

# A CLINICOPATHOLOGICAL AND SURVIVAL ANALYSIS OF NON-SQUAMOUS CERVICAL CANCERS IN INDIA

ABSTRACT

## AIM AND OBJECTIVE-

An clinicopathological and survival analysis 22 cases cases of nonsquamous 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 nonsquamous carcinoma of cervix were included in the studyand few cases were ihc confirmed.

**INCLUSION CRITERIA-** Primary non squamous cacinoma 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 [10-12].

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.

### **Key words**

**Os – disease free survival**

**Dfs – disease free survival**

**Ctrl - chemoraditherapy**

Doi- depth of invasion

Lvsi- lymphovascular space

Ru- residual urine

### **INTRODUCTION-**

The global incidence of cervical cancer burden is disproportionately high in low and middle income countries, where 83% of all new cases and 85% of cervical cancer deaths occur(1). India accounts for nearly one fourth of the world's cervical cancer deaths, with 60,078 deaths and 96,922 new cases in 2018(2,3). Cervical cancer is the most prominent cause of maternal mortality in Indian women.(4)

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

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

Management of adenocarcinoma is the same as for squamous.

Whereas squamous carcinomas disseminate via lymphatics and adenocarcinoma via the haematogenous route(6)

This is evident as after lymphatic dissemination adenocarcinoma has a poor prognosis compared to squamous cell carcinoma.(7)

Other evidence in support of haematogenous spread: 1. The largest series of surgically treated cervical cancers demonstrated a significantly higher rate of ovarian metastasis with adenocarcinoma (5% vs 8%  $p < .01$ )

2. A study of 367 patients 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 to 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 (7.9mths vs 19monthsp-.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%.(9)gloria salvo et al

## Methodology -

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 nos caese 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) nos cases, aub were 4(18.2) and pcb 4(18.2) TABLE 1

*Table.1: Clinical Statistics*

Variables		Values
Age (in years)	Mean $\pm$ SD	46.04 $\pm$ 9.20
	Median	46
	Range (Max, Min)	34 (62, 28)
	< 46, n (%)	09 (40.9)
	$\geq$ 46, n (%)	13 (59.1)
Parity, n (%)		
	Nulliparity	04 (18.2)
	Multiparity	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*

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

**Table.3: Histopathological Statistics**

Variables		Values
Histology		
Adenosquamous		2
Adenocarcinoma		20
Basaloid carcinoma		1
<b>Size of lesion (in cm)</b>		
Mean $\pm$ SD		3.46 $\pm$ 1.5
Median		3
Range (Max, Min)		5.5 (7, 1.5)
< 3, n (%)		07 (33.3)
$\geq$ 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)
$\geq$ 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 were less than 3 and 15(66.7%) cases are more than 3 cm margins positive in 10(45.4%) cases and negative in 12 (54.6%) lvs positive in 7(31.8%) and 15 cases (66.7 %) negative

nos of grade 1 10(45.4) and grade2 6(27.3%) and grade3 6(27.3%)

Nodal status shows the pelvic node 8 (36.4%). Paraaortic2(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 (77.3%) 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.

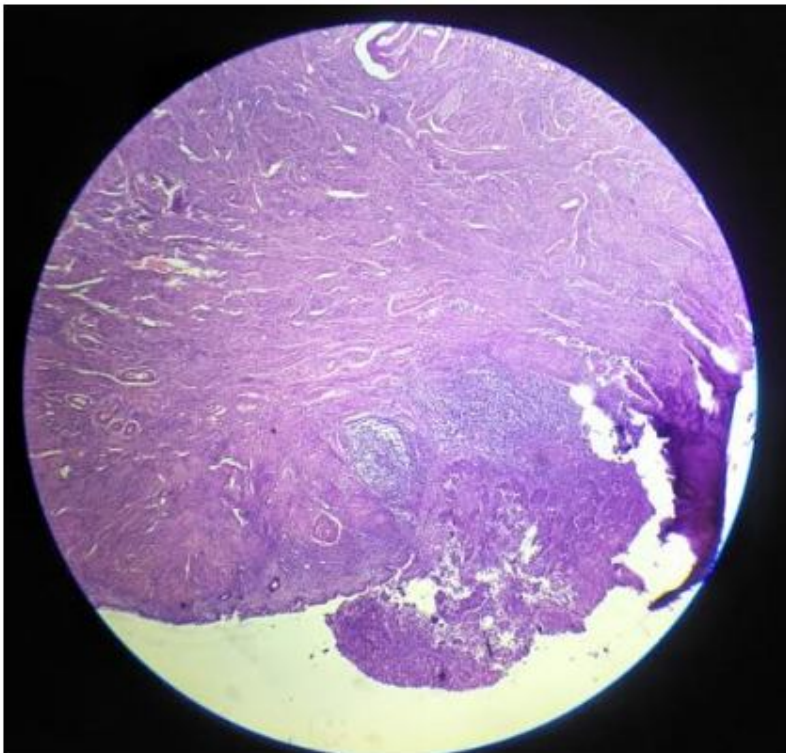


Image -1

Adenocarcinoma of cervix

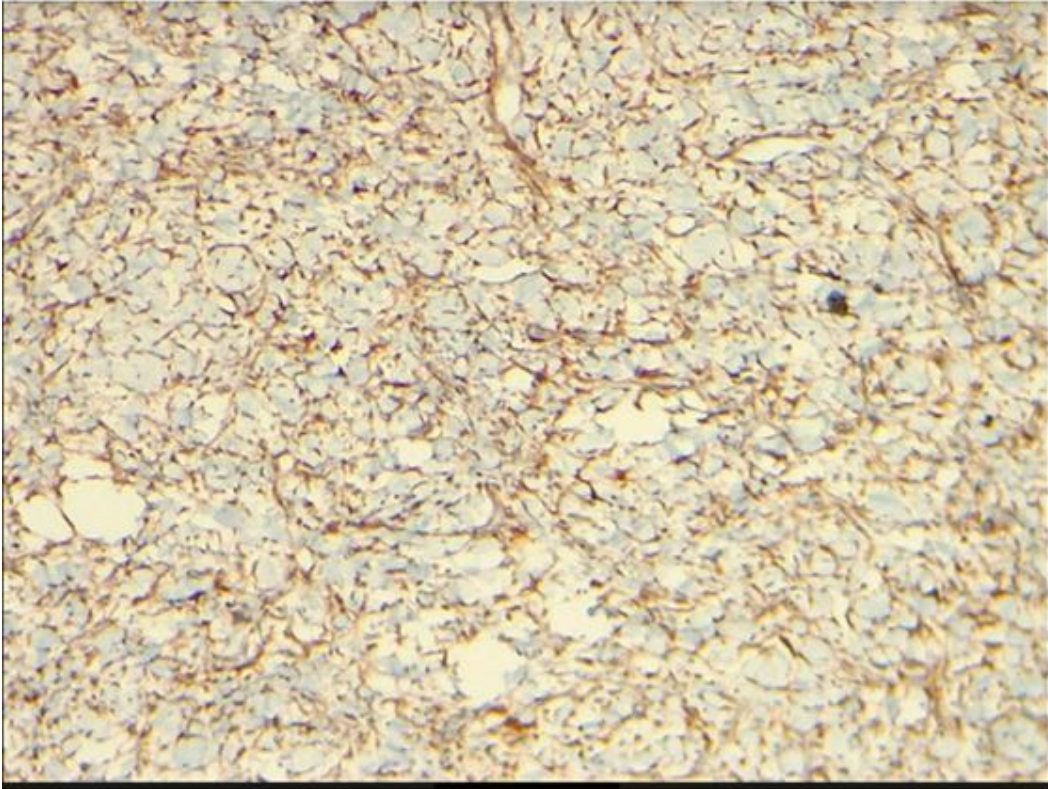


Image -2 THE endocervical adenocarcinoma stained positive ihc pi6 +ve

**TABLE4 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
Pelvicnode	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, Pelvicnode, 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 nos 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 positive**

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**

<i>Covariates</i>	<i>Category</i>	<i>Num. of Patient</i>	<i>Observed Event</i>	<i>Expected Event</i>	$\frac{(O - E)^2}{E}$	<i>Chisq. Value</i>	<i>d.f.</i>	<i>p-value</i>
<i>parametrium</i>	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

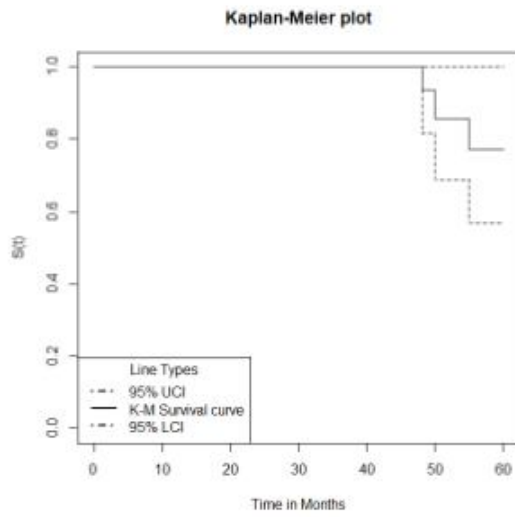


Figure.1: Kaplan-Meier Plot for Overall Survival of Cervical Cancer Patients

Fig.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.

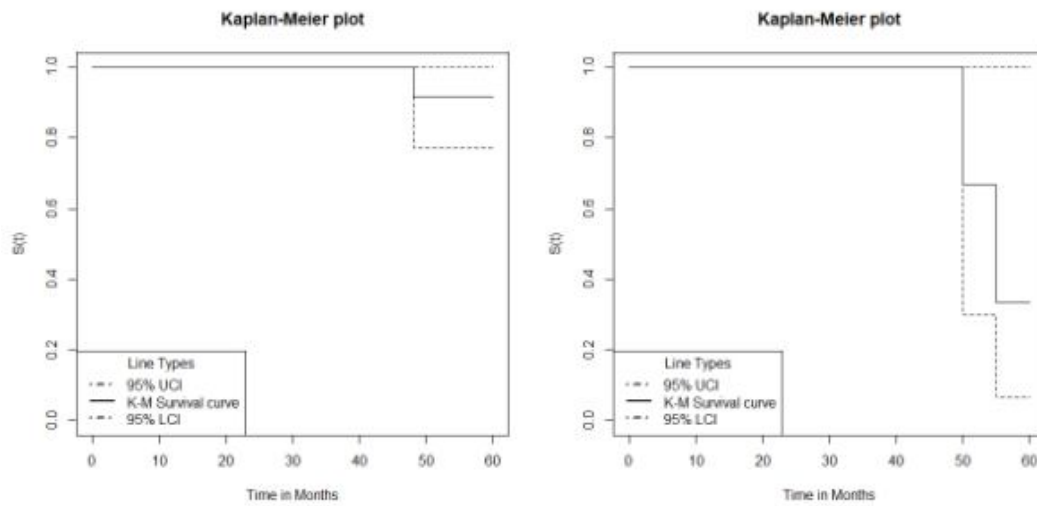


Figure.2: Kaplan-Meier Plot of the patients with (i) Parametrium positive (left) and (ii) Parametrium negative (right) of Cervical Cancer Patients.

Fig.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.

Chart 1 and figure 3 : Overall, 5-year disease free survival

**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**

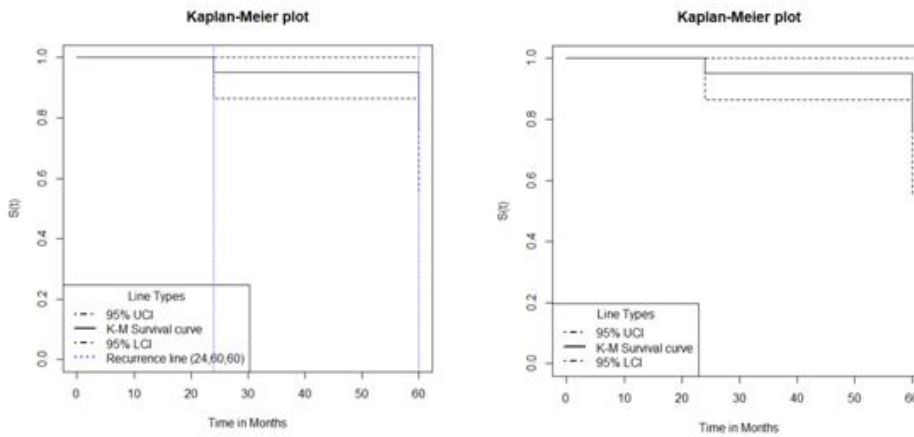
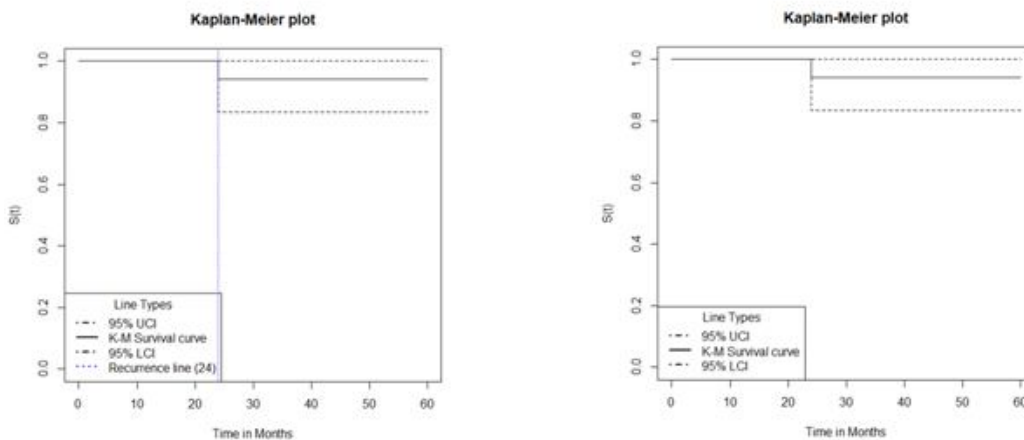


Chart 2 and figure 4 : 5-year disease free survival of parametrium –ve patients

**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 para metrium -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**

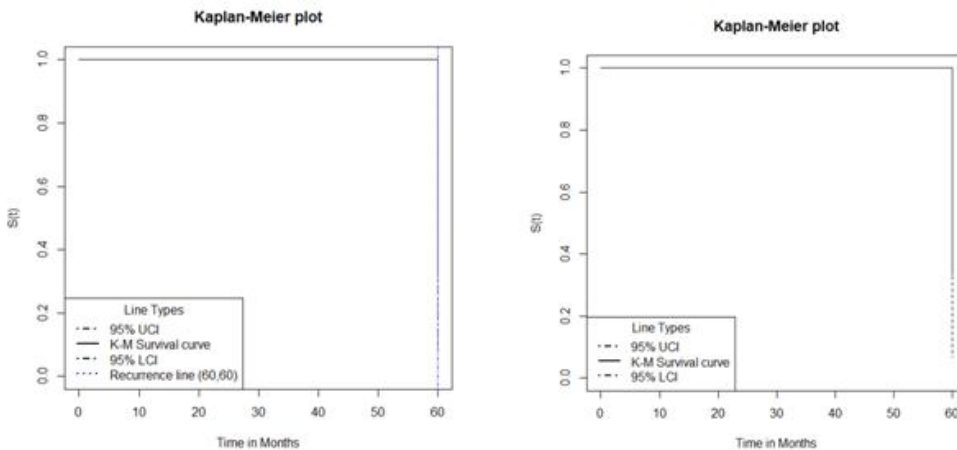


Chart 3 and figure 5: 5-year disease free survival parametrium +ve patients

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

<i>Covariates</i>	<i>Category</i>	<i>Num. of Patient</i>	<i>Observed Event</i>	<i>Expected Event</i>	$\frac{(O - E)^2}{E}$	<i>Chisq. Value</i>	<i>d.f.</i>	<i>p-value</i>
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.

Chart 4 and figure 6 : long rank test outcomes for disease free survival differences

**Results and Discussion** - 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 chrt was not statistically significant. Although the parametrium negative cases showed increase in overall survival of 55mths and disease free survival of 60 mths.

## Consent

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

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