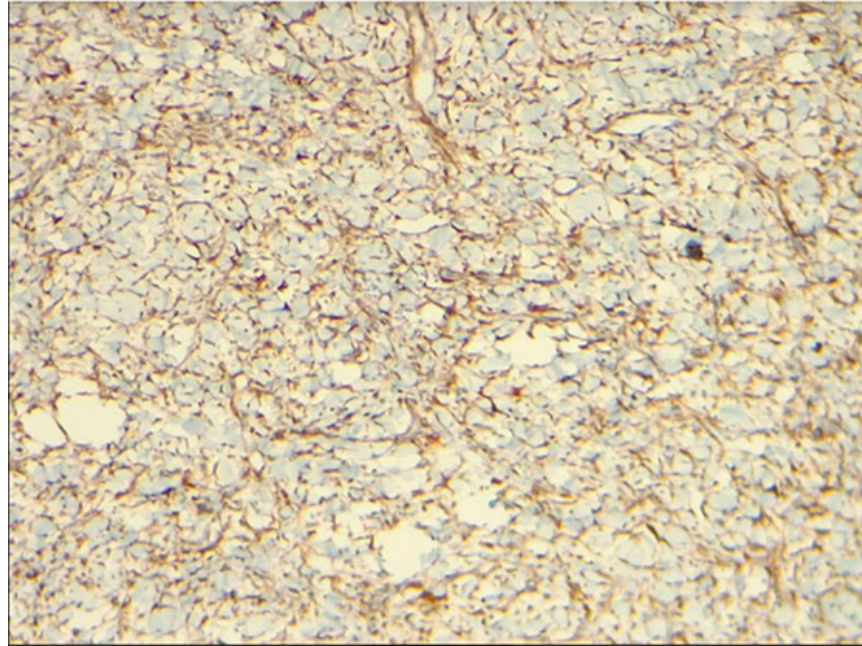
There were 2 (9.09%) were adenosquamous, 1 (4.55%) case was basaloid carcinoma and rest 20 (91%) cases were adenocarcinoma.

The median size of the lesion is 3 cm .7 (33.3%) cases we less than 3 and 15(66.7%) cases ae more than 3cm mains positive in 10(45.4%) cases and negative in12 (54.6%) lvsI positive in 7(31.8%) and 15 cases (667 %) negative no. of grade1 10(45.4) and grade2 6(27.3%) and grade3 6(27.3%). Nodal status shows the pelvic node 8 (36.4%). Paaaortic2 (9.1%). The depth of invasion >5mm 25(31.8%) and <5mm 7(68.2%)

**The parametrium was positive in 5 cases (22.7%)** cases was negative in 17 (77.3%) cases adnexa was not positive in any of cases 17 were in stage 1. With no case in 1a, 6 cases in 1b1, 9 cases in 1b2 and 2 cases in 1b3. There were 5 cases in stage 3. None of the cases presented in stage 2 and stage 4.



**Figure: 1** Adenocarcinoma of Cervix



**Figure 2:** The Endocervical Adenocarcinoma Stained Positive ihc pi6 +ve

**Table 4: Regression Analysis**

Coefficients:	Estimate ( $\beta$ )	Std. Error	z-value	OR	Pr(> z )
(Intercept)	-16.807	8.412	-1.998	.000	0.0457
Age	0.228	0.142	1.612	1.257	0.107
Pelvic node	3.407	2.210	1.541	30.163	0.123
Sizeoflesion	0.778	0.512	1.519	2.177	0.129
Variable(s): Dependent Variable: Parametrium Predictor Variable: Age, Pelvic node, Sizeoflesion.					

Not a single predictor variable is significant in predicting Parametrium Status.

**Table 5: Regression Analysis**

Coefficients:	Estimate ( $\beta$ )	Std. Error	z value	OR	Pr(> z )
(Intercept)	3.427	3.824	0.896	30.784	0.370
Age	-0.118	0.073	-1.607	0.889	0.108
Parametrium	2.637	1.775	1.486	13.97	0.137
Sizeoflesion	0.173	0.380	0.454	1.189	0.650
Depthofinvasion	-0.227	1.306	-0.174	0.797	0.862
Variable(s): Dependent Variable: Pelvic node Predictor Variable: Age, Parametrium, Sizeoflesion, Depthofinvasion					

Not a single predictor variable is significant in predicting Pelvic nodal status

**Table 6: Survival Statistics**

Variables	Values
Lost To Follow-up, n (%)	03 (13.6)
NAD, n (%)	16 (72.8)
Death, n (%)	03 (13.6)

The no. of cases lost to follow up 3(13.6%).16 cases were normal on follow up and 3 cases succumbed (13.6%)

**Survival Analysis****Table: 7 Overall Survival**

Time	No of Patients at risk	No of event(s)	Survival Probability	St. Error	Lower 95% CI	Upper 95% CI
48	15	1	0.933	0.064	0.815	1.000
50	12	1	0.856	0.095	0.688	1.000
55	10	1	0.770	0.118	0.570	1.000

Here, overall 5-year survival probability for the patients is 0.770 i.e 55 months with 95% CI (0.570, 1.000).

**Table 8: Survival Status of the Patients with Parametrium Negative**

Time	No of Patients at risk	No of event(s)	Survival Probability	St. Error	Lower 95% CI	Upper 95% CI
48	12	1	0.917	0.079	0.773	1.000

Here, the 5-year survival probability for the patients with parametrium positive status is 0.917 48months 95% CI (0.773, 1.000).

**Table 9: Survival Status of the Patients with Parametrium Negative**

Time	No of Patients at risk	No of event(s)	Survival Probability	St. Error	Lower 95% CI	Upper 95% CI
50	3	1	0.667	0.272	0.299	1.000
55	2	1	0.333	0.272	0.067	1.000

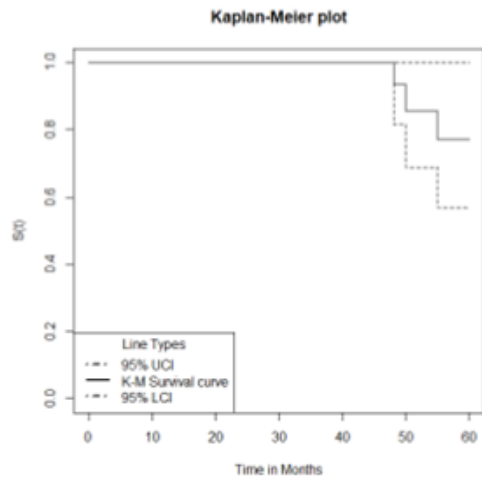
Here, the 5-year survival probability for the patients with parametrium negative status is 0.333i..e 55months with 95% CI (0.067, 1.000).

**Table 10: Log-Rank Test Outcomes for Survival Differences**

Covariates	Category	Num. of Patient	Observed Event	Expected Event	(O-E) <sup>2</sup> / E	Chisq. Value	d.f.	p-value
parametrium	Negative	18	1	2.35	0.776	3.59	1	0.06
	Positive	4	2	0.65	2.804			

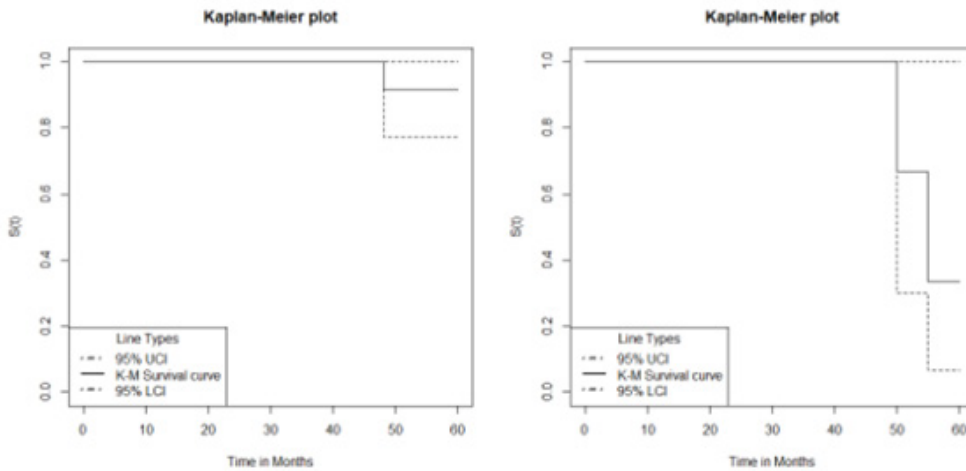
The log rank test for change in survival between two parametrium groups i.e., negative and positive of cervical cancer patients gives chi-square value 3.59 (d.f.=1, p-value = 0.06), which indicates two groups do not differ in their survival.

# Survival Plots



**Figure 1:** Kaplan-Meier Plot for Overall Survival of Cervical Cancer Patients

Figure 1 Shows the proportion of individuals who have survived up to the specified time in the solid black line and their 95% confidence interval in black dashed lines.



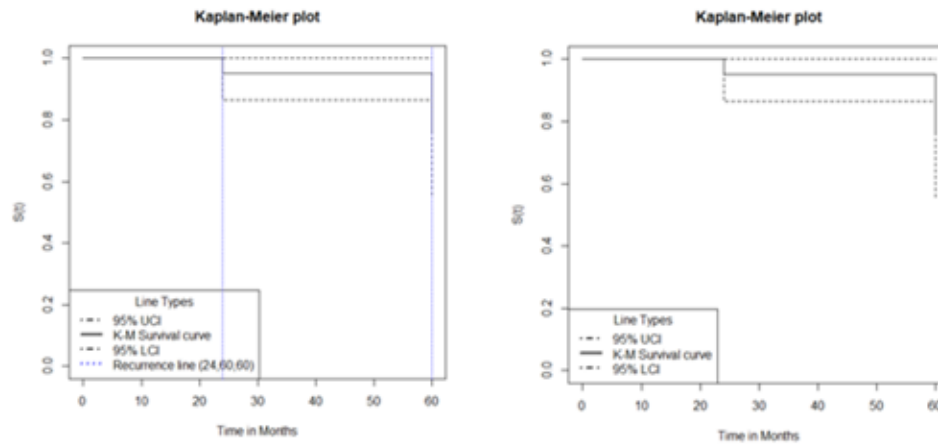
**Figure 1:** Kaplan-Meier Plot of the Patients with (i) Parametrium Positive (Left) and (ii) Parametrium Negative (Right) of the Cervical Cancer Patients.

Figure 2 Shows the proportion of individuals who have survived up to the specified time in the solid black line and their 95% confidence interval in black dashed lines.

**Overall,5-year disease free Survival**

time	No of Patients at risk	No of event(s)	Survival Probability	St. Error	lower 95% CI	upper 95% CI
24	21	1	0.952	0.046	0.866	1.000
60	10	2	0.762	0.126	0.551	1.000

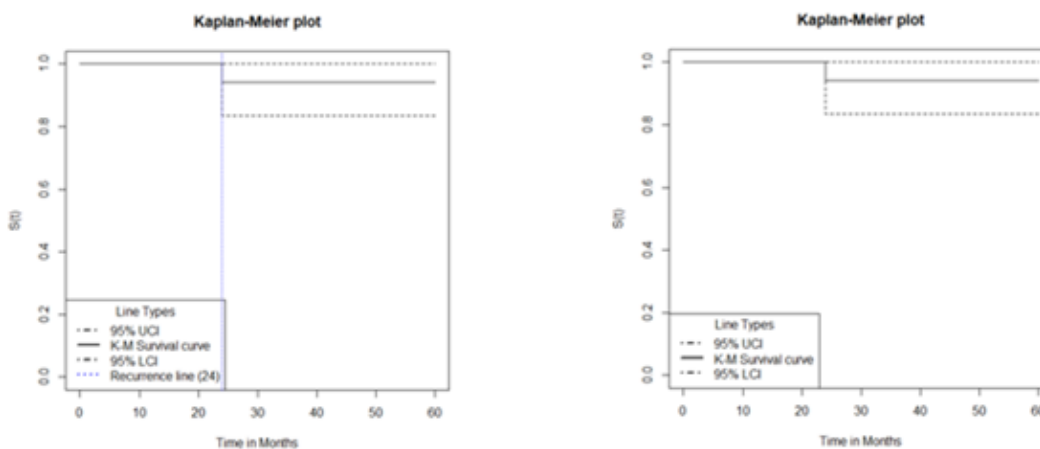
**KM plot for overall 5-year disease free survival with & without recurrence lines**



**5-year disease free survival of parametrium -ve patients**

time	No of Patients at risk	No of event(s)	Survival Probability	St. Error	lower 95% CI	upper 95% CI
24	17	1	0.941	0.057	0.836	1.000

**KM plot for 5-year disease free survival of parametrium -ve patients with & without recurrence lines**

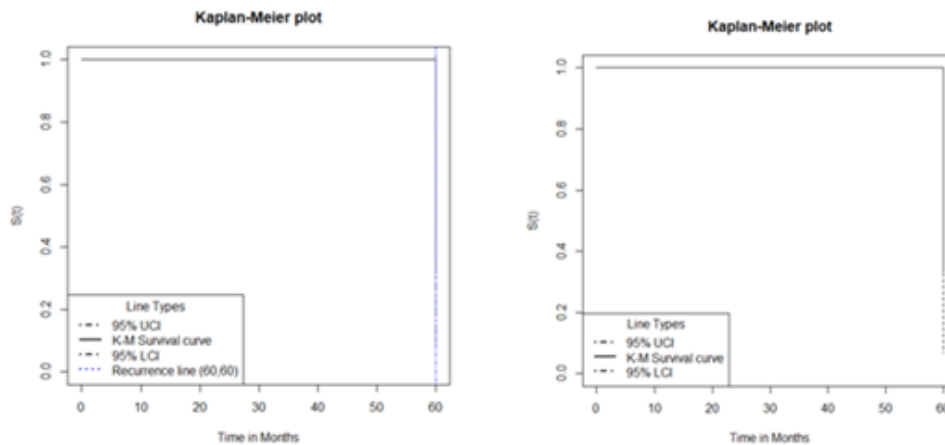




### 5-year disease free survival of parametrium +ve patients

time	No of Patients at risk	No of event(s)	Survival Probability	St. Error	lower 95% CI	upper 95% CI
60	3	2	0.333	0.272	0.067	1.000

### KM plot for 5-year disease free survival of parametrium +ve patients with & without recurrence lines



### Log-rank test outcomes for disease free survival differences

Covariates	Category	Num. of Patient	Observed Event	Expected Event	$\frac{(O - E)^2}{E}$	Chisq. Value	d.f.	p-value
parametrium	negative	18	1	2.21	0.662	2.8	1	0.1
	positive	4	2	0.79	1.851			

The log rank test for survival difference between two parametrium groups i.e., negative and positive of non squamous carcinoma patients gives chi-square value 2.8 (d.f.=1, p-value = 0.1), which indicates two groups do not differ in their disease free survival.

## Results

On regression analysis with dependent variable as the pelvic node was analysed with age, depth of invasion and size of lesion and parametrium, none of factors were significantly influencing the nodal status.

Similarly, the parametrium positivity taken as the dependent variable was analysed with age, size of lesion, depth of invasion. None of the factors could predict the parametrial involvement. Overall 5-year survival probability for the patients is 0.770 i.e 55 months with 95% CI (0.570, 1.000). Here, the 5-year survival probability for the patients with parametrium positive status is 0.917 i.e 48 months 95% CI (0.773, 1.000). The log rank test for change in

survival between two parametrium groups i.e., negative and positive patients gives chi-square value 3.59 (d.f.=1, p-value = 0.06), which indicates two groups do not differ in their survival.

Disease free survival of the parametrium -ve/ parametrium+ve(60/24 mths). The log rank test for change in survival between two parametrium groups i.e., negative and positive patients gives chi-square value 2.8 (d.f.=1, p-value = 0.1), which indicates two groups do not differ in their disease free survival.

## Conclusion

The parametrium and nodal positivity of non-squamous cancers are not dependent on each other. Thus, we conclude from

overall survival of parametrium positive/parametrium negative (48mths/55mths) or the disease free survival of the two groups (24mths/60 mths) after radical hysterectomy with adjuvant crrt was not statistically significant. Although the parametrium negative cases showed increase in overall survival of 55mths and disease free survival of 60 mths.

Thus, we can subject the patients to either of a single modality of treatment i.e either a radical hysterectomy or crrt.

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