AN CLINICOPATHOLOGICAL AND SURVIVAL ANALYSIS OF NON-SQUAMOUS CERVICAL CANCERS AT AHPGIC

ABSTRACT

AIM AND OBJECTIVE-

An clinicopathological and survival analysis 22 cases cases of nonsquamous carcinomas of cervix from2010- 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 confimed.

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.

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 0.917i.e 48months 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/ parametium+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

Ctrt - chemoraditherapy

Doi- depth of invasion

Lvsi- lymphovascular space

Ru- residual urine

INTRODUCTION-

The global incidence of cervical cancer burden is disproportionally 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 worlds cervical cancer deaths , with 60,078 death and 96,922 new cases in 2018(2,3).Cancer cervix the most probe cause of maternal mortality in Indian women.(4)

Adenocarcinoma represent 20-25%of cervical cancersin 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 i9ncease the risk adenocarcinoma.squamous and non squamous differ in hpv status(5). Hpv 18 accounts fo 50%of non-squamous cell cancer (adenocarcinoma)of 15% of squamous cell carcinomas

Management of adenocarcinoma is same as squamous.

Whee as squamous disseminate via lymphatics and adenocarcinoma haematogenous route(6)

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

Other evidence in support of haematogenous spread 1.the largest series of surgically teated cervical cancers demonstrated a significantly highe rate of ovaian metastasis with adenocarcinoma(5%vs .8%p<.01)

2.a study of 367 pts of adenocarcinoma from M.D ANDERSON hospital reported a higher rate of distant metastasisfor stage II

(46%VS13%) and stage III disease (38%vs21%)when compared squamous carcinoma.

Thee are are very few studies regading the prognostic factors ie clinical and pathological factors influencing the parametrium positivity and nodal status of non squamous carcinoma.that is the reason they ae ovetreated by multimodalityi.e(radical sugery with adjuvant)

Studies done by M.d Anderson on 29patients 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 1A2to IIB disease treated by radical hysterectomy with o without adjuvant radiation found no difference in ecurence ate or patterns of ecurences between the two groups, in both low risk , intermediate risk high isk 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 etal

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 nos caese more than 46 yrs 13(59.1). 4 cases i.e18.9% cases were multiparous and 4(18.2) cases were nulliparous.the spectrum of presentation varied from pmb 9(40.9) cases, watery discharge9(22)noscases, aub were 4(18.2) and pcb 4(18.2)TABLE1

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 (%)		
	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 wee 4(18.2) cases with a high residual urine and rest had minor bladde dysfunction18(81.8) table -2.

The high residual urine post op for the four cases wee200 ml, 90ml, 150ml, 150ml. After adjuvant treatment all four case required recatherterisation.

Table.2: Surgical Statistics

Variables	Values
Surgical Procedure, n (%)	
Laparotomy	22 (100)
Radical Hysterectomy (type-2)	20 (90.9)
Radical Hysterectomy (type-3)	02 (09.1)
Laparoscopy	NIL
Surgical Complications, n (%)	
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

Vacriables		Values
Histology		
Adenosquamous		2
Adenocacinoma		20
Basaloid carcinoma		1
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)
Margins, n (%)		
Positive		10 (45.4)
Negative		12 (54.6)
LVSI, n (%)		
Positive		07 (33.3)
Negative		15 (66.7)
Grade, n (%)		
Grade-1		10 (45.4)
Grade-2		06 (27.3)
Grade-3		06 (27.3)
Nodal Status, n (%)		
Pelvic		
Negative		14 (63.6)
Positive		08 (36.4)
Internal iliac		04
Obturator		01
Upper External iliac		02
Low External iliac		01
Common iliac		NIL
Para aortic		
Negative		20 (90.9)
Positive		02 (09.1)
Depth of stomal invasion, n (%)		
< 5 mm		07 (31.8)
≥5 mm		15 (68.2)
Parametrium, n (%)		
Positive		05 (22.7)
Negative		17 (77.3)
Adnexa, n (%)		
Positive		NIL
Negative		22 (100)
Stage, n (%)		
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 wee less than 3 and 15(66.7%) cases ae moe than 3 cm mmagins positive in 10(45.4%) cases and negative in12 (54.6%) lvsi positive in 7(31.8%) and 15 cases (667 %) negative

nos of grade 1 10(45.4) and grrade2 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 postive in 5 cases(22.7%) cases was negative in 17 (77.3%) casesadnexa 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. Thee were 5 cases in stage 3. None of the cases pesented in stage 2 and stage 4.

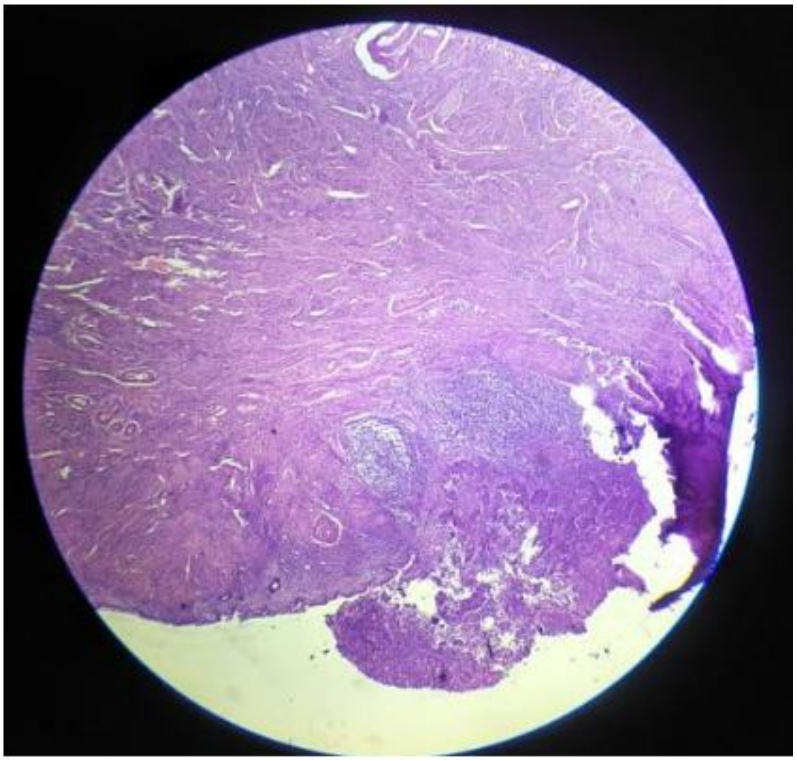


Image -1

Adenocarcinoma of cervix

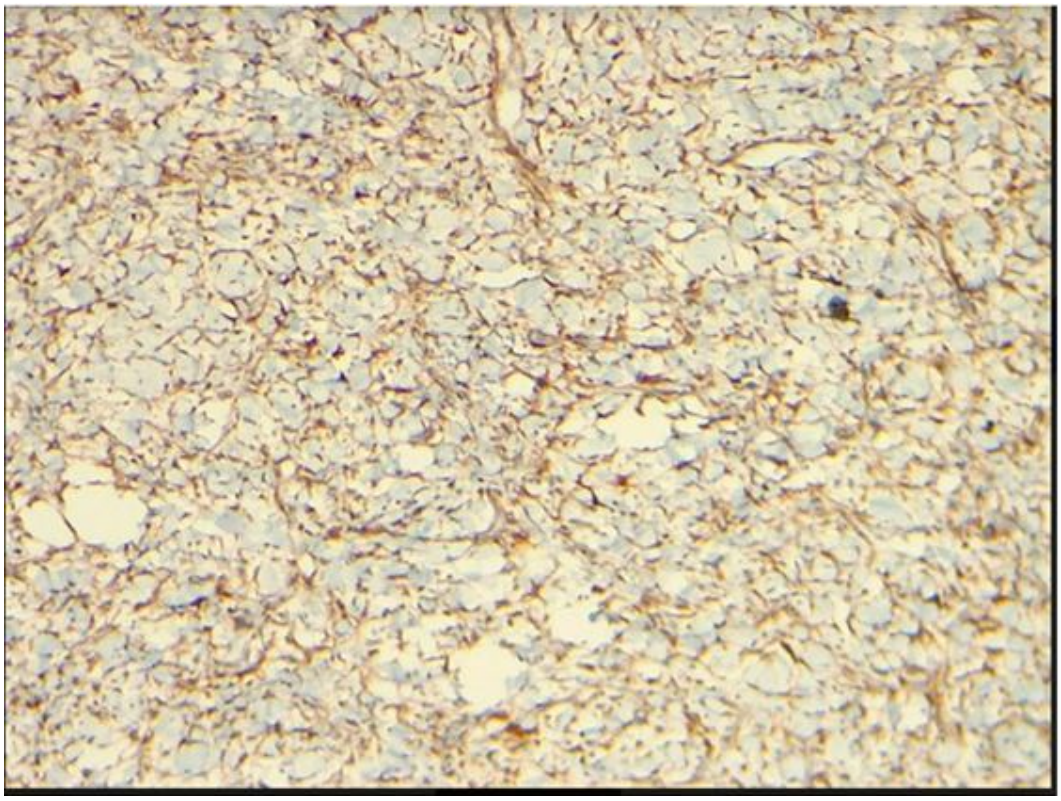


Image -2 THE endocervical adenocarcinoma stained positive ihc pi6 +ve

TABLE4 Regression Analysis

Coefficients:	Estimate (β)	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 predicter variable is significant in predicting Parametrium Status.

TABLE-5 Regression Analysis

5

Coefficients:	Estimate (β)	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:Pelvicnode Predictor Variable: Age,Parametrium, Sizeoflesion,Depthofinvasion					

Not a single predicter variable is significant in predicting Pelvicnodal 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 withParametrium 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

Covariates	*Category*	*Num. of Patient*	*Observed Event*	*Expected Event*	$\frac{(O-E)^2}{E}$	*Chisq. Value*	*d.f.*	*p-value*
parametrium	Negative	18	1	2.35	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

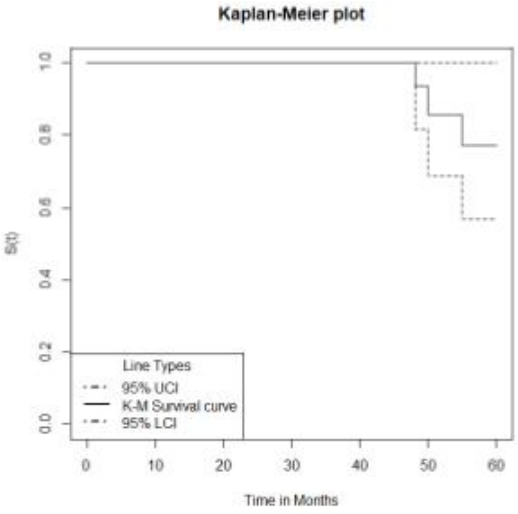


Figure.1: Kaplan-Meier Plot for Overall Survival of Cervical Cancer Patients

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.

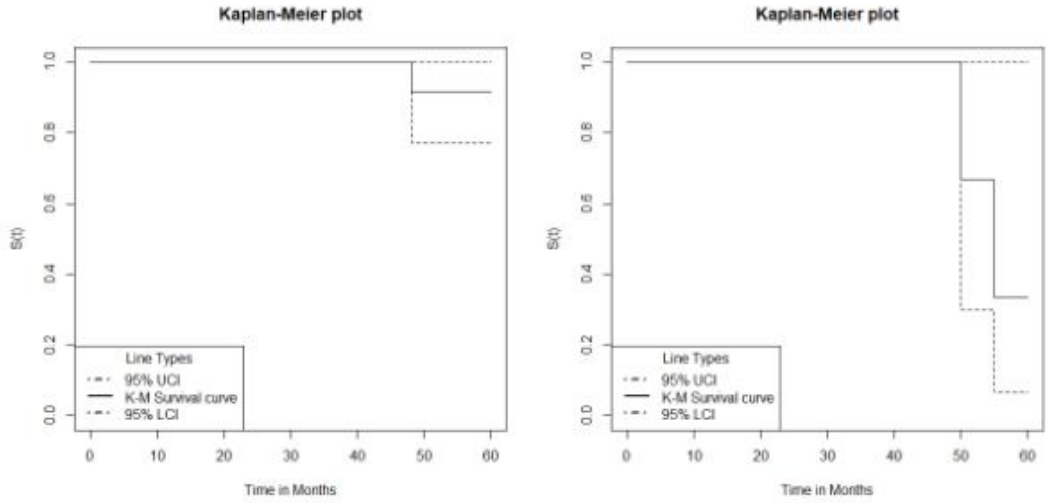


Figure.2: Kaplan-Meier Plot of the patients
with (i) Parametrium positive (left) and (ii) Parametrium negative (right) of Cervical Cancer Patients.

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

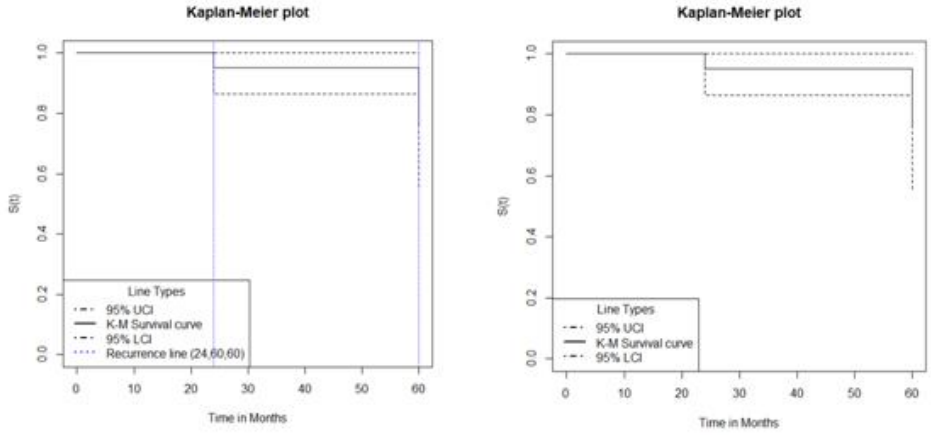
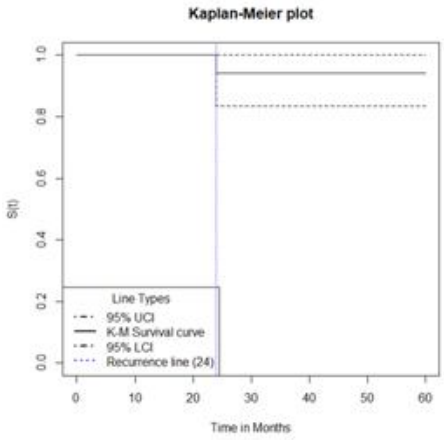


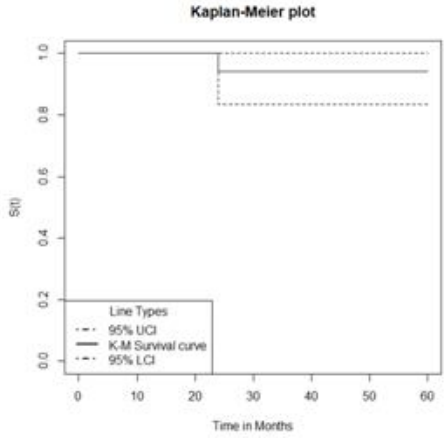
Chart 2 and figure 4 : 5-year disesase free survival of parametrium – ve patients

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 survivalof 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

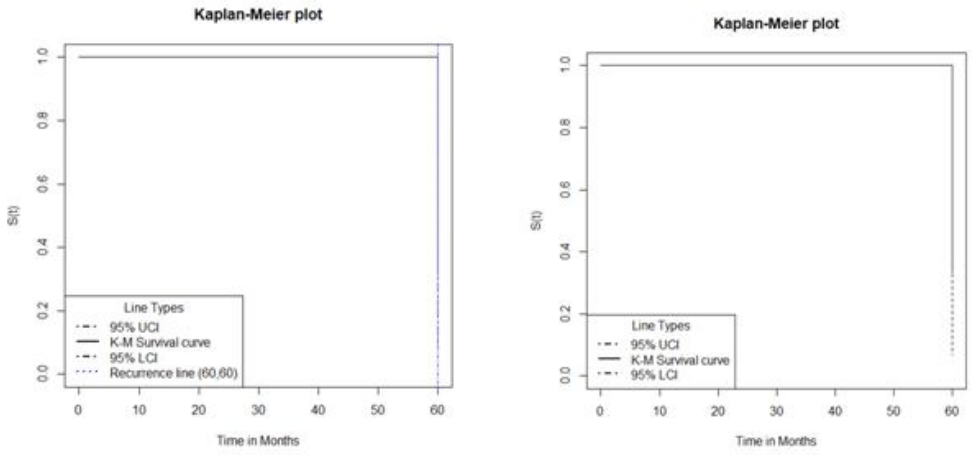


Chart 3 and figure 5: 5-year disease free survival parametrium +ve patients

Log-rank test outcomes for disease free survival differences

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.

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

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 0.917i.e 48months 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/ parametium+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 ae not dependent on each other.Thus we conclude fom 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 ctrt was not statisticaly 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 ctrt.

References

1alif,kueikerr,wassieb.understanding cervical cancer in context of developing countries. Ann top med public health 2012.

2.ferlay j etal globocan intjournal 2015

3.Bruni etal

4

5Castellsagu etalljnatlcancer 2006

6.eifel jp etal1990

7.jeun alti beuchimean juonal gynaecology 1990

8. mabuchhi etal international jounal of oncology 2001

9. Gloria salvo etal nectur study ijc 2021