A Study on pattern of Survival of Cervical Cancer Patients

By

AANCHAL JAIN

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As members of the Viva Voce Committee, we certify that we have read the dissertation prepared by AANCHAL JAIN entitled "A STUDY ON PATTERN OF SURVIVAL OF CERVICAL CANCER PATIENTS" and recommend that it may be accepted as fulfilling the thesis requirement for the award of Degree of Doctor of Philosophy.

Chairman - DR. UMESH MAHANTSHETTY	Date: 20 AUG 2018
Guide / Convener - DR. B. GANESH	Date: 20 AUG 2018
Co-guide -	Date:
Examiner - DR. SREEKUMARAN NAIR	Date: 20 AUG 2018
Member 1- DR. SANTOSH MENON	Date: 20 AUG 2018
Member 2- DR. R. SWAMINATHAN	Date: 20 AUG 2018

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(DR. B. GANESH)
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DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University.

AANCHAL JAIN

List of Publications

Published

1. **Jain A**, Bobdey S, Sathwara J, Ganesh B, Saoba S, Khan A. "Role of monocyte and lymphocyte counts in prognosis of cervical cancer". Int J Reprod Contracept Obstet Gynecol. **2016**; 5(7): 2243-49.

Other Publications

1. Bobdey S**, Jain A**, Ganesh B. Epidemiological review of laryngeal cancer: An Indian perspective. Indian J Med Paediatr Oncol 2015;36:154-60.
2. Bobdey S**,** Ganesh B, Kumar A, **Jain A**. Cancer Screening: Should Cancer Screening be essential component of Primary Health Care in Developing countries?. Int J Prev Med. 2015 ;6: 56.
3. Bobdey S, **Jain A,** Sathwara J, Ganesh B. Pretreatment SerumAlbumin: A prognostic indicator of survival in Oral Cancer. International Journal of Research in Medical Sciences. 2016; 4(6):2135-41.
4. Bobdey S, Ganesh B. Mishra PS**, Jain A**. Role of Monocyte Count and Neutrophil-to-Lymphocyte Ratio in Survival of Oral Cancer Patients. Int Archives of Otorhinolaryngol 2017; 21: 21–27.
5. Bobdey S, Sathwara J, **Jain A**, Ganesh B. Burden of Cervical cancer and role of screening in India. Indian J Med Paediatr Oncol 2016; 37: 278-85.

CERTIFICATE

I certify that the thesis titled '**A study on pattern of survival of cervical cancer patients**' submitted for the degree of Doctor of Philosophy by **Mrs. Aanchal Jain** is a record of the research carried out by her under my supervision. This work has not formed the basis for the award of any degree, diploma, associateship or fellowship at this or any other institute or university.

Dr B Ganesh

Mumbai

Date 20-AUG-2018

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SYNOPSIS OF Ph. D. THESIS

3. **Name of the Student: AANCHAL JAIN**
4. **Name of the Constituent Institution: TATA MEMORIAL CENTRE**
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A study on pattern of survival of cervical cancer patients

INTRODUCTION

Worldwide, thousand of peoples are diagnosed with cancer. Cancer become common chronic disease in men and women in low, middle and high income countries (1). Since cancer incidence and mortality increases, cancer becomes a disease of attention. Worldwide cancer of lung, prostate, colorectum, stomach and liver are major sites of incidence among men. Among women; cancer of breast, colorectum, lung, cervix uteri and stomach are major site of incidence (2). Cervical cancer is the fourth most common cancer in females and seventh overall. Furthermore, on the basis of Human Development Index (HDI) cervical cancer incidence is 3.5 time more for low HDI as compare to High HDI. Mortality due to carcinoma of cervix uteri in low HDI countries is higher (213 thousands) as compare to high HDI countries (62 thousands) (3). There is a marked difference in the distribution of cervical cancer across different regions of the world. In contrast to developed countries cervical cancer is a public health problem in developing countries like India, which accounts for one quarter of the worldwide burden of cervical cancers [(2), (4)]. It is one of the leading cause of cancer mortality, accounting for 17% of all cancer deaths among women aged between 30 to 69 years. It is estimated that cervical cancer will occur in approximately 1 in 53 Indian women during their lifetime compared with 1 in 100 women in more developed regions of the world (4).

In India, cervical cancer is a second leading site of cancer mortality with age specific death rate of 12.4 per 100,000 (2). The data obtained from Indian Cancer Registries indicates that deaths from cervical cancer contribute to approximately 1-28% of all cancer deaths in females. The age-adjusted mortality rate of cancer cervix was found to vary widely among registries, highest being 10.5 per 100,000 in Barshi Rural, followed by 4.7 per 100,000 in Bhopal and the lowest being 0.1 per 100,000 in Manipur State. (5)

Survival rates describe the percentage of people with a specific cancer type who will be alive for a certain time after diagnosis. In order to have complete experience of cancer in a population, one has to know not only incidence and mortality due to cancer, but also survival of cancer patients. The need to compute survival as an outcome measure of treatment was realized in the early's 1970 in low and medium resource countries. Survival rate is an indicator of cure. It represents the average prognosis of a cancer patient and is useful for assessing progress in cancer control, including the effect of early detection, diagnosis, treatment, and follow-up on cancer outcomes. These data are also helpful in making informed decisions to ensure improved and equitable cancer care (6). There are wide variation in survival of cervical cancer patients; both within country and between countries. The 5-year age-standardized relative survival rate for cervical cancer in India is approximately 46% (34%–60%) (7).

Till date, majority of published studies focus on cervical cancer risk factors, incidence & mortality rates. Most of the studies based on cervical cancer survival and prognostic factors were from developed world; of which researchers have studied survival and factors in piecemeal, focusing on one or more specific variable which was of interest to their study. There is dearth of published literature portrays cervical cancer survival and prognostic factors in developing countries specifically to Indian population. This study was planned to comprehensively study survival rates and to evaluate the impact of patient characteristics and tumor related factors on overall survival of cervical cancer patients in Indian cohort.

HYPOTHESIS

Patient characteristics and tumor related factors affect survival rates of cervical cancer patients.

AIM: To determine and study factors affecting survival in cervical cancer patients.

OBJECTIVE OF THE STUDY

The objectives of this study are separated into primary and secondary objective:

Primary Objective:

1. To compute overall survival of cervical cancer patients.
2. To identify and study the difference in survival with regards to patient characteristics and tumor related characteristics.

Secondary Objective:

1. To study the factors which contribute to loss to follow-up and to compute loss adjusted rates for lost to follow up cases.

2. To identify time lines between registration and diagnosis, diagnosis and commencement of treatment, treatment commencement and treatment completion and to further evaluate its effect on overall survival.

MATERIAL AND METHODS

Study Design

The study was a retrospective analysis of hospital records of cervical cancer patients from the Tata Memorial Hospital (TMH). All newly diagnosed cervical cancer patients enrolled in TMH from 1st January 2007 to 31st December 2008 & have completed at least one of the treatment modality in the hospital were included in the study. Data were retrieved from the patient file and hospital based electronic medical record system (EMR).

Inclusion Criteria

- All newly diagnosed cervical cancer patients enrolled in TMH from 1st January 2007 to 31st December 2008

- All cases who have completed at least one modality of cancer directed treatment at TMH.

Exclusion Criteria

- All cases who have received any form of cancer directed therapy before registering in Tata Memorial Hospital.

Data Collection:

On the basis of inclusion-exclusion criteria a total of 1036 cases were included in the study & their medical records were analyzed retrospectively. Variables included in the study were demographic factors, co-morbid conditions, tumor grade, stage, histology, largest tumor dimension, hydronephrosis, parametrium involvement, treatment modality, pre-treatment performance status, selected baseline laboratory parameters, dates of important evolutions during treatment in the hospital (date of registration, diagnosis, treatment start date, etc) and vital status of the patient on the last date of follow-up, for each case was retrieved from the patient medical case file and hospital based electronic medical record system (EMR).

Statistical Analysis

The end point of our study is **Overall Survival**. This was calculated as the time (in months) from date of diagnosis to the date of death or date of loss to follow-up or the closing date, whichever was earliest. The closing date for the study was taken as 31 December 2014. The only event in the study was death from any cause. Overall Survival and Loss Adjusted Rates (LAR) were calculated on all cases. Differences in survival with respect to various patient and tumor related characteristics were analyzed for each FIGO regrouped stages I-IIA, IIB and III-IVA patients received curative treatment separately. Overall survival was calculated by using actuarial method (8). The difference in survival rates with regards to various factors were studied by Kaplan-Meier curves (9) and the Log-rank test (10). The Cox - regression models was used to investigate the effect of these factors simultaneously on overall survival

in a multifactorial setting (11). All statistical analysis were performed using the SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). A p value of <0.05 was considered to be statistically significant.

Analysis for Loss Adjusted Rates (LAR):

Loss adjusted survival rates was computed by using method developed by Ganesh B et al, 1995 (12).

Analysis for Timelines:

Time in days were calculated from the date of registration to date of diagnosis, diagnosis to treatment commencement and treatment commencement to treatment completion. The median value was taken as cut-off for studying the effect of timelines on overall survival. Survival rates were calculated and compared using K-M curve and Log-rank test for studying the differences in survival with respect to timelines.

RESULTS & DISCUSSION

This study includes 1036 cases of cervical cancer. Three year & five year overall survival (OS) of patients were found to be 73% & 67% respectively. Yeole et al. (13) in his study reported a five year absolute survival rates for cervical cancer as 42.2%, which is much lower than our study. This difference can be because Yeole's study is based on Mumbai cancer registry data which also included both treated and untreated cases. In contrast, our study comprised of only those patients who were diagnosed and had completed atleast one modality of cancer directed treatment at our institution. Indian studies reporting survival statistics specifically on cervical cancer are sparse. Few Indian studies, enrolled cervical cancer patients diagnosed before year 2000, reported 5-year overall survival of cervical cancer patients as 34.4%, 44.0% & 47.4% respectively [(14), (15), (16)]. All these studies had a high proportion of advance & unknown stage patients (A Nandkumar-70.5%, Yeole BB-78.5% and R Sankaranarayanan-66%) as compare to our study. Also these studies included both

treated and untreated cases. Another explanation of such differences in survival as compare to our study may be explained with respect to time frame. Shrivastava et al. 2013 analyzed the disease outcome of cervical cancer patients in relation to time periods. They found significant ($p < 0.001$) improvement in DFS from 35% for 1979-1983 and 45% for 1984-1987 to 55% at 8 years for 1988-1994 not only for the whole group, but also for individual stages. This significant improvement is also reflected in the change in treatment protocols, continuous advancements in treatment over time (17) and this might be partially explained due to improved services quality.

Saptarshi Ghosh et al. (18) conducted a study in Kolkata and reported two year OS of 81.2%, which is comparable to 2 year OS observed in our study (80%). However, Radha Munagala et al.2010 reported five year OS of 81.4% which is much higher than our study. This difference could be because of high proportion of advanced stage (stage III & IV-48.9%) cases in our study as compared to only 33.7% advanced stage cases in study conducted by Radha Munagala et al. (19).

Till date there are sufficient publications on role of clinical stage as a prognostic factor for cervical cancer survival. In this study, we also found stage is significantly predicting survival of cervical cancer patients. Stage is well known & widely used prognostic factor, but several studies also showed huge variability in survival probability within each stage and this variability reduces the accuracy of individual outcome predictions [(20), (21)]. Keeping this in mind we studied difference in survival with respect to patient and tumor related characteristics for early stage (I-IIA), IIB & III-IVA patients received curative treatment separately.

We did not find any of the socio-demographic factors as a predictor of OS, could be because of it was a single institutional study and all the patient were treated as per same protocol regardless of caste, education or socioeconomic status. Stage wise analysis showed that in

stage (I-IIA); largest tumor dimension and patients treated with radiotherapy alone were associated with poor survival. In stage IIB; presence of co-morbidity, bi-lateral parametrium involvement, elevated monocyte counts and patients treated with radiotherapy alone were associated with poor prognosis. In stage III-IVA patients; presence of co-morbidity, high grade tumors, elevated monocyte counts, patients treated with radiotherapy alone, non-squamous histology, largest tumor dimension and hydronephrosis were associated with poor prognosis (Table1).

Table1: Summary of Independent predictors of overall survival of Cervical cancer

Early Stage (I-IIA)	**Locally Advanced stage IIB**	**Locally advanced stage III-IVA (curative treatment)**
Largest Tumor Dimension	Co-morbidity	Co-morbidity
Treatment Modality	Laterality of Parametrium Involvement	Tumor Grade
	Pretreatment Monocyte Counts	Pretreatment Monocyte Counts
	Treatment Modality	Treatment Modality
		Hydronephrosis
		Tumor Histology
		Largest Tumor Dimension

One major finding of our study is that we found largest tumor dimension was associated with poor OS of early stage cervical cancer patients. This study is in accordance with S Polterauer et al. 2012 (22). For locally advance stage IIB cervical cancer patients we did not find any difference in survival with respect to largest tumor dimension. This finding of our study can be supported with reference to earlier studies that did not confirm tumor size as an independent factor [(23)(24)]. Further we found in our study that tumor size of more than 4 cm was associated with poor OS in Stage III-IVA patients. This finding of our study is similar to other previous studies [(20) (25)].

In early stage I-IIA, we found significant difference with respect to treatment modality. In multifactorial analysis significant difference in survival was observed only for radiotherapy

treated cases when compared to surgically treated cases. Although it's important to note that in the present study only a very small number of patients were treated with radiotherapy alone, which is too small to drawn any conclusion about importance of significance found in this study. Our finding of difference in survival of early stage cervical cancer patients with respect to treatment modality were similar to various studies [(26), (17)]. Further in the present study, we found significant difference in OS with respect to treatment modality for locally advance stage IIB & III-IVA patients. A number of studies showed an absolute benefit in overall survival and progression-free survival with chemo radiotherapy in patients with stage 1B-2 to IVA disease as well as high risk patients after hysterectomy (27).

One finding of our study was that elevated monocyte counts was associated with poor OS of locally advance stage IIB-IVA patients received curative treatment. This result is with concordance of other published literature probing the role of monocyte count in prognostication of breast cancer (28), gastric cancer(29), and cervical cancer patients [(30) (31)]. However, the exact underlying mechanism explaining the association between elevated number of monocyte and unfavorable cancer prognosis has not been elucidated.

We found no difference in survival with respect to tumor grade in early stage cervical cancer, which is similar to several studies (32). In stage IIB, tumor differentiation was significant in univariate analysis but losses it's statistical significance in multivariate analysis. In stage III-IVA patients we found tumor differentiation was associated with OS. Our study results are similar to other studies (33).

Co-morbidity is also competing cause of death, particularly for older patients with cancer. Numerous studies have shown poor survival outcome among cancer patients with co-morbidity. In case of cervical cancer there are very few studies reported the prognostic effect of co-morbidity on survival outcome. In this study we have investigated the role of co-morbidity on prognosis of cervical cancer. In stage I-IIA, we did not find any difference in

OS with respect to presence or absence of co-morbidity. This finding is similar to several studies [(34) (35)]. In stage IIB and III-IVA patients; we found presence of co-morbidity is associated with poor prognosis of cervical cancer patients. These results of our study are similar to other literature [(36), (37)]. The likely reason for poor prognosis of patients suffering from co-morbid condition might be due to patients with co-morbid conditions usually receive less active treatment. Presence of co-morbidity may also cause in prolonged treatment time. Also different co-morbid condition can affect survival in different way, the underlying mechanism is not known till yet, but likely reason for diabetes and HIV was reported by Ingporn Jiamset et al. 2016 (35) & Scott Dryden-Peterson 2016(36) respectively. Other significant findings of our study like parametrium involvement [(38)(39)]; hydronephrosis [(40) (41)]; tumor histology (20) is in line with many published literatures.

In the present study we did not find any significant difference in survival with respect to time taken between registration and diagnosis; time taken between diagnosis to treatment commencement; time taken between treatment commencement and treatment completion for surgically treated cases only and time taken between treatment commencement and treatment completion for surgery and adjuvant or neo-adjuvant chemo/radiotherapy treated cases. However time taken between treatment initiation and treatment completion was found to be significant for patients treated with radiotherapy alone or chemo-radio therapy treated patients and more time taken between treatment initiation and treatment completion was associated with poor overall survival. This finding is similar to existing literature [(42),(43)].

In this study we found small difference between the absolute (actuarial) survival and LAR, which is much less than in other studies. However, S Sriamporn et al 2004 (44) reported only 2.1% difference between the loss-adjusted and observed survival at 5 years, which was very small and comparable to the small difference reported by us. Thus in this study, the

assumption of independence of loss to follow up and death was seems to be reasonable, so that calculation of survival by the actuarial method without adjusting for losses to follow-up is likely to have resulted in no material bias in the estimates. Another reason to found small difference may be due to exclusion of not treated cases in this study. No treatment taken is one of the most important determinant of loss to follow up. However, this small difference in actuarial survival and LAR may not true in general and requires appropriate adjustment of survival estimates.

SUMMARY & CONCLUSION

Summary

- The overall 5-year survival of cervical cancer was found to be 67%.
- In early stage (FIGO stage I-IIA) cervical cancer the independent predictors of survival were treatment modality and largest tumor dimension.
- In stage IIB cervical cancer the independent predictors of survival were co-morbidity, parametrium involvement, pre treatment monocyte counts and treatment modality.
- In stage III-IVA patients received curative treatment the independent predictors of survival were co-morbidity, high grade tumors, pre treatment monocyte counts, treatment modality, non-squamous histology, largest tumor dimension and hydronephrosis.
- The median time from registration to pathological confirmation of diagnosis was 3 days, from diagnosis to treatment commencement was 27 days. We did not find any significant difference in survival for time lag between registration and diagnosis & diagnosis and treatment commencement.

- Prolonged time taken between treatment commencement and treatment completion was associated with poor survival for patients treated with radio/chemo-radiotherapy but not for surgically (alone or in combination) treated patients.

- **A** small difference in 5-year overall survival was seen between loss-adjusted survival rates and actuarial survival of cervical cancer patients.

Conclusion

This present study is one of the few Indian studies to comprehensively analyze and present a holistic picture of cervical cancer survival. The 5-year survival rates were better in patients with the early stages of cervical cancer than in those with advance stages. There was no significant impact of various socio demographic factors on overall survival. There was no significant difference in survival for time lag between registration and diagnosis & diagnosis and commencement of treatment. Further we found poor survival with prolonged time taken between treatment commencement and treatment completion in patients treated with radio/chemo-radiotherapy but not for surgically (alone or in combination) treated patients. Further analysis for secondary objectives showed small difference between LAR and actuarial survival of cervical cancer patients.

Utility of this study can be explain in several ways: **first**, stage wise survival estimates are more relevant to individual patients than estimates based on large numbers of heterogeneous patients, and thus could be used as an aid for patient counseling; **second**, there are few studies reporting prognostic effect of co-morbidity on OS of cervical cancer patients. In this study we found presence of co-morbid condition as an independent predictor of OS of stage IIB and III-IVA patients received curative treatment; **third**, there are very few studies reporting on prognostic effect of WBC count and it's component, on cancer survival. In this study we investigated such an association and found that elevated monocyte counts were associated

with poor prognosis of locally advanced cervical cancer. Since, Complete Blood Count test is cost effective, easily accessible and reproducible, pretreatment monocyte counts can be used as a prognostic factor in clinical practices.

However, present study is limited by the fact that it is a retrospective review of a single-institution experience. Larger, prospective multi-centric studies are warranted to evaluate further.

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LIST OF ABBREVIATIONS

CDT	Cancer Directed Treatment
CI	Confidence Interval
CT	Chemotherapy
DFS	Disease Free Survival
FIGO	International Federation of Gynecology and Obstetrics staging systems
Hb	Hemoglobin
HR	Hazard Ratio
LAR	Loss Adjusted Rate
LFU	Loss to follow-up
OS	Overall Survival
RT	Radiotherapy
S	Surgery
WBC Counts	White Blood Cell Counts

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CHAPTER 1

INTRODUCTION

Worldwide, thousand of peoples are diagnosed with cancer. Cancer become common chronic disease in men and women in low, middle and high income countries (1). Since cancer incidence and mortality increases, cancer becomes a disease of attention.

1.1 Burden of Disease

The global burden of cancer continues to increase largely because of the aging and growth of the world population and an increasing adoption of cancer-causing behaviors within economically developing countries (1). Every year about 14.1 million new cancer cases are detected and 8.2 million people die of cancer (2). Cervical cancer is the fourth most common cancer in females and seventh overall (2). Furthermore, on the basis of Human Development Index (HDI) cervical cancer incidence is 3.5 time more for low HDI as compare to High HDI. Mortality due to carcinoma of cervix uteri in low HDI countries is higher as compare to high HDI countries (3).

There is a marked difference in the distribution of cervical cancer across different regions of the world. In contrast to developed countries cervical cancer is a public health problem in developing countries like India, which accounts for one quarter of the worldwide burden of cervical cancers [(2), (4)]. It is one of the leading cause of cancer mortality, accounting for 17% of all cancer deaths among women aged between 30 to 69 years. It is estimated that cervical cancer will occur in approximately 1 in 53 Indian women during their lifetime compared with 1 in 100 women in more developed regions of the world (4).

1.2 Incidence of Carcinoma of a uterine cervix

Cervical cancer is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012. As with liver cancer, a large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers. High-risk regions, with estimated ASRs over 30 per 100,000, include Eastern Africa (42.7), Melanesia (33.3), Southern (31.5) and Middle (30.6) Africa. Rates are lowest in Australia/New Zealand (5.5) and Western Asia (4.4). Cervical cancer remains the most common cancer in women in Eastern and Middle Africa (2) (Figure1.2.1).

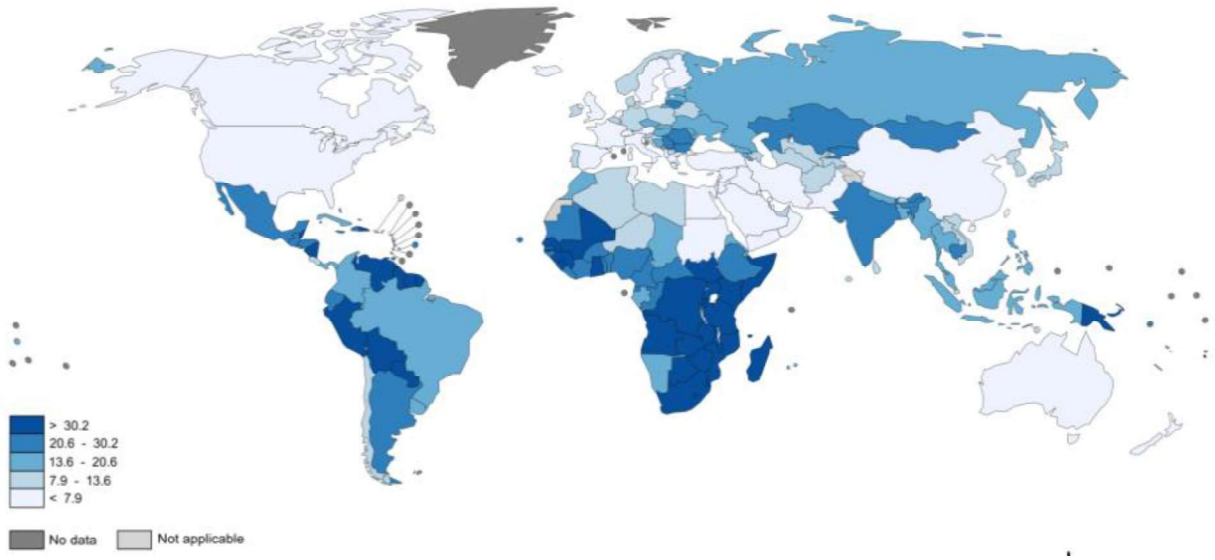

Figure1.2.1: Estimated Cervical Cancer Incidence worldwide in 2012

In Indian females, cancer of the cervix uteri is second leading side of cancer incidence with age standardised incidence rate of 22 per 100,000 (2).

As of March 2016, there are 29 Hospital based Cancer registries (HBCRs) (including all Regional Cancer Centres) and 29 Population based Cancer registries (PBCRs) in India [(5) (6)]. The data obtained from these Indian Cancer Registries indicates that cervical cancer contributes

to approximately 6-29% of all cancer in females. The age-adjusted incidence rate of cancer cervix was found to vary widely among registries, highest being 23.07 per 100,000 in Mizoram State, followed by 22.54 per 100,000 in Pasighat and the lowest being 4.91 per 100,000 in Dibrugarh District. The older PBCR's such as Bangalore, Bhopal, Chennai, Delhi and Barshi Rural reported an age-adjusted incidence rate between 13 - 16 per 100,000 (5)[Table-1.2.1].

Table 1.2.1: Age-adjusted (world) incidence rates of Cervix Uteri cancer*

Registry	Incidence (AAR)#	Truncated Rate
Ahemdabad Urban (2012-13)	6.91	16.2
Aurangabad(2012-14)	14.30	32.9
Banglore(2012)	15.33	34.6
Barshi Rural(2012-14)	16.09	36.8
Barshi Expanded(2012)	14.65	33.0
Bhopal(2012-13)	13.83	29.7
Cachar Dist. (2012-14)	12.65	34.9
Chennai(2012-13)	15.88	35.6
Delhi(2012)	15.53	36.9
Dibrugarh Dist. (2012-14)	4.91	12.8
Kamprup Urban Dist. (2012-14)	14.52	34.0
Kolkata(2012)	10.43	23.8
Kollam(2012-14)	6.69	14.7
Manipur State(2012-14)	6.14	13.9
Meghalya State(2012-14)	9.55	23.9
Mizoram State(2012-14)	23.07	62.0
Mumbai(2012)	9.03	18.7
Nagaland(2012-14)	13.14	34.2
Nagpur(2012-13)	12.88	30.2
Pasighat(2012-14)	22.54	66.3
Patiala(2012-14)	11.46	29.0
Pune (2012-13)	8.95	20.0
Sikkim State(2012-14)	10.05	24.5
Thrivananthapuram(2012-14)	7.00	14.6
Tripura(2012-14)	9.15	23.6
Wardha(2012-13)	8.64	19.9

* ICD 10-C53, # AAR- Average Age -adjusted rate per 100,000

Only a very small percentage of cases were reported in 20-29 years of age group amounting to 1.32% of all cervical carcinoma cases. More than 85% of patients in both were from age group 40 years and above. The maximum numbers of cases were reported in 50-59 years of age group amounting to 27.37% of all cervical carcinoma cases followed by 40-49 years of age group amounting to 26.32% of all cervical cancer cases (5) [Table-1.2.2].

Table 1.2.2: Age-wise distribution of Cervix Uteri Cancer

Age Range (years)*	Number of Cases (%)
20-29	109 (1.32%)
30-39	842 (10.20%)
40-49	2171 (26.32%)
50-59	2258 (27.37%)
60-69	1856 (22.49%)
70+	1012 (12.26%)

1.3 Mortality of Carcinoma of a uterine cervix

Global cancer deaths are projected to increase from 7.4 million in 2004 to 11.8 million in 2030. Cervix uteri cancer is the number one cause of cancer death in the South-East Asia Region and the African Region (7).

There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths. Almost nine out of ten (87%) cervical cancer deaths occur in the less developed regions. Mortality varies 18-fold between the different regions of the world, with rates ranging from less than 2 per 100,000 in Western Asia, Western Europe and Australia/New Zealand to more than 20 per 100,000 in Melanesia (20.6), Middle (22.2) and Eastern (27.6) Africa (2) (Figure 1.3.1).

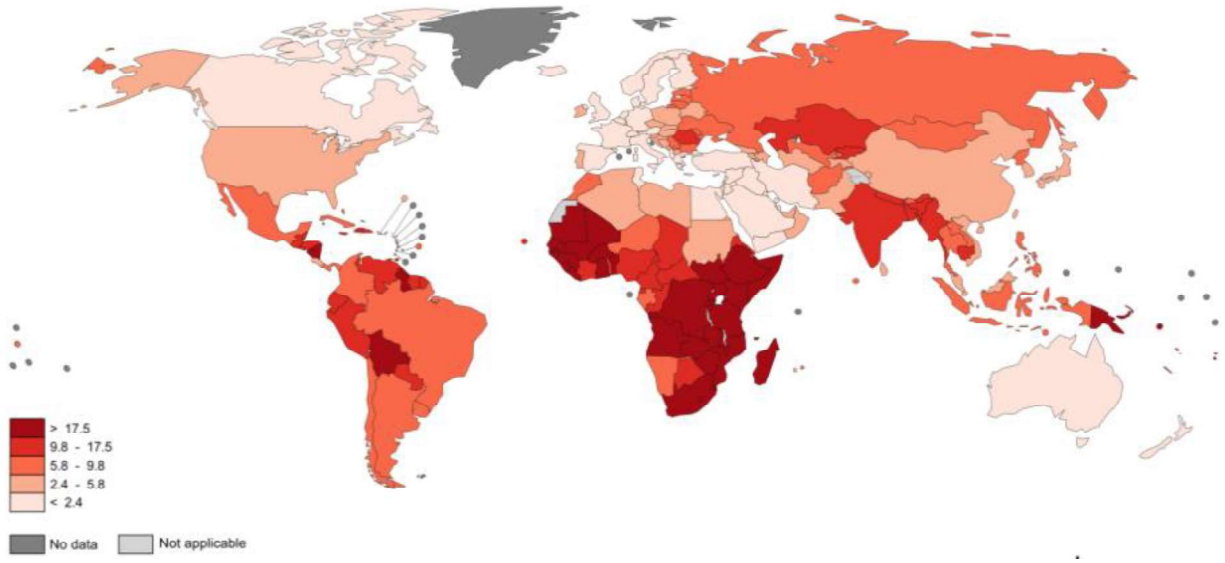

Figure1.3.1: Estimated Cervical Cancer Mortality worldwide in 2012

In India, cervical cancer is a second leading site of cancer mortality with age standardised mortality rate of 12.4 per 100,000 (2). The age-adjusted mortality rate of cancer cervix was found to vary widely among registries (8).

1.4 Survival rates for carcinoma of a uterine cervix: Worldwide and India

Survival rates describe the percentage of people with a specific cancer type who will be alive for a certain time after diagnosis. For example time from diagnosis to death. Survival rates can be describe for any given length of time. However, researchers usually give cancer statistics as a 5-year relative survival rate. In order to have complete experience of cancer in a population, one have to know not only incidence and mortality due to cancer, but also survival of cancer patients. The need to compute survival as a outcome measure of treatment was realized in the early's 1970 in low and medium resource countries. The study of cause and effect relationships is a basis of research and measurement of survival time is necessary for evaluation of chronic diseases (9). Survival rate is a indicator of cure. It represents the average prognosis of a cancer patient and is

useful for assessing progress in cancer control, including the effect of early detection, diagnosis, treatment, and follow-up on cancer outcomes. These data are also helpful in making informed decisions to ensure improved and equitable cancer care (10). Cancer patients are also interested to know survival rates by sites and stage of diagnosis.

There are wide variation in survival of cervical cancer patients; both within country and between countries. The 5-year relative survival rate for cervical cancer in India is approximately 46% (34–60) (11).

Table 1.4.1: Five-Year Age Standardized (0-74 years) Relative Survival for Cervical Cancer by Country

Country	5-Year Relative Survival (%)
Africa	
The Gambia	22
Uganda	13
Asia	
China	67 (48–79)
India	46 (34–60)
Philippines	37
Singapore	66
South Korea	79 (76–79)
Thailand	61 (54–63)
Turkey	63

Table 1.4.1 indicates that despite improvement in health infrastructure and treatment modalities, prognosis of cervical cancer in India remains poor as compared to other Asian countries such as China, Thailand, South Korea and Singapore. The intra-country variations in survival imply that the levels of development of health services and their efficiency to provide early diagnosis, treatment and clinical follow-up care have a profound impact on survival from cancer.(12)

Furthermore, the majority of published studies focus on cervical cancer risk factors, incidence & mortality rates. Most of the studies based on cervical cancer survival and prognostic factors were from developed world. Of which researchers have studied survival and factors in piecemeal, focusing on one more specific variable which was of interest to their study. There is dearth of published literature portrays cervical cancer survival and prognostic factors in developing countries specifically to Indian population. To date, there is a knowledge gap between factors affecting survival of cervical cancer patients in Indian context. Therefore, this study was planned to comprehensively study survival rates and to evaluate the impact of patient characteristics and tumor related factors on overall survival of cervical cancer patients in Indian cohort.

CHAPTER 2

REVIEW OF LITERATURE

2.1 Overall Survival

Overall Survival is a key indicator of cure. It has long been recognized as an important component in monitoring cancer control activities. It reflect different socio-demographic factors, Health seeking behaviors, natural histories & the efficiency of the health-care services to provide early diagnosis, prompt treatment, and follow-up care (11). Cancer registries have long served as potential sources of data for estimating survival. The International Agency for Research on Cancer (IARC) has been collating data on worldwide cancer incidence for five decades, in collaboration with the International Association of Cancer Registries and registries in various countries, with a particular focus on low and middle income countries [(13) - (14)].

Table 2.1.1: 5-year Absolute and Relative Survival of cervical cancer in Indian PBCR

Place	Registration year	5-year Absolute Survival	5-year Relative Survival
Barshi	1993-2000	32.2	35.1
Mumbai	1992-1999	42.2	46.1
Karunagappally	1992-1997	46.7	56.3
Bhopal	1991-1995	33.1	35.4
Chennai	1990-1999	54.0	59.4

Source: SURVCAN

There is a wide variation in survival rates according to geographical location. Five-year absolute and relative survival varies from 32-54% and 35-60% in Indian PBCR (Table2.1.1) [(15),(16), (17), (18), (19)].

In addition, few studies, enrolled cervical cancer patients diagnosed before year 2000, reported 5-year overall survival of cervical cancer patients as 34.4%, 44.0% & 47.4% respectively [(20),

(21), (22)]. However, many clinical trials and meta-analyses have shown a significant improvement in overall and progression-free survival with decreased local and distant recurrences with the use of concurrent chemotherapy with radiation. Most of these trials have been done in women from developed countries where the patient and disease profile are entirely different from ours. A recent study enrolled 76 patients reported a 2-year overall survival of 81.2% (23). A study in Chennai reported 5-year overall survival of 81.4% for FIGO stage I-III cervical cancer patients diagnosed in between year 2000 and 2005 (24). There are dearth of recent studies reflecting overall survival experience of Indian patients suffering from cervical cancer.

2.2 Factors affecting survival of cervical cancer patients

The simple question patient, their family or clinicians have in mind is "Is he/ she die due to cancer?" or "What are the chances of survival of an individual patient after dignosed with cancer". The answer is "Survival Probability". There are various studies reporting risk factors associated with cervical cancer such as early age at marriage, early age at first sexual intercourse, more number of sexual partners, high parity, smoking, use of oral contraceptives, tobacco chewing, immune suppressed states such as HIV infection [(25)(26)(27)]. Very few studies explore prognostic factors for cervical cancer, especially in Indian context. The variables needed to study survival are under three major headings: the person, the disease and the follow-up (12). In our study, we investigated the differences in survivalwith respect to patient and tumor related characterstics.

2.2.1 Age

Older age is well known factor for late stage presentation of almost all the cancer sites (28). This is well reported for cervical cancer too. Although in published literature it's role as a prognostic factor is controversial. Some studies reported age as a prognostic factor for cervical cancer survival. Survival was found to be decreased in older ages as compare to younger ages [(21),(29)]. Also age affects treatment policy for cervical cancer. Old age patients with FIGO stage IB-IIA, elderly and those with comorbidity underwent less surgery. For patients with FIGO stage IB2, IIB-IVA, age affected the choice of chemo-radiation significantly (30). Older age patients diagnosed with advanced stage and thus have poor survival as compare to younger age patients (31). On a contradictory, some studies showed no effect of age on overall survival or disease free survival of cervical cancer patients [(20), (22),(32),(33), (34),(35)].

2.2.2 Place of Residence:

Place of residence can be consider in two ways: one is well known urban-rural classification; other is on the basis of distance from treating hospital or broadly patient is permanent resident of the same place as treating hospital or patient is permanent resident of some other place than treating hospital. One analysis of such classification was done on breast cancer (9). Rural - urban differences in cancer incidence and mortality is reported by several authors [(36)(37)]. Role of place of residence in affecting survival is controversial, varying from one site to another and geographical area. Some studies have suggested a strong association between place of residence and overall survival/mortality in different cancer sites (38) including cervical cancer [(38) (36)], while others shows place of residence is independent of survival [(39)] Michelle Kaku et al.(2008) found that district of patient is independent of late stage diagnosis (p=0.12) (40). Radha

Munagala et al.(2010) reports that they did not found any association between rural and urban residence and event free survival & overall survival (24). Katherine S. Eggleston et al. (2006) found that there was no significant difference in stage at diagnosis on the basis of rural urban residence ship (41).

2.2.3 Educational level

Education can be taken as an indirect and important indicator of social class. Although, illiteracy or low socio-economic status is well known risk factor for cervical cancer incidence and mortality [(42), (43)], it's role as a prognostic factor remains unclear. Jissa V Thulaseedharan reported that compared to those with no formal education, women with some formal education had a reduced risk of cervical cancer and a significant dose-response relationship was observed with increasing education level(42). Swaminathan R(2009) found that the high burden of cancer among women with no education is predominantly contributed by the high risk of cervical cancer(43). A Nandakumar et al (1995) reported marginally significant difference in survival between illiterate and literate patients (20). Vishma B.K. (2016) did not found any difference in survival on the basis of education level(44) . Some studies reported illiterate or low educated people were diagnosed at advanced stage of cervical cancer as compare to highly educated patients. Katherine S. Eggleston et al (2006) reported that socio-economic status was independently associated with stage at diagnosis and late stage at diagnosis was a strong predictor of cervical cancer mortality. Women residing in areas with lower SES had significantly shorter survival times when diagnosed at an early stage (HR =3.0, 95% CI 2.1-4.3). Thus they concluded that lower SES was independently associated with poorer cervical cancer survival (41). There are contradicting views of different authors on effect of educational attainment on overall survival of cervical cancer patients.

2.2.4 Marital Status

Marriage is a social institution that affects individuals' lives in many aspects. Marriage is associated with family life, wellbeing, and mutual support in times of hardship. In most cultures and populations, entering adulthood is closely related to finding the partner and starting a family. Raising children, achieving physical, mental and economic happiness and stability are some of the traditional reasons to exchanging vows. Marriage has been traditionally found to improve many health outcomes for both spouses. Although healthier persons may be selectively more likely to marry, overall, marriage has been found to be health protective (45–47). an early study found that age-adjusted incidence rates of cervical cancer were lowest in married women compared to single, divorced, or widowed (48). The effect of marital status on disease specific survival (DSS) in patients with cancer has been reported across several malignancies, although the reason for a survival benefit provided by marriage has not been completely elucidated(49–55). Zachary Klaassen et al.(2015) reported that marital status is significantly associated with survival in patients with adrenocortical carcinoma and suggest that the decreased survival seen among Single/Divorced/Widowed individuals. In these patients hazard for all cause mortality and cancer specific mortality were found to be HR (95% CI)= 1.28 (1.09-1.51); p=0.003and 1.30 (1.07-1.56); p= 0.007 respectively (56). Anne Kvikstad etal.(1996) also reported adjusted hazard ratio for unmarried as compare to married [HR=1.48, 95%C.I.= 1.05-2.09] (57). In terms of late stage at diagnosis, Ferrante and colleagues found that unmarried women from Florida had a significant 63% increase in likelihood of being detected at an advanced stage compared to married women (OR 1.63; 95% CI = 1.18-2.25) (58). Another study reported that compared with married women, risks of death for single, separated/divorced, and widowed women were 1.13 (95% CI = 1.03-1.25), 1.41 (95% CI = 1.28-1.57), and 2.51 (95% CI = 2.29-2.76), respectively.

After adjustment, marital status was not independently associated with risk of death (p = 0.21), although it interacted with tumor stage and cancer-directed radiation therapy. Married women with early stage disease who did not receive radiation therapy had improved survival compared with single, separated/divorced, or widowed women(59).

On a contrary there are many studies reported that marital status is not an independent prognostic factor for cervical cancer survival. Vishma B. Kaverappa et al.(2015) reported that marital status was not associated with survival in cervical cancer (p=0.240) (60). Similar findings were reported by Radha Munagala et al. (2010) for event free survival and overall survival of cervical cancer patients(p=0.775 & 0.179 respectively) (24).

2.2.5 Religion

Religion in India is characterized by a diversity of religious beliefs and practices. The incidence of Cancer of uterine cervix has been reported to be very low amongst Muslims as compared to Hindu females (61), (62). This type of work has been carried out by many others to find out the association of religion with the development of cervical cancer (63–66). Jussawalla & Yeole (1984) carried out a study on cervical cancer problem in Greater Bombay by undertaking epidemiological investigations to identify its etiology. The age adjusted incidence rate (per 100,000) was highest in the Hindus (27.7), followed by the Christians (l7.0), Moslems (15.7) and Parsis (6.6). Thus the age-adjusted incidence rate for Hindus is 1.6, 1.8, and 4.2 times that reported for Chris- tians, Moslems, and Parsis, respectively (64). Wahi et al (1972) studied the prevalence rates and distribution of dysplasias and cancer of the uterine cervix were studied on 26,110 women in the Agra District of India. They found that Hindu women (6.6 per1000) had approximately twice the prevalence of cervical cancer seen as compare to Muslims (3.2per 1000) (65). Roopali et al. (2014) found that the incidence of the cervical cancer in Jammu and was

found to highest in Hindu women (61.8%) followed by Muslims (26.2%), Christans (7.1%) & Sikh(4.7%) (66). However there are many studies reported incidence and prevalence according to religion, there are very few reported the effect of religious affiliation on cervical cancer survival. In this regards A NandKumar et al.(1995) found no difference in survival on the basis of religion in Bangalore. He reported 5 year survival for Hindus, Muslims & Christians were 34.4%, 34.0% and 34.5% respectively (p=0.52) (20). Similar results was found by a hospital based study in Mysuru conducted by Vishma B. Kaverappa et al (2015) (p=0.224) (60). Although Rajesh Dikshit et al.(2012) reported that Muslim women had notably low age-standardised mortality ratios for cervical cancer as compare to Hindu women (67).

2.2.6 Menopausal Status

Menopause means cessation of menstruation for at least one year with declining ovarian hormonal activity. It's a consequence of biological aging. Menopause does not cause cancer, but the risk of developing cancer increases as a woman ages. (68). In addition to aging another risk factor for development of cervical cancer in postmenopausal women is that they are prone to have persistent human papillomavirus (HPV) infection. A study concluded that postmenopausal women are infected with persistent oncogenic HPV at a substantial rate, supporting the need for continued screening in postmenopausal women to detect pre-neoplastic genital lesions (69). There are very few studies reported the prognostic effect of menopausal status on cervical cancer survival. Munagala et al.(2010) reported that there is no difference in event free survival and overall survival among patients attained menopause and not attained menopause (24). Another study also reported the same finding that menstrual status had no impact on cervical cancer patient's survival (70). Although menstrual status is not usually cited in the literature as a risk factor for recurrence of carcinoma of uterine cervix, a study reported that post menopausal status

was independent risk factor for recurrence (71). However authors argued that the factor of age is possibly a reflection of these women's postmenopausal status and in their study, the women aged 50 years or over had significantly shorter DFS than younger women. Thus on the basis of literature, we can draw a conclusion that in general, menopausal status is not a prognostic factor in cervical cancer.

2.2.7 Parity

Differences in reproductive habits may have contributed to differences in cervical cancer incidence between developed and developing countries (27). High Parity (having three or more children) is well known factor for cervical carcinogenesis (72). There are several studies showing odds of having cervical cancer to high parity women is much more higher than those having two or less children (73) (74) (75). In order to explore the effect of parity on survival, there is published literature reporting that parity is not determining a difference in survival of cervical cancer patients. Munagala et al.(2010) reported that there is no difference in event free survival and overall survival among patients having parity >3 and having parity ≤3 (24). Another study by Lukaszuk K et al.(2007) also reported the same finding that they did not discovered statistical significance as regards number of pregnancies and deliveries in relation to survival (76). Contradictory to this L. Flores-Luna et al. (2001) reported that median number of pregnancies was associated with clinical stage (31) and clinical staging is a well known strong prognostic factor for cervical cancer survival.

2.2.8 Abortion History

The association between sexual behavior and cervical cancer is well established. A significantly positive trend was found between those women having had increasing numbers of induced

abortions and the incidence of cervical dysplasia (77) An article reviewed several studies and reported that the majority of cervical cancers were registered in cities where induced abortion rates have been high. Where induced abortion rates have been lower in other regions, cervical cancer incidence has also been lower. The author suggested that mechanisms of induced abortion influence on cervical carcinogenesis may be multiple. The first mode of action may be via general endocrine stress in the reproductive system resulting from termination of pregnancy related processes. Another is through mechanical trauma and possible infection associated with the dilation and curettage or incomplete evacuation of the embryo and placenta. Chronic inflammatory lesions may arise in cervical tissue on the site of this trauma, as well as cell abnormalities. In the course of time, the latter may undergo malignant transformation and/or facilitate the action of exogenous carcinogenic agents (78). Another study reported that history of one or more induced abortions has a relative risk of 2.5 for cervical adeno carcinoma compared to women with no induced abortion (79). There are very few Indian studies reporting the role of number of abortions as a prognostic factor for cervical cancer survival. Munagala et al.(2010) reported that there is no difference in event free survival and overall survival among patients do not did any abortion and those had a abortion (24). Another study by Lukaszuk K et al.(2007) also reported the same finding that they did not discovered statistical significance as regards abortion in relation to survival (76).

2.2.9 Co-morbidity

Co-morbidity has been defined as any additional clinical entity that has existed or that may occur during the clinical course of a patient with an index disease under study (80,81). Conditions described as co-morbidities are often chronic or long-term conditions. Other names to describe co-morbid conditions are coexisting or co-occurring conditions and sometimes also “multi-

morbidity" or "multiple chronic conditions. Co-morbid illness is a noteworthy concern in cancer patients (82,83). Co-morbidity may influence the clinical management of cancer patients during or after treatment. For example, patients with severe chronic obstructive pulmonary disease are not good candidates for resection of a lung malignancy and therefore there chance of cure is decreased (84,85). Similarly a diagnosis of congestive heart failure precludes some cancer treatments (86,87). Co-morbidity is also competing cause of death, particularly for older patients with cancer. Numerous studies have shown poor survival outcome among cancer patients with co-morbidity (88–97). In case of cervical cancer there are very few studies reported the prognostic effect of co-morbidity on survival outcome. A study in Netherlands reported that co-morbidity was found to be affect treatment policy and survival of cervical cancer patients (30). Similarly a study in Kentucky reported that more than two co-morbid conditions was correlated with overall survival of cervical cancer patients [HR 4.25 (95% CI: 1.00, 18.13)] (98). G. Ferrandina et al. 2012; reported that there is no difference in DFS and OS of locally advanced cervical cancer patients (99). Each co-morbid condition separately plays a role in caner survival. For example, Scott Dryden-Peterson et al 2016; reported that HIV infection was associated with poor overall survival of cervical cancer patients (100). Jeong In Choi et al. 2015; evaluated the impact of diabetes mellitus on the prognosis of cervical cancer and found that Diabetes mellitus was not a poor prognostic factor for such patients (101). Similarly Ingporn Jiamset et al. 2016 reported significant difference in Overall Survival of early stage cervical cancer patients while marginally non-significant on Recurrence Free Survival (RFS). This study also evaluate the prognostic effect of DM with in 5 year of diagnosis and after 5 years of diagnosis and they found significant difference in RFS with respect to DM only after 5 year of diagnosis (102). Peipert JF

et al 1994 reported that after adjusting for other factors composite symptom-comorbidity stage remained statistically significant in estimating prognosis of cervical cancer (103).

2.2.10 **Clinical Presentation: Performance Status**

A number of studies have examined the prognostic impact of patients' "performance status" at the time of cancer diagnosis. Performance status is a measure of a cancer patient's well-being defined as the amount of normal daily activity the patient can maintain (104,105). Peter G. Rose etal. 2010; found that Eastern Cooperative Oncology Group (ECOG) performance status (2,3 vs 0,1) was significant for determining the difference in overall survival while for studying the difference in progression free survival performance status was not remained significant (106). Peter G. Rose et al. 2015; reported that performance status (0,1,2/3) was associated with poorer 2-year progression free survival, 5-year OS and pelvic recurrence (107). Jin-hong Park et al. 2010; found that ECOG performance status (0,1vs 2) was independent prognostic factor for 5 year OS while it looses its prognostic effect to determine cancer specific survival(CSS) (108). On the other hand, William E. Winter III et al. 2004; reported that Kamofsky performance status (≥90 vs<90) was significant for determining PFS (109). Hyunsoo Janget al. 2013 reported that performance status was not an independent prognostic factor for OS of Cervical cancer patients (110). Similarly Jeung Eun Lee et al. 2004 also found non-significant effect of ECOG performance status (0,1 vs 2,3) on OS and DFS (111).

2.2.11 FIGO Stage

Stage at diagnosis is used to guide selection of primary or adjuvant treatment and to evaluate treatment results. Therefore, cancer stage of presentation is a major predictor of prognosis. For

cervical cancer, regional and distant stages have the poorest outcomes interms of survival. The five-year survival rate for cervical cancer drops from 91% for localized stage, to 57% and 16% for regional and distant stages respectively(112). Table shows published literature by different authors on cervical cancer survival according to clinical stage.

Table 2.2.1: Publications reported 5-year survival estimates as per stage

Author	**Number**	**Five year estimated survival (%)**			
		Stage I	**Stage II**	**Stage III**	**Stage IV**
Meanwell C (113)	10022	79	47	22	7
Perez CA(114)	1178	85	70	52	0
Hopkins M (115)	175	N.R.	N.R.	37	4
Thoms W* (116)	158	83	39	26	0
Clarke F (117)	359	83	38	26	0
Jones W(118)	5904	94	66	38	11
Bernd-Uwe S (119)	301	75	55	N.R.	N.R.
Werner-Wasik M (120)	125	86	81	N.R.	N.R.
Kosary CL (121)	17119	88	58	34	12
L. Flores-Luna (31)	378	82	73	47	21
Radha Munagala (24)	89	100	88	61	N.R.
N.R.=Not Reported; *Four-year estimated survival					

Thus till date there are sufficient publications on role of clinical stage as a prognostic factor for cervical cancer survival.

2.2.12 Tumor Grade

Tumor grade is the description of a tumor based on how abnormal the tumor cells and the tumor tissue look under a microscope. It is an indicator of how quickly a tumor is likely to grow and spread. It's not same as stage of a cancer. Role of tumor grade as a prognostic factor had investigated by several authors with controversial findings in different cancer sites included colon cancer, breast cancer and oral cavity cancer (122–128). Xi Cheng et al. 2004 reported that tumor grade is associated with OS [RR= 2.196, 95% C.I.= 1.104-4.370; p=0.025] (129). M.P. Hopkins et al. 1991 also reported that in cervical cancer, patients with a well differentiated tumor had an 85% survival rate while those with a poorly differentiated tumor had a 57% survival rate and tumor grade maintained significance in the multiple proportion hazard analysis (130). Carol L. Kosary 1994 also reported that tumor differentiation is independent predictor of overall survival of cervical cancer patients (131). C.-M. Ho et al. 2004 reported that in early stage cervical cancer patients (stage Ib-II) undergoing radical hysterectomy tumor grade was not found to be statistically significant in univariate analysis for both overall survival (p=0.380) and recurrence free survival (p=0.074) (132). Nuranna, et al.2014 reported no difference in 5 year OS of cervical cancer patients with respect to tumor grade in univariate analysis, but in a multivariate analysis they found it as independent predictor of stage I-IVcervical cancer survival (133).

2.2.13 Tumor Histology

Role of histology as a prognostic factor for cervical cancer is controversial mainly because of the lack of prospective studies focusing on the prognostic differences between adenocarcinoma, adenosquamous carcinoma and squamous cell carcinoma. Although some previous retrospective studies of early stage cervical cancer patients that were treated with radical surgery did not detect

any survival differences between AC/ASC and SCC(134,135), the majority of the reports about this topic suggested that patients with AC/ASC have a worse prognosis than patients with SCC(136–140). Also there is little known about significance of histology in locally advance cervical cancer and reported results are conflicting(141–144). Histology was found to be non significant for DFS and OS (99). S Polterauer et al. 2012 compared the OS of patients diagnosed with adenocarcinoma and other histological types with squamous cell as reference category. They used histological type as predictor of OS to construct a nomogram (32). Asmis et al. 2017 reported no difference in survival according to histological subtype (93). J.M. de Rijke et al.2002 found marginally non significant association between histological type and excess mortality [RR(95%C.I.= 1.4 (1.0–2.0); p=0.06] (145). S.-H. Shim et al. 2013 found histology as an independent predictor of overall survival of locally advanced cervical cancer [HR(95%C.I.)= 3.605 (1.674–7.764); p=0.001] (146).

2.2.14 Tumor Dimension

Tumor size or diameter plays crucial role in planning and management of various cancer sites including cervical cancer. S Polterauer et al. 2012 compared the OS of patients on the basis of tumor size and found that tumor size of 2-4 cm and more than 4 cm had more hazard after taking less than or equal to 2 cm as reference category. Further they used tumor size (less than or equal to 2 cm vs more than 2 cm) as predictor of OS to construct a nomogram for cervical cancer patients (32). S.-H. Shim et al. 2013 tried to explore the effect of tumor size on overall survival of locally advanced cervical cancer. They studied the prognostic effect of tumor size in two ways: one as a continuous variable ; other as categorical variable ($\leq$4; > 4to$\leq$5 and >5cm). In both the ways they found significant effect of tumor size on overall survival (146). Tseng et al detailed a prognostic nomogram for overall survival in patients with stage IIB-IVA disease

treated with concurrent chemoradiation based on retrospective analysis of 251 eligible patients. In their nomogram, patients with tumor 4-6 cm and >6 cm had a worse prediction of overall 5-year survival compared to patients with tumor of <4cm. (147). Daisuke Endo et al. 2014 also found significant effect of tumor diameter on overall survival (148)**.** Nuranna, et al.2014 reported no difference in 5 year OS of cervical cancer patients with respect to tumor diameter [≤4cm(56%) vs >4cm(47%); p=0.070] (133). Kate Parker et al. 2009, study included more than 50% of stage IIB patients reported that for patients receiving fully planned radiation, tumor size was not independent predictor of OS. (149).

2.2.15 Treatment Modality

Gynecologic malignancies may be treated either alone or with a combination of surgery, chemotherapy, or radiotherapy. Surgery and/or radiation are the primary treatment modalities used to treat cancers of the lower genital tract (vulva, vagina, and cervix). Primary radiation may be appropriate for all cancers of all 3 organs or radiation may be given as adjuvant treatment or in a palliative care setting [(150),(151)]. In a phase III randomized trial Fabio Landoni et al. 1997 obtained similar cure rates for stage IB squamous carcinoma of the cervix patients treated with surgery or radiotherapy (150). Maaike A et al,2009; reported that there was a survival difference of early stage I to IIA cervical cancer patient treated with radical hysterectomy, radiotherapy and other treatment (76% vs 41% vs 49%; p=0.002). They also found survival difference among FIGO stage IIb to IVA patients treated with radiotherapy and chemo-radiotherapy(36% vs 47%; p=0.03) (152). Radiotherapy remains the mainstay of treatment for advance stages. Platinum based concomitant chemo-radiation improves survival. There were several studies reported the comparison between radical RT vs concurrent CT-RT, and their meta-analysis have shown an absolute benefit in OS and PFS with chemo-radio therapy in patiens with stage IB2 to IVA

disease as well as high risk patients after hysterectomy (153–157).A systematic review & meta analysis of concurrent CT-RT from Cochrane Database Systematic Review collected data from 24 trials and 2491 patients strongly suggested that benefit of adding chemotherapy in both DFS and OS with absolute benefits of 10% and 13% respectively. There was also some suggestions that the benefit is greater in stages I & II; there was benefit in both local and distant failure rates (153). Similar findings were obtained by Claire Vale et al. 2008. On the basis of 13 trials that compared chemoradiotherapy versus the same radiotherapy, there was a 6% improvement in 5-year survival with chemoradiotherapy. (158). A Nandakumar et al. 2015 also found significantly better survival for those who received RTCT comared to those who received RT alone (159). Robert et al. 2000 reported that 4 year actuarial survival rates for radiotherapy with Chemotherapy and radiotherapy alone were 72% and 56%, respectively (160).

2.2.16 Parametrium Involvement

Parametrial invasion is an important factor associated with OS and DFS of cervical cancer patients. It's also one of the criterion in FIGO staging. S Polterauer et al. 2012 compared the OS of patients had parametrium involved by taking no parametrium involvement as reference category. They found it statistically significant in univariate analysis and used parametrium involvement as predictor of OS to construct a nomogram (32). Coia et al.et al. 1990 analyze the importance of unilateral *versus* bilateral parametrial involvement on 4 year actuarial survival and find marginally non-significant results with 57% actuarial survival for unilateral involvement and 48% actuarial survival for bi-lateral involvement (p=0.06). For patients with Stage IIb cancer, there was a trend toward decreased survival in patients with bilateral parametrial involvement compared with unilateral (67%vs 54% ; p=0.10). For Stage III patients there was, however, no difference in survival or in-field failure for unilateral *versus* bilateral parametrial

involvement. However, in a subgroup having Karnofsky>80 4 year survival % was significantly different (p=0.04). They also found that bilateral parametrium involvement is associated with 4 year actuarial distant metstasis as compare to unilateral involvement (28% vs 13%; p<0.05) (161). Souhami *et al.* **1987** reported a significant decrease in survival for bilateral parametrial involvement compared with unilateral involvement in Stage III patients (162). Sinistrero ***et at.1988*** also found that the extent of parametrial infiltration was associated with survival, particularly in patients with Stage IIIb disease. In their study the 5-year survival in patients with Stage IIb disease was 68% for unilateral parametrial infiltration and 52% for bilateral. The 5-year survival in Stage IIIb with one parametrium fixed to the pelvic wall and limited (less than a half) involvement of the other side was 66%. With one parametrium fixed and the other with more than half involved, the survival was only 15% (P = 0.01)(163) . RACHELLE M. LANCIANO et al.1990 reported that in stage IIb cervical cancer patients bi-lateral parametrium involvement (as compare to uni-lateral involvement) is associated with poor 4 year survival rate (52% vs 70%, p=0.001) while for stage III patients, the separation by extent of pelvic disease used in this analysis had significant prognostic value with respect to infield pelvic control and survival (44% vs 34%, p=0.04) (164)**.** On the other hand S.-H. Shim et al. 2013 studied the prognostic role of bilateral and unilateral parametrium involvement with reference to no involvement of parametrium, and they found both unilateral and bi-lateral parametrium involvement were unable to predict differences in overall survival of cervical cancer patients (146).

2.2.17 Hydronephrosis

Hydronephrosis is frequently encountered in advanced stage cervical cancers. Association of hydronephrosis with mortality/survival was reported by several authors. S.-H. Shim et al. 2013

found that presence of hydronephrosis is not a significant prognostic factor for overall survival of locally advanced cervical cancer patients [HR(95%C.I.)= 1.448 (0.723–2.898); p=0.296] (146). Masateru Fujiwara et al. 2015 studied the prognostic factor for FIGO stage IB2 to IVA cervical cancer patients and found no association between presence or absence of hydronephrosis and PFS (165). Peter G. Rose etal 2010 reported that hydronephrosis at presentation is a significant but not independent prognostic factor associated with poor survival (106). Mehmet Rıfat Goklu et al. 2015 reported that when compared to mean survival in patients who did not have hydronephrosis, survival was significantly shortened in patients who had bilateral and unilateral hydronephrosis ($p < 0.05$). There was no significant survival difference between patients with unilateral and bilateral hydronephrosis ($p>0.05$) (166). Tseng et al2010, developed a prognostic nomogram for overall survival in patients with stage IIB-IVA disease treated with concurrent chemoradiation based on retrospective analysis of 251 eligible patients. In their nomogram, the presence of HN had a worse prediction of overall 5-year survival: relative risk of 2.82 (95% CI, 1.89-4.67; $p <0.001$) compared to non-HN patients (relative risk of 1.0) (147). Krishna Patel et al. 2015 also reported that in univariate analyses, hydronephrosis was associated with advanced cancer stage ($p<0.0001$). In multivariate analyses, stage and tumor histology were associated with hydronephrosis. In landmark univariate survival analyses, hydronephrosis was associated with worse survival at all time points. In landmark multivariate analyses (adjusted for patient age, stage, cancer treatment, and tumor histology), hydronephrosis was associated with a trend toward worse survival over time (hazard ratios ranged from 1.47 to 4.69) (167). Tana S. Pradhan et al. 2011 found median time to death was significantly shorter for patients with unilateral HN (27 months; 95% confidence interval [CI]= 10-48) and bilateral HN (12 months; 95% CI= 6-23) versus patients without HN(68 months; 95%CI= 39-∞; P G 0.001). Unadjusted hazard ratio (HR)

for HN (both unilateral and bilateral) was 2.4 (95% CI, 1.5-3.8); p< 0.001. Of potential covariates evaluated, performance status and sidewall involvement were significantly associated with HN (P = 0.021 and P = 0.014, respectively). Proportional hazards regression revealed that controlling for use of radiation, chemotherapy, and for performance status, HN was still significantly associated with poor prognosis (HR unilateral HN= 2.0, 95%CI=1.2-3.5; HR bilateral HN= 3.2, 95% CI= 1.7-6.0); P ≤ 0.001) (168).

2.2.18 Pre-treatment Hematological parameters:

Parametrium infiltration, lymph node involvement, depth of invasion, surgical margin, number of positive lymph node and lympho vascular space involvement (LVSI) were found to be independent predictors of overall survival and recurrence in cervical cancer patients. (169)(132). But unfortunately these factors can be accessed only after surgery and in cervical cancer radiotherapy or chemo-radiotherapy is main treatment modality. Therefore, a low cost, standardized and reliable marker is required to be evaluated for it's possible prognostic role in cervical cancer. It has been suggested that host immunological factors have an impact on treatment response and prognosis (170). Increase release of pro-inflammatory cytokines produces a systemic inflammatory response reflected in changes in circulating markers of inflammation, such as C-reactive protein and white blood cells (171,172). There are several studies to date suggesting that total white blood cell counts as well as it's components can predict survival in many cancers including cervical cacner, breast cancer, oral cavity, gastric cancer, hepatocellular cancer, Hodgkin's lymphoma and lung cancer. However, information regarding tumor related leukocytosis in cervical cancer is limited and discussed in the following sections.

2.2.18.1 Hemoglobin Level

Several studies were found the effect of Hb on OS in several studies including K. PARKER et al 2009(149); Lim A, Sia S.2012 (173) Wataru Kudaka et al. 2013 (174) and (170) P.J. Hoskin et al. (2014). Na-Ri Shin, et al. 2014 shows non significant effect of pre-treatment hemoglobin level (<11.2 g/dL vs ≥11.2 g/dL) on OS in early stage(IB to IIA) cervical cancer patients (34). S.-H. Shim et al. 2013 tried to explore the effect of pretreatment hemoglobin level on overall survival of locally advanced cervical cancer. They studied the prognostic effect of pretreatment hemoglobin in two ways: one as a continuous variable ; other as categorical variable (<8;≥8-12 and >12g/dL). In both the ways they found non significant effect of pretreatment hemoglobin level on overall survival [{HR(95%C.I.)=0.896(0.784-1.025; p=0.110)}; {HR(95%C.I.)=2.150(0.817-5.658;p=0.121)} and {HR(95%C.I.)=1.218(0.678-2.186); p=0.509} respectively for continuous value of hemoglobin level, <8g/dL and ≥8to<12g/dL taking ≥12g/dL as reference category] (146). Daisuke Endo et al. 2014 also found non-significant effect of pretreatment hemoglobin level on overall survival (148). Although, the optimal time to access pre-treatment hemoglobin for the purpose of evaluating prognostic effect is varies widely in literature. At one hand studies focuses prognostic effect of pre-treatment Hemoglobin level, on the other hand some studies show hemoglobin during treatment and not pre-treatment as the independent predictor(175–177). It's also important to note that to evaluate the prognostic effect of pretreatment hemoglobin level on OS various studies used different cut-off points, varying from one study to another and various number of categories.

2.2.18.2 White Blood Cell Counts

There seems to be an increasing evidence that inflammation leads to cancer. WBC counts is one of the easily accessible marker of inflammation and many studies provide evidence for an association of white blood cells counts (WBCs) with cancer prognosis. Elevated baseline WBC counts were found to be associated with OS and DFS of many cancer sites including ovarian cancer (178), cervical cancer (179), lung cancer (180), Hodgkin's lymphoma (HL) (181).

However on a contradictory, in a recent past there are some studied reported that pretreatment Leukocyte counts were not significant in determining the prognosis of various cancer [(182), (183), (184)].

2.2.18.3 Neutrophil Counts

Many of the cells and mediators involved in the development of the systemic inflammatory response are also found in the microenvironment of tumors; it is believed that these factors support tumor growth and progression, affecting host antitumor activity, which underlies the importance of identifying markers associated with cancer-inflammatory response (185,186). Neutrophils are central to this inflammatory response. The prognostic significance of the absolute neutrophil count (ANC) has been extensively studied by several authors in different cancer sites with conflicting results including stage III and IV non small cell lung cancer (187), cervical cancer [(188) (189)], endometrial cancer (190) and oral cancer (184).

2.2.18.4 Lymphocyte Counts

The absolute lymphocyte count (ALC) has been studied in hematologic and solid malignancies as a marker of host antitumor immunity. Till that he prognostic significance of the absolute

neutrophil count (ANC) has been extensively studied by several authors in different cancer sites with conflicting results [(181) (170) (191) (184) (189)].

2.2.18.5 Monocyte Counts

The evidence that peripheral circulating monocyte count may have a prognostic role in cancer is limited because studies dealing with monocytes are rare. In the human innate immune system, antigen-presenting cells (APCs), such as dendritic cells and macrophages, display antigen complexes which present major histo compatibility complex on their surfaces so that T-cells can recognize the complex using their T-cell receptors (192). Interestingly these APCs, which play pivotal roles in the initiation, programming, and regulation of tumor-specific immune responses (193), are derived from peripheral monocytes (192,194). Moreover, it was recently reported that SCC of the head and neck influences monocyte phenotype (195), and the circulating monocyte count can be used to independently predict incident cancer and mortality (196), which suggests an association between cancer prognosis and monocyte. Role of monocyte count as a prognostic factor was published in many studies including breast cancer(182), gastric cancer(197), Head and Neck cancer [(184),(198)] endometrial cancer (190). Y.-Y. Lee et al. 2012 reported that pretreatment monocyte count is associated with overall survival of locally advanced stage (IIB to IVA) cervical cancer patients (194).

2.2.18.6 Blood Group

ABO blood group system classifies human blood based on the presence or absence of the antigens A and B carried on the surface of erythrocytes. It's a cost effective and easily accessible marker in individuals and have been statistically associated with many diseases including coronary heart diseases (199), (200); parkinson's disease (201); respiratory diseases (202) and

hodgkin's disease (203) etc. Recently Role of Blood Group in cancer risk was reported by several authors. Blood type A, B, AB and O were found to be associated with cancer risk for various site including breast cancer (204,205); gynecological cancers (75), (206,207); bladder cancer (208,209); gastric cancer (210). There are few studies reporting prognostic effect of Blood group on different cancers including breast cancer(211) (212), ovarian cancer (213), laryngeal cancer(214) and cervical cancer (29), (215). The effect of blood group on prognosis of cancer is still controversial and need to be further investigated.

2.2.19 Loss Adjusted Rates (LAR)

Survival can be computed only when we have information on patient's follow up. In developing countries, including India, follow up information is not completed. Thus, lost to follow up is a major problem for estimating survival rates. There are very few Indian studies reported overall and disesase free survival may be because of lack of follow up information of patients. If patient is lost to follow up, survival results obtained are more likely to be biased. Socio-demographic and clinical characteristics may help to predict loss to follow up. Information on the association between prognostic factors and loss to follow-up can be used to reduce the bias in estimates of survival. Ganesh B et al. seen that the corrected survival rates by LAR method when compared with the actuarial (AR) method showed the possible bias caused due to the losses on follow up [(9) (216) (217)] These studies were on hospital based series. However in a population based cancer registry data S Sriamporn et al (2004) was not found any difference in survival between Loss Adjusted method and Actuarial method. (218)

2.2.20 Time Lines:

There are very few studies reported effect of delay in diagnosis on cancer outcome (219) and authors measure this time from different time points. Keeping in mind about existing literature,

it's unclear whether more timely cancer diagnosis brings favorable outcomes, with much of the previous evidence, in some cancers, being equivocal (220–223).

Treatment is usually either chemoradiation or radical hysterectomy/trachelectomy with lymph node dissection in early stages and chemoradiation in advanced stages. In many institutions, patients experience a delay between diagnosis and initiation of treatment. The effect of treatment delay on the risk of recurrence and mortality is a matter of concern to both patients and physicians (224). The question of whether a delay between the diagnosis of cancer and its treatment has a negative effect on the patient's clinical outcome has been examined in several malignancies, with conflicting results (225–232). Umezu et al. 2012 (224) reported that waiting time from diagnosis to surgical intervention was not associated with adverse overall survival in early-stage cervical cancer, whereas Choan et al 2005 (233) reported that delay in radiotherapy had a consistently adverse effect on survival regardless of the duration of delay.

However literature reports this effect for other cancer sites (234), (235), in cervical cancer patients treated with surgery or adjuvant or neo-adjuvant chemotherapy plus surgery, we found only one study reporting the effect of overall treatment time (OTT) on PFS and OS. Jeongshim Lee et al. 2016 showed no difference in OS with respect to OTT (236).

Evidences suggest that OTT has an impact on prognosis of locally advanced cervical cancer. It's very important to minimize the treatment completion time once it has been started for radiotherapy or chemo-radio therapy treated cases. Radical Radiation / concomitant chemo-radiation should be completed within 8 weeks without significant treatment breaks. Prolonged overall treatment time result is poor outcome [(237),(238),(239),(240),(241),(242)]. However Sara C. Erridge et al.2002 showed no effect of prolong treatment time on prognosis of cervical cancer patients, almost all of whom were treated in less than 7 weeks (243).

CHAPTER 3

AIMS & OBJECTIVES

Aim

To determine and study factors affecting survival in cervical cancer patients.

Objective of the Study

Objective of this study is separated in to primary and secondary object:

Primary Objective

1. To compute overall survival of cervical cancer patients.
2. To identify and study the difference in survival with regards to patient characteristics and tumor related characteristics.

Secondary Objective

1. To study the factors which contribute to loss to follow-up and to compute loss adjusted rates for lost to follow up cases.
2. To identify time lines between registration and diagnosis, diagnosis and commencement of treatment, treatment commencement and treatment completion and to further evaluate its effect on overall survival.

CHAPTER 4

MATERIAL AND METHODS

4.1 Study Design

It's a retrospective cohort study on cervical cancer survival. All newly diagnosed cervical cancer patients enrolled in Tata Memorial Hospital (TMH) from 1st January 2007 to 31st December 2008 & have completed at least one of the treatment modality in the hospital were included in the study.

4.2 Inclusion Criteria

- All newly diagnosed cervical cancer patients enrolled in TMH from 1st January 2007 to 31st December 2008
- All cases who have completed at least one modality of cancer directed treatment at TMH.

4.3 Exclusion Criteria

- All cases who have received any form of cancer directed therapy before registering in Tata Memorial Hospital.

4.4 Selection of cases:

On the basis of inclusion-exclusion criteria a total of 1036 cases were included in the study. Flow chart for selection of cases represents the stepwise selection of cases. (Figure4.4.1)

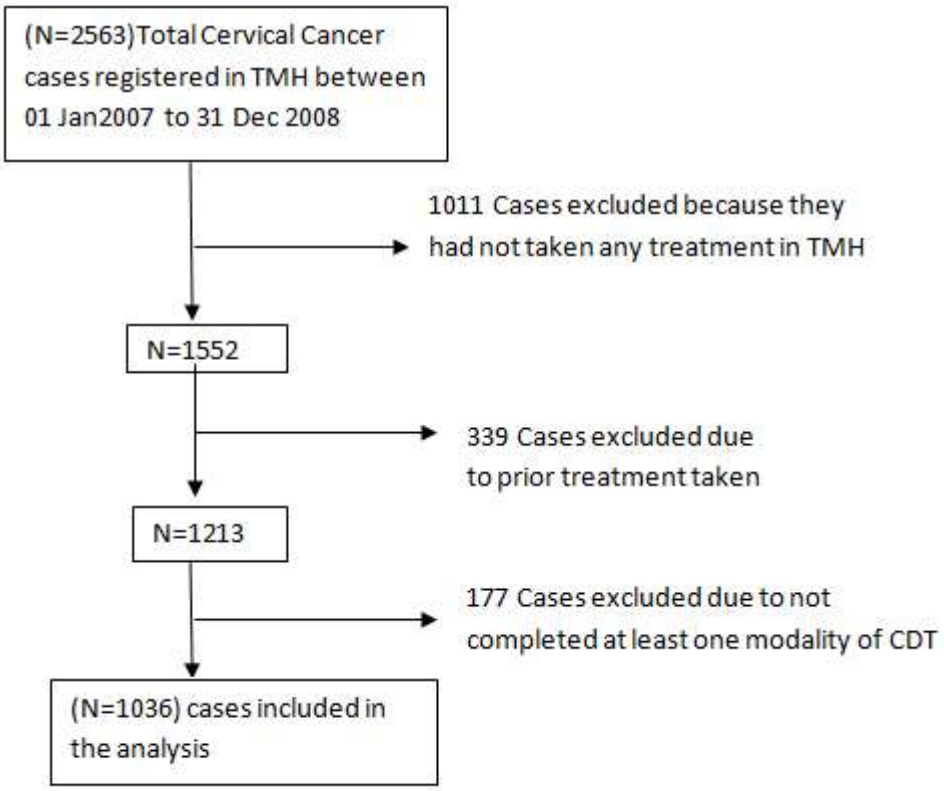

Figure 4.4.1: Selection of Cases on the basis of Inclusion/ Exclusion Criteria

4.5 Data Source

Data were retrieved from the patient file and hospital based electronic medical record system (EMR).

4.6 Variables Under Study and it's Classification

The variables needed to study survival are under three major headings: the person, the disease and the follow-up. In this study, we divide the factors accordingly in to two groups:

- Patient's Characteristics
- Tumor related factors.

For each patient under this study, the following data were collected for analysis:

4.6.1: Patient's Characteristics

It includes demographic factors such as age, place of residence, education, marital status, religion, co-morbid conditions, menopausal status, parity, number of abortions and pre-treatment performance status. Details of each of the variable is as follows:

4.6.1.1 Age

This refers to the age in completed years. Age was divided into four groups on the basis of decades. To study the effect of age on overall survival age was considered into four age groups as follows:

- Less than or equal to 44
- 45-54
- 55-64
- 65 & Above

4.6.1.2: Place of Residence

Place of residence was categorized in to two categories on the basis of duration of stay at the place of usual residence from date of diagnosis, namely; **Mumbai**: Patients whose permanent resident address in medical records was of Mumbai or who have been residing in Mumbai for a period of more than one year; **Outside Mumbai**: All other were grouped in to Outside Mumbai Category.

4.6.1.3: Educational Status

Information on Educational Status of the patient was initially collected on different educational level that is: Illiterate, Primary, Middle, Secondary, High School, intermediate and College & Above. For analyzing the differences in survival with respect to educational status it's grouped broadly in to two groups namely Literate and Illiterate.

4.6.1.4: Marital Status

Information on Marital status at the time of registration was obtained as unmarried, married, widow, divorcee, separated. For analysis point of view it's divided as Married, Widow and Others. Others category includes unmarried women, separated and divorcee.

4.6.1.5: Religion

Religion was categorized as Hindu, Muslim, Christian, Sikh, Neo-Budhist, Jain, Parsi, Jew and Anglo Indian. Here we grouped religion into two categories as:

- Hindu and
- Non-Hindus.

4.6.1.6: Co-morbid Condition's

Co-morbidity may play a very important role in survival. In this study, we have taken following conditions as co-morbid conditions to study it's effect on overall survival of cervical cancer patients: Hypertension, Asthma, Diabetes, HIV/AIDS, Hepatitis/ HBSAg+ and Ischemic Heart Disease (IHD).

4.6.1.7: Menopausal Status

It is broadly classified in to two groups: pre-menopausal and post-menopausal.

4.6.1.8: Parity

Parity was grouped in to two categories as less than or equal to two and more than two.

4.6.1.9: Number of Abortions

This is categorized as no abortion and atleast one abortion in women's life time.

4.6.1.10: Clinical Presentation

It includes performance status at the time of diagnosis. It was accessed on the basis of the criteria defined by the Eastern Cooperative Oncology Group (ECOG) (244).

4.6.2: Tumor related factors

4.6.2.1: FIGO Stage

Staging of cervical cancer is based on clinical evaluation. In this study, cases were staged as per FIGO staging criteria.

4.6.2.2: Tumor Grade

Classification of tumor grade is in accordance with ICD-O (245). For Analysis point of view Grade1 and Grade 2 were combined as Low grade (246).

4.6.2.3: Tumor Histology

For studying the effect of histological type on cervical cancer survival information was collected into two categories: Squamous and Non-Squamous.

4.6.2.4: Tumor Dimension

Tumor dimension was taken as the one having largest dimension. Information on largest tumor dimension was obtained from hospital records.

4.6.2.5: Treatment Modality

Treatment options for Cervical Cancer depends on FIGO staging. Early stage (I-IIA) cervical cancer patients were treated by surgery or radiotherapy alone or in combination with chemotherapy. Adjuvant therapy after radical surgery were given according to high, intermediate or low risk groups. Locally advanced stage (IIB-IV) cervical cancer patients were treated either by radiotherapy alone or in combination with chemotherapy. Details of the cancer directed treatment was obtained from the patient‘s medical records and the hospital based electronic medical record system (EMR).

4.6.2.6: Laterality of parametrium involvement

Data on Involvement of Parametrium was obtained from the patient‘s medical records and the hospital based electronic medical record system (EMR).

4.6.2.7: Laterality of Hydronephrosis

Presence or absence of hydronephrosis at the time of diagnosis and laterality of involvement was recorded as no hydronephrosis, unilateral involvement and bi-lateral involvement from the patient‘s medical records and the hospital based electronic medical record system (EMR).

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4.6.2.8: Selected Baseline laboratory parameters

We was also studied the effect of some selected pre-treatment laboratory parameters on Overall survival of cervical cancer patients. It includes pre-treatment Hemoglobin level (Hb), Total & differential White Blood Cell Counts (WBC) which includes neutophil counts. Monocyte counts & lymphocyte counts. Pretreatment counts means the levels of selected heamatological parameters analyzed from the patient‘s blood sample drawn before the onset of any type of caner directed therapy. To study the effect of such factors on survival median was taken as cut-off value & groups were formed on the basis of median value of the variable under study. Effect of Blood Group on overall survival of cervical cancer patients was also accessed.

4.6.3: Variables related to timelines

Timelines refers to time taken from registration to treatment completion. In this study, we made an attempt to study effect of timelines on overall survival of cervical cancer patients received curative treatment. To study differences in survival with respect to timelines it’s divided in three sections:

- Time from registration to diagnosis
- Time from diagnosis to treatment commencement
- Time from treatment commencement to treatment completion

Further, since treatment completion time is different according to treatment modality received, cohort was divided into three categories:

- Surgically treated cases

- Surgery with other combinations
- Radiotherapy or chemo-radiotherapy treated cases (Curative treatment)

4.7: Statistical Analysis

The only event in this study was death due to any cause. Patients'overall survival (OS) duration was defined as the time interval between the date of diagnosis and the date of death or the date of the last follow-up, whichever was earlier. The closing date for recording the last follow-up was taken as 31st December 2014. Overall survival was calculated by using actuarial method (247). The difference in survival rates with regards to various factors were studied univariately by Kaplan-Meier curves (248) and the Log-rank test (249). The Cox regression model was used to investigate the effect of these factors simultaneously on overall survival in a multifactorial setting (250). All statistical analyses were performed using the Statistical Package for Social Science program (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). A probability, p value < 0.05 was considered to be statistically significant.

4.7.1 Analysis for Loss Adjusted Rates (LAR):

Loss adjusted survival rates was computed by the method developed by Ganesh B et al, 1995(216).

4.7.2 Analysis for Timelines:

Time in days were calculated from the date of registration to date of diagnosis, diagnosis to treatment commencement and treatment commencement to treatment completion. The median value was taken as cut-off for studying the effect of timelines on overall survival. Survival rates were calculated and compared using K-M curve and Log-rank test for studying the differences in survival with respect to timelines.

4.8: Schema of Analysis

Analysis for overall survival and Loss adjusted rates were carried out for all the cases under study. To evaluate the differences in survival with regards to patient's and tumor related characteristics, cohort was divided according to stage and intention to treat patients. The following groups were evaluated for differences in survival:

1. Early Stage I-IIA
2. Advance stage IIB
3. Advance stage III-IVA patients received curative treatment

Differences in survival with respect to timelines were studied only on those patients received curative treatment.

CHAPTER 5

RESULTS

5.1: Descriptive Statistics

Description of cervical cancer patients with respect to various socio-demographic and clinical factors are presented in subsequent tables. Table 5.1.1 shows age wise distribution of cervical cancer patients. Median age of patient was 50 years ranging from 21-85 years. Nearly 75 % patients had diagnosed at the age of 45 years and above.

Table 5.1.1: Age wise Distribution

Age Group	Number (%)
≤44	260(25.1)
45-54	352(34.0)
55-64	292(28.2)
65 & Above	132(12.7)
Total	**1036(100.0)**
Median Age(Years)	**50**
Range (Years)	**(21-85)**

Table 5.1.2 shows religious group of patients. Majority were Hindus followed by Muslims and Neo-Buddhists. Only 2.5% were from other communities.

Table 5.1.2: Distribution according to Religion

Religion	Number (%)
Hindu	882(85.1)
Muslim	90(8.7)
Neo Buddhist	38(3.7)
Others*	26(2.5)
Total	**1036(100.0)**
*Others includes Christian, Sikh, Jain & Parsi.	

Table 5.1.3 shows educational status of cervical cancer patients at the time of diagnosis. Almost half of the patients were illiterate followed by one fourth patients taken only primary education. A small percentage (4.5%) were college educated or above.

Table 5.1.3: Distribution according to Educational Level

Educational Level	Number (%)
Illiterate	533(51.4)
Primary	254(24.5)
Secondary	202(19.5)
College and Above	47(4.5)
Total	1036 (100.0)

Table 5.1.4 explore the marital Status of cervical cancer patients. Cervical cancer patients were either currently married (74%) or widow (25.2%). Only negligible number (0.8%) of patients were either unmarried, divorcee or separated.

Table 5.1.4: Distribution according to Marital Status

Marital Status	Number (%)
Married	767 (74.0)
Widow	261 (25.2)
Others*	8 (0.8)
Total	1036 (100.0)
Others includes Divorce, unmarried or separated.	

Table 5.1.5 shows the place of residence of patients. Only 23.5% of patients were Mumbai resident.

Table 5.1.5: Distribution according to Place of Residence

Place	Number (%)
Mumbai	243 (23.5)
Outside Mumbai	793 (76.5)
Total	1036 (100.0)

Table 5.1.6 shows Menopausal status of cervical cancer patients. Almost two-third of patients were post-menopausal and rest one third were pre-menopausal.

Table 5.1.6: Distribution according to Menopausal Status

Menstrual Status	Number (%)
Pre Menopausal	341(32.9)
Post Menopausal	695(67.1)
Total	**1036(100.0)**

Table 5.1.7 shows parity of cervical cancer patients. This table explore that approximately 20% patients have parity two or less.

Table 5.1.7: Distribution according to Parity

Parity	Number (%)
≤2	213 (20.6)
>2	650 (62.7)
Unknown	173 (16.7)
Total	**1036 (100.0)**

Table 5.1.8 shows almost 70% patients have not done abortion in their life time, while 13.8% have done at least one abortion.

Table 5.1.8: Distribution according to Number of Abortion

Abortions	Number (%)
No	720 (69.5)
Yes	143 (13.8)
Unknown	173(16.7)
Total	**1036 (100.0)**

We consider hypertension, diabetes, heart disease, asthma, hepatitis/ HBsAG+ and AIDS/HIV positive as a co-morbid condition. In these series of cervical cancer patients we found only 24.0% cases suffering from any of the above co-morbid condition. Rest 76.0% patients were free

from co-morbidity. Among these co-morbid conditions hypertension (14%) is the leading co-morbid condition followed by diabetes (7%) and AIDS/HIV positive (2.5%). (Table 5.1.9)

Table 5.1.9: Distribution according to Comorbid Conditions

Co-morbidity	Number (%)
Co-morbidity Absent	**787(76.0)**
Co-morbidity Present	**249(24.0)**
Hypertension	145(14.0)
Diabetes	72(6.9)
Heart Disease	12(1.2)
Asthma	12(1.2)
Hepatitis/HBsAG+	19(1.8)
AIDS/HIV+	26(2.5)

Table 5.1.10 shows tumor histology of cervical cancer patients. Majority of the patients were squamous carcinoma (91.0%). It means that 9 patients out of 10 were diagnosed with squamous carcinoma of cancer cervix.

Table 5.1.10: Distribution according to Tumor Histology

Histology	Number (%)
Squamous Carcinoma	943 (91.0)
Non-Squamous	93 (9.0)
Total	**1036 (100.0)**

Table 5.1.11 shows distribution of cervical cancer patients according to tumor grade (tumor differentiation). Very few (approximately 5%) were diagnosed as well differentiated. Majority of patients have unknown tumor grade. 31% were poorly differentiated and 20% were moderately differentiated.

Table 5.1.11: Distribution according to Tumor Differentiation (Tumor Grade)

Grade	Number (%)
Well Differentiated	49(4.7)
Moderately Differentiated	210(20.3)
Poorly Differentiated	322 (31.1)
Not determine	455(43.9)
Total	**1036 (100.0)**

Table 5.1.12 reflect the distribution of well known prognostic factor, that is FIGO staging. It's clear from the table that only very small percentage of patients (5.7%) were diagnosed with too advanced stage (stage IV). Majority of patients were diagnosed at stage II (38.6%) or stage III (43.2%). Approximately 13% patients were diagnosed at early stages of cervical cancer. Further among stage II patients 85% were diagnosed at stage IIB while only 15% were IIA. Similarly among stage III, majority were diagnosed at stage IIIB (96%). In patients diagnosed with stage IV, 85% patients were stage IVA and rest were diagnosed as stage IV B.

Table 5.1.12: Distribution according to FIGO Staging

FIGO Stage	Number (%)
Stage I	**129(12.5)**
IA	1
IB	128
Stage II	**400(38.6)**
IIA	59
IIB	341
Stage III	**448(43.2)**
IIIA	17
IIIB	431
Stage IV	**59(5.7)**
IV A	50
IV B	9

Table 5.1.13 shows the largest tumor dimension of cervical cancer patients at diagnosis. 31.6% patients were diagnosed with largest tumor dimension of less than or equal to 4 cm. 58.6% patients were diagnosed with largest tumor dimension of more than 4 cm.

Table 5.1.13: Distribution according to Largest Tumor Dimension

Largest Tumor Dimension (cm)	Number (%)
Less than or equal to 4cm	327 (31.6)
More than 4 cm	607(58.6)
Unknown	102 (9.8)
Total	**1036 (100.0)**

Table 5.1.14 shows presence of hydronephrosis at the time of diagnosis of cervical cancer patients. 127 patients (approximately 12%) were diagnosed with hydronephrosis of which 90 were suffered from uni-lateral hydronephrosis and 37 were suffered from bi-lateral hydronephrosis.

Table 5.1.14: Distribution according to Hydronephrosis

Hydronephrosis	Number (%)
Absent	909 (87.74)
Uni-lateral	90 (8.69)
Bi-lateral	37 (3.57)
Total	**1036 (100.0)**

Table 5.1.15 shows pre-treatment performance status of cervical cancer patients. This score is based on ECOG criteria. Most of the patients (three fourth) were recorded as performance status of "0" which means they were capable of doing all activities without any restriction. Almost 21% of patients were restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. Only 3% were ambulatory and capable of all self care but unable to carry out any work activities; up and about

more than 50% of waking hours and approximately only 1% of patients were capable of only limited self care; confined to bed or chair more than 50% of waking hours.

Table 5.1.15: Distribution according to Pre-treatment Performance Status

ECOG Performance Status	Number (%)
0	781 (75.4)
1	212 (20.5)
2	30 (2.9)
3	13 (1.3)
4	0 (0.0)
Total	**1036 (100.0)**

Table 5.1.16 shows cross tabulation between treatment received and FIGO staging. It is clear from the table that surgery is the main treatment option for early stage (FIGO stage I to IIA) cervical cancer. Radiotherapy alone or in combination with chemo therapy is main treatment for advanced stage cervical cancer. Only 3 patients out of 341 of stage IIB were treated with surgery and other modalities. Similarly only 25 and 34 patients of FIGO stage IB and IIA respectively were treated with radiotherapy alone or in combination with chemo therapy. In stage III-IVA patients were treated with either radiotherapy alone or in combination with chemotherapy.

Table 5.1.16: Cross-tabulation between FIGO stage and treatment received (n=953 curative cases)

Treatment/Stage	IA	1B	IIA	IIB	IIIA	IIIB	IVA	Total
Surgery Only	1	68	9	0	0	0	0	78
Surgery + other combinations	0	35	16	3	0	0	0	54
RT Only	0	12	4	114	4	173	6	313
RT + CT	0	13	30	224	13	217	11	508
Total	1	128	59	341	17	390	17	953

Table 5.1.17 shows descriptive statistics for some selected baseline laboratory parameters for cervical cancer patients received curative treatment. It includes mean ± standard deviation,

median and range of the baseline hematological parameters, i.e. hemoglobin level, total WBC counts, neutrophil counts, lymphocyte counts and monocyte counts. The median value of pretreatment hemoglobin level, total WBC counts, neutrophil counts, lymphocyte counts and monocyte counts were found to be 11.5g/dL, $8.39x10^9$/L, $5.13x10^9$/L, $2.12x10^9$/L and $0.52x10^9$/L respectively.

Table 5.1.17: Descriptive data of pretreatment hematological parameters (Curative cases only; n=855)

Sl	Pre treatment parameters	Mean ± SD	Median	Minimum	Maximum
1.	Hemoglobin (g/dL)	11.21± 1.79	11.5	3.60	15.10
2.	WBC (10^9/L)	8.87 ± 3.04	8.39	2.20	34.70
3.	Neutrophil (10^9/L)	5.62 ± 2.59	5.13	0.75	29.60
4.	Lymphocyte (10^9/L)	2.18± 0.77	2.12	0.28	5.72
5.	Monocyte (10^9/L)	0.54 ± 0.21	0.52	0.02	2.07

5.2: Survival Analysis

Survival analysis was carried out to compute overall survival (OS) & study differences in survival of cervical cancer patients with respect to patients & tumor related characteristics. OS was computed on all cases enrolled in the study, while difference in survival was studied for each FIGO regrouped stage separately.

5.2.1 All Cases

This study includes 1036 cases of cervical cancer patients. The median follow up period of the cohort was 60 months ranging from 1 to 96 months. The only event in this study was death from any cause. There were 313 (30.2%) total number of deaths occurred.

5.2.1.1 Overall survival

Table 5.2.1.1 shows overall survival of cervical cancer patients. Three year & five year overall survival of patients was found to be 73% & 67% respectively.

Table No. 5.2.1.1: Overall Survival of Cervical Cancer patients

Total Number	Survival in percentage				
	1 Yr	2 Yr	3 Yr	4Yr	5Yr
1036	91	80	73	69	67

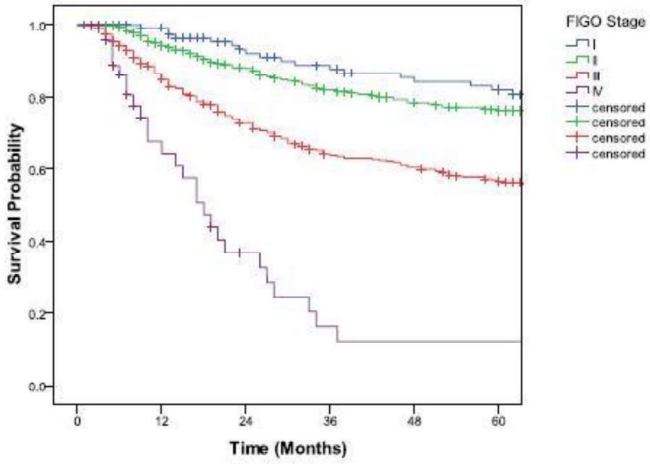
5.2.1.2 Difference in survival with respect to Stage

Table 5.2.1.2 shows the differences in survival with respect to FIGO stage. Five year overall survival of the cervical cancer patients diagnosed at stage I was 82.8%, Stage II was 75.9%, stage III was 56.5% and stage IV was 12.2%. Further it shows there is a significant difference in 5-year observed survival rate with respect to FIGO stage. Hazard ratio was 10 times for those diagnosed with FIGO stage IV cervical cancer (95% C.I.= 5.75-18.81 ; p<0.001) as compared to those diagnosed at stage I. Similarly hazard ratio was 3 times for those patients diagnosed at stage III cervical cancer (95% C.I.= 1.94-5.02 ; p<0.001) as compare to those diagnosed at stage I. There was non significant hazard ratio of 1.45 times for stage II cervical cancer patients (95% C.I.= 0.88-2.37; p=0.140) as compare to those patients diagnosed at stage I.

Table No. 5.2.1.2: Observed Survival rate (%) according to FIGO Stage

FIGO Stage	**Total**	**Survival in percentage**					**p Value**
		1 Yr	**2 Yr**	**3 Yr**	**4Yr**	**5Yr**	
I	129	99.1	92.4	88.3	85.0	82.8	<0.001
II	400	94.0	87.7	81.7	78.1	75.9	
III	448	84.9	72.8	63.8	60.4	56.5	
IV	59	64.2	36.6	16.3	12.2	12.2	
Univariate Analysis							
	Hazard Ratio						**p-value**
I	1						
II	1.451 (0.885-2.379)						0.140
III	3.128 (1.948-5.021)						<0.001
IV	10.408 (5.758-18.812)						<0.001
Calculated using Log Rank Test							

Figure 5.2.1.1 shows Kaplan Meier curve for overall survival with respect to FIGO staging system.



Number at risk						
StageI	129	112	92	85	79	76
StageII	400	355	311	279	257	243
StageIII	448	336	270	231	218	197
StageIV	59	20	9	4	3	3

Figure 5.2.1.1: Survival (%) of cervical cancer patients according to FIGO stage

5.2.1.3 Pair wise comparison of overall survival with respect to FIGO staging

Table 5.2.1.3 explore pair wise differences in overall survival with respect to FIGO staging. It gives comparison of overall survival for stage I cervical cancer patients with stage II, III & IV respectively. Similarly comparison of overall survival for stage II cervical cancer patients with stage III & IV respectively and comparison of overall survival for stage III cervical cancer patients with stage IV. Five year overall survival were found to be highly significant ($p<0.001$) for all possible pairs excluding comparison of five year overall survival for stage I with stage II ($p=0.138$).

Table 5.2.1.3: Pair wise Comparison of overall Survival with respect to FIGO staging

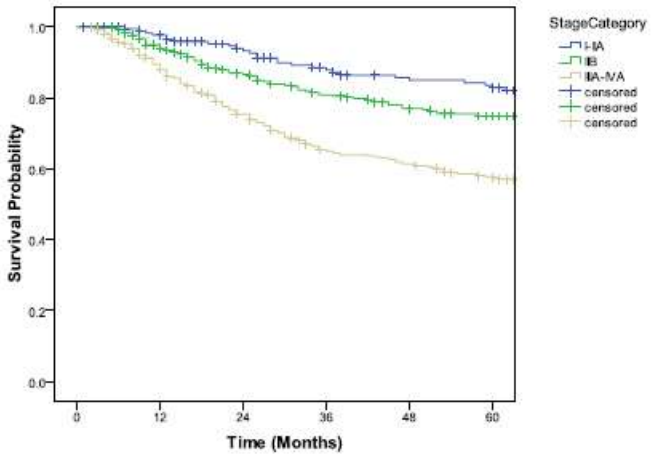
Stage	5-year survival	p-value
I	82.8	0.138
II	75.9	
I	82.8	<0.001
III	56.5	
I	82.8	<0.001
IV	12.2	
II	75.9	<0.001
III	56.5	
II	75.9	<0.001
IV	12.2	
III	56.5	<0.001
IV	12.2	

5.2.1.4 Observed survival rate (%) with respect to clinical extent of disease

Table 5.2.1.4 shows difference in overall survival with respect to clinical extent of disease. Here clinical extent was defined by regrouping the FIGO staging. Comparison were made between three groups, i.e. early stage cervical cancer patients (FIGO stage I to IIA), locally advanced stage IIB and advanced stage III-IVA received curative treatment. Further cox regression shows 1.576 times hazard ratio for those cervical cancer patients diagnosed at locally advanced stage IIB as compare to early stage cervical cancer (p=0.038) and 3.0 times hazard ratio for those patients diagnosed with locally advanced stage III-IV A and received curative treatment compared with early stage cervical cancer patients. Figure 5.2.1.2 shows Kaplan Meier curve for the same.

Table No. 5.2.1.4: Observed Survival rate (%) according to Clinical Classification (Curative cases only, n=953)

Clinical Classification	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Early Stage (I-IIa)	188	97.6	93.2	87.8	85.0	82.8	<0.001
IIb Locally Advanced	341	94.0	86.5	80.8	77.0	74.8	
IIIa-IVa	424	87.9	75.4	65.0	61.4	57.5	
Univariate Cox Regression							
	Hazard Ratio						p-value
Early Stage (I-IIa)	1						
IIb Locally Advanced	1.576(1.026-2.421)						0.038
IIIa-IVa	3.041(2.039-4.536)						<0.001



Number at risk

I-IIA	188	164	141	128	119	116
IIB	341	303	262	236	217	203
III-IVA	424	345	279	235	221	200

Figure 5.2.1.2: Survival of cervical cancer patients according to Clinical classification

Analysis for study the differences in survival with regards to patient characteristics & tumor related characteristics were carried out separately for cervical cancer patients diagnosed at early stage I to IIA, locally advance stage IIB and advance stage III-IVA received curative treatment respectively.

5.2.2: Early Stage (I to IIA)

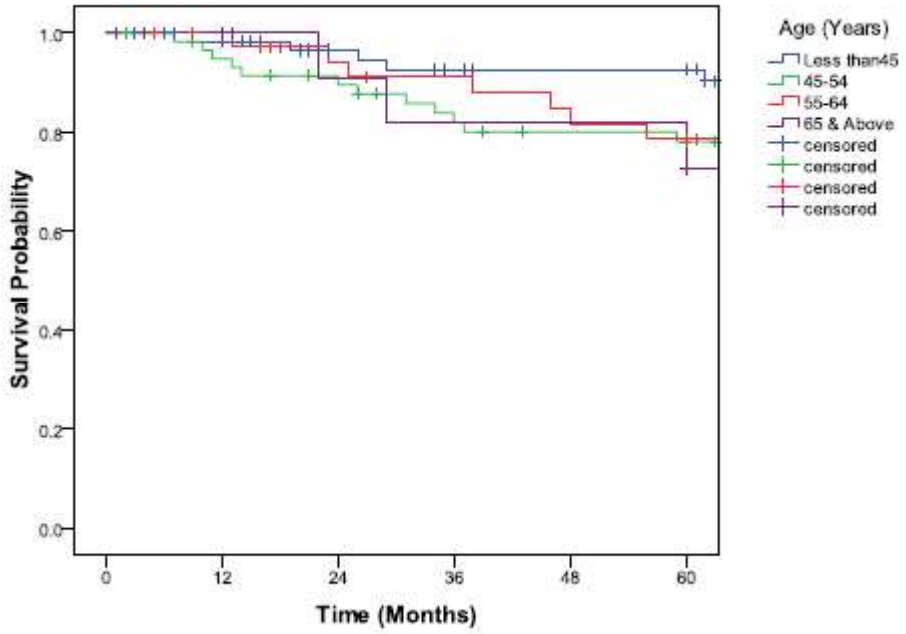
In this study we found 188 cervical cancer patients diagnosed with FIGO stage I to IIA. The median follow-up period for this cohort was 65 months, ranging from 1 to 94 months. There were total 28 (14.89%) death occurred in early stage. The 3 year and 5 year overall survival of early stage cervical cancer patients were 87.8% and 82.8% respectively (Table 5.2.1.4).

5.2.2.1 Survival according to age

Table 5.2.2.1 shows five year observed survival rate according to age of patients at the time of diagnosis. Overall survival was not found to be statistically significant according to age. Five year survival for patients aged less than or equal to 44 years, aged 45-54 years, 55-64 years and more than 64 years were found to be 92.7%, 78.1%, 78.6% and 72.7% respectively. Figure 5.2.2.1 shows Kaplan-Meier curve shows overall survival experience of early stage cervical cancer patients according to age at diagnosis. This figure also shows clearly that there is no difference in overall survival of early stage cervical cancer patients with respect to age at diagnosis.

Table No.5.2.2.1: Observed Survival rate (%) of early stage cervical cancer according to age

Age (Years) decades	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
≤44	66	98.4	96.6	92.7	92.7	92.7	0.414
45-54	68	94.9	89.6	82.0	80.1	78.1	
55-64	38	100.0	94.2	91.1	81.7	78.6	
≥65	16	100.0	90.9	81.8	81.8	72.7	



Number at risk

≤44	66	60	50	46	43	43
45-54	68	55	50	44	40	39
54-64	38	36	31	29	27	25
≥65	16	13	10	9	9	9

Figure 5.2.2.1: Survival rate (%) of early stage cervical cancer patients according to age

5.2.2.2 Survival according to Educational Status

Table 5.2.2.2 reflects the difference in survival with respect to educational status of cervical cancer patients. The 5- year overall survival for illiterate and literate patients were found to be 80.1% and 84.1% respectively. Thus we found only a difference of 4% between illiterate and literate patients, which was statistically highly non significant (p=0.767).

Table No.5.2.2.2: Observed Survival rate (%) of early stage cervical cancer according to Education Status

Education Status	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Illiterate	75	98.3	92.9	86.6	84.5	80.1	0.767
Literate	113	97.2	93.4	88.4	85.2	84.1	

Figure 5.2.2.2 shows Kaplan Meier curve of observed overall survival with respect to educational status. Curves representing Illiterate and literate patients overall survival experience over the period of time overlapped.

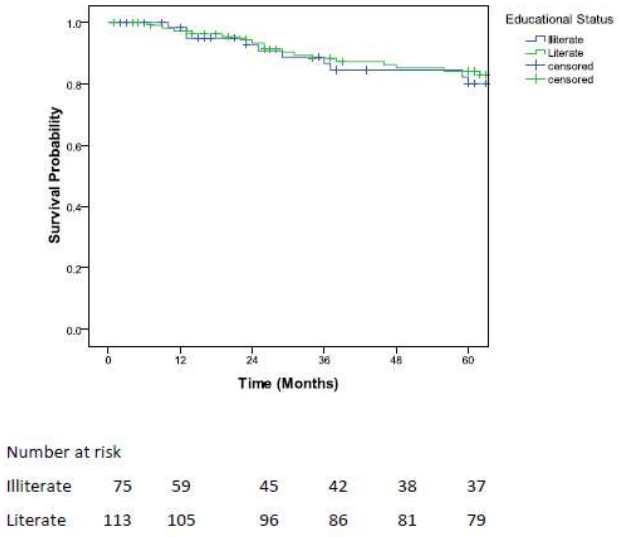


Figure 5.2.2.2: Survival rate (%) of early stage cervical cancer patients according to educational status

5.2.2.3 Survival according to Marital Status

Table 5.2.2.3 reflects the difference in survival with respect to marital status of cervical cancer patients. We found no difference in overall survival with respect to marital status. The five year overall survival for married and widow patients were found to be 84.4% and 73.6% respectively. Thus we found only a difference of 10.8% between currently married and widow patients. Althogh it was unable to obtain statistical significance (p=0.399) (Figure 5.2.2.3).

Table No.5.2.2.3: Observed Survival rate (%) of early stage cervical cancer according to Marital Status

Marital Status	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Currently Married	160	97.2	93.4	87.8	85.2	84.4	0.399
Widow	27	100.0	91.8	87.5	82.9	73.6	

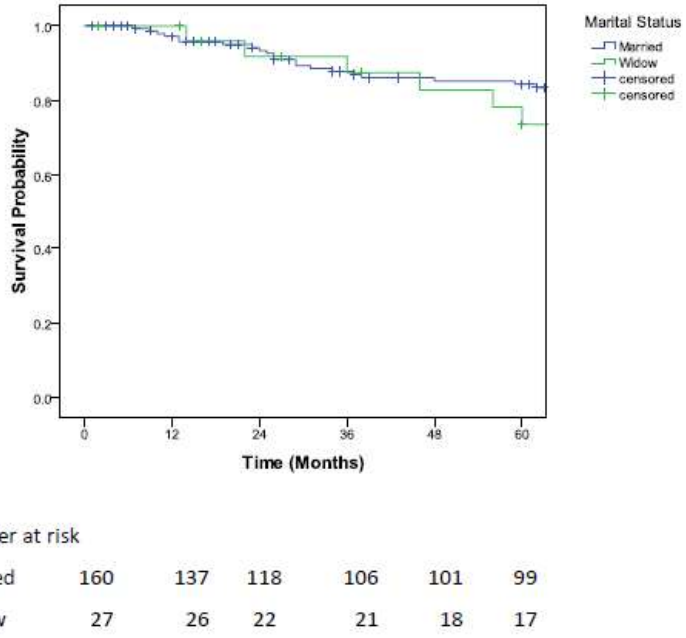


Figure 5.2.2.3: Survival rate (%) of early stage cervical cancer patients according to marital status

5.2.2.4 Survival according to Place of Residence

Table 5.2.2.4 reflects the difference in survival with respect to place of residence of cervical cancer patients. We found no difference in overall survival with respect to place of residence. The five year overall survival for Mumbai residents and patients coming from outside Mumbai were found to be 77.8% and 84.5% respectively (Figure 5.2.2.4).

Table No.5.2.2.4: Observed Survival rate (%) of early stage cervical cancer according to Place of Residence

Place of Residence	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Mumbai	47	95.5	88.1	80.4	80.4	77.8	0.397
Outside Mumbai	141	98.4	95.0	90.4	86.5	84.5	

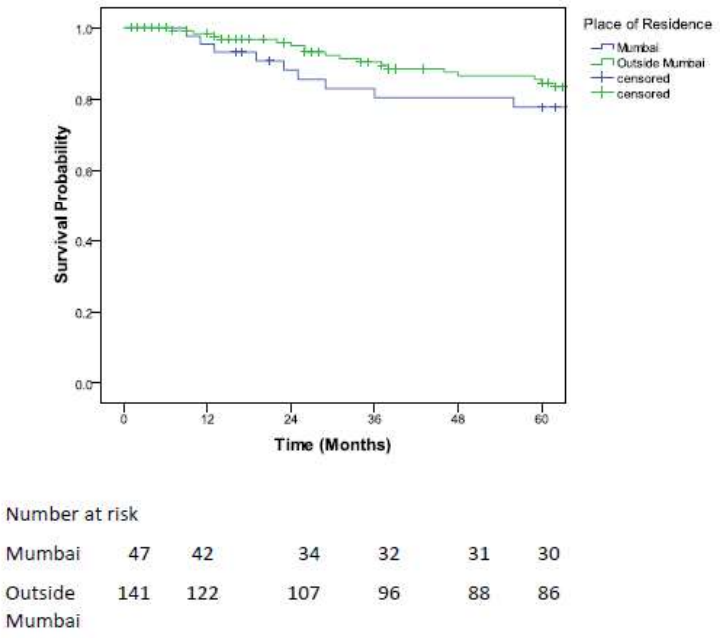


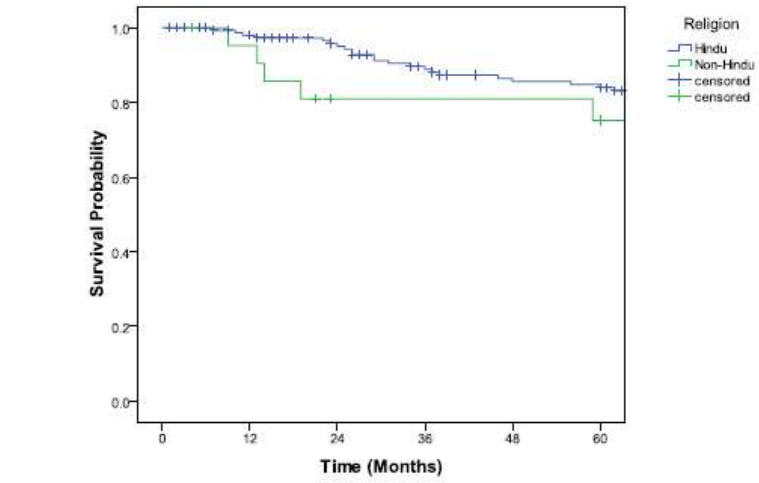
Figure 5.2.2.4: Survival rate (%) of early stage cervical cancer patients according to Place of Residence

5.2.2.5 Survival according to Religion

Table 5.2.2.5 reflects the difference in survival with respect to religion of cervical cancer patients. We found no difference in overall survival with respect to religion. The five year overall survival for Hindus and non-Hindus were found to be 84.0% and 75.2% respectively (Figure 5.2.2.5).

Table No.5.2.2.5: Observed Survival rate (%) of early stage cervical cancer according to Religion

Religion	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Hindu	166	98.0	95.0	98.9	85.7	84.0	0.084
Non-Hindu	22	95.2	81.0	81.0	81.0	75.2	



Number at risk						
Hindu	166	144	127	114	105	103
Non-Hindu	22	20	14	14	14	13

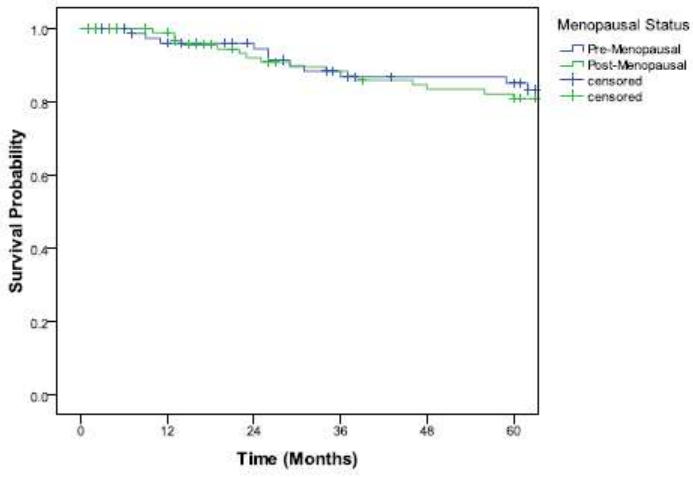
Figure 5.2.2.5: Survival rate (%) of early stage cervical cancer patients according to Religion

5.2.2.6 Survival according to Menopausal Status

Table 5.2.2.6 reflects the difference in survival with respect to menopausal status of cervical cancer patients. The five year overall survival for pre menopausal patients and post menopausal patients were found to be 85.2% and 81.0% respectively. Thus there is only 4% difference in survival among pre menopausal and post menopausal patients and is unable to achieve statistical significance (Figure 5.2.2.6).

Table No. 5.2.2.6: Observed Survival rate (%) of early stage cervical cancer according to Menopausal Status

Menopausal Status	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Pre-Menopausal	84	96.0	94.5	86.9	86.9	85.2	.604
Post-Menopausal	104	98.9	92.1	88.4	83.5	81.0	



Number at risk

PreMenopausal	84	72	64	56	51	50
Post Menopausal	104	92	77	72	68	66

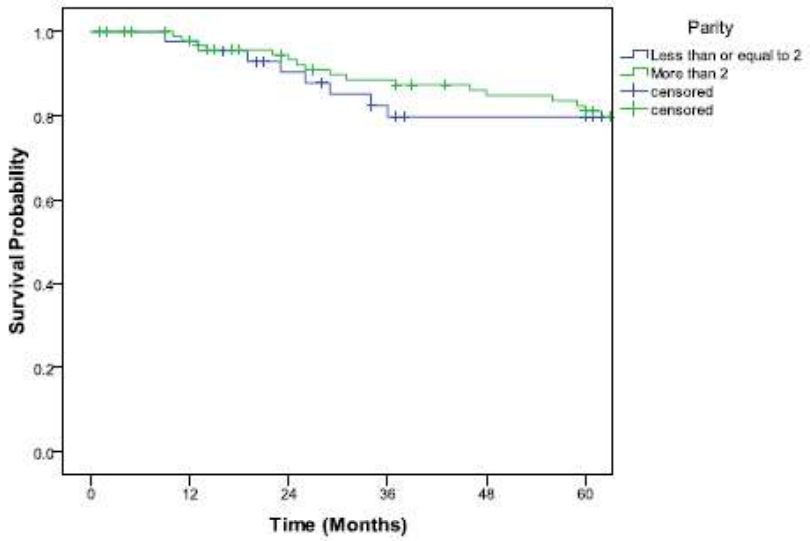
Figure 5.2.2.6: Survival rate (%) of early stage survival of cervical cancer patients according to Menopausal Status

5.2.2.7 Survival according to parity

Table 5.2.2.7 reflects the difference in survival with respect to parity of women suffering from early stage cervical cancer. We found no difference in overall survival with respect to parity (p=0.620). The five year overall survival for women having parity two or less and women have parity more than two were found to be 79.8% and 81.2% respectively (Figure 5.2.2.7).

Table No.5.2.2.7: Observed Survival rate (%) of early stage cervical cancer according to Parity

Parity	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
≤2	47	97.7	90.4	79.8	79.8	79.8	0.620
≥3	105	97.9	93.4	88.6	84.9	81.2	



Number at risk

≤2	47	43	35	30	27	27
≥3	105	92	80	74	69	66

Figure 5.2.2.7: Survival rate (%) of early stage of cervical cancer patients according to Parity

5.2.2.8 Survival according to abortion

Table 5.2.2.8 reflects the difference in survival with respect to number of abortions of cervical cancer patients. We found no difference in overall survival with respect to number of abortions women ever had (p=0.449). The five year overall survival for patients had no abortion and patients had atleast one abortion were found to be 82.3% and 73.5% respectively (Figure 5.2.2.8).

Table No.5.2.2.8: Observed Survival rate (%) of early stage cervical cancer according to number of abortion

Abortion	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
No	126	98.2	92.6	86.5	84.4	82.3	0.449
Yes	26	96.0	92.0	83.0	78.4	73.5	

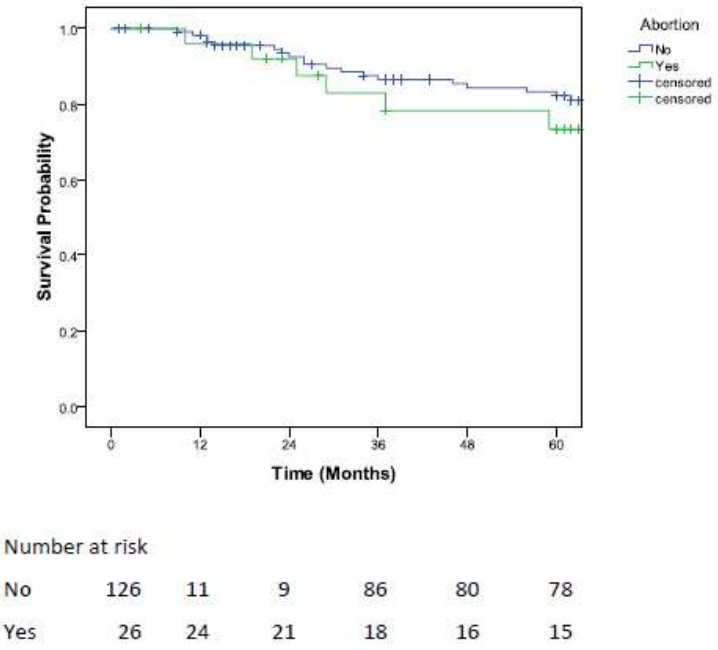


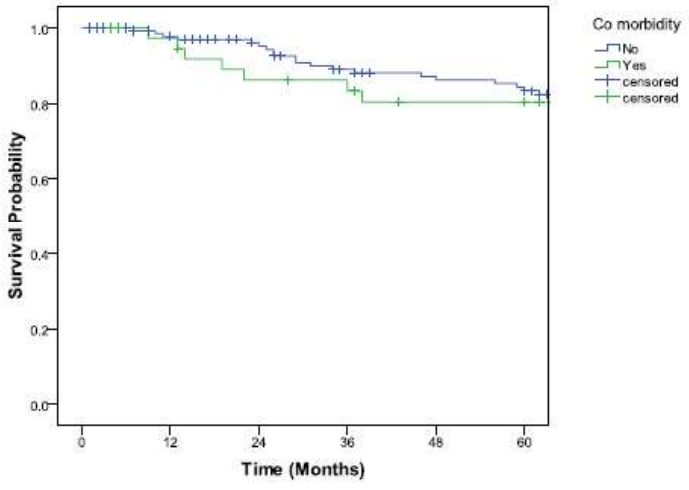
Figure 5.2.2.8: Survival rate (%) of early stage cervical cancer patients according to Number of Abortion

5.2.2.9 Survival according to comorbid conditions

Table 5.2.2.9 reflects the difference in survival with respect to presence or absence of co-morbid conditions among cervical cancer patients. We found no difference in overall survival with respect to co-morbidity(p=0.731). The five year overall survival for cervical cancer patients suffering from co-morbidity and cervical cancer patients not having any co-morbid condition were found to be 80.4% and 83.4% respectively (Figure 5.2.2.9).

Table No. 5.2.2.9: Observed Survival rate (%) of early stage cervical cancer according to presence of comorbidity

Comorbidity	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Present	40	97.3	86.2	83.4	80.4	80.4	0.731
Absent	148	97.7	95.2	89.0	86.3	83.4	



Number at risk

No	148	128	110	98	93	90
Yes	40	36	31	30	26	26

Figure 5.2.2.9: Survival rate (%) of early stage cervical cancer patients according to comorbidity

5.2.2.10 Survival according to Tumor Grade

Table 5.2.2.10 reflects the difference in survival with respect to tumor differentiation of cervical cancer patients. We found no difference in overall survival with respect to tumor differentiation (p=0.872) (Figure 5.2.2.10).

Table No. 5.2.2.10: Observed Survival rate (%) of early stage cervical cancer according to tumor differentiation

Tumor Differentiation	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Low (1+2)	68	98.4	93.4	88.1	84.4	80.8	0.872
High	80	95.6	94.0	87.2	83.6	83.6	

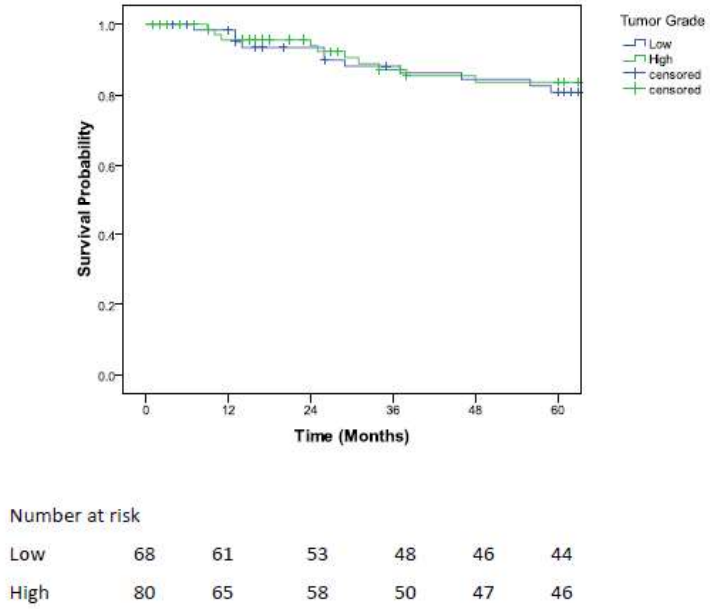


Figure 5.2.2.10: Survival rate (%) of early stage cervical cancer patients according to tumor differentiation

5.2.2.11 Survival according to Tumor Histology

Table 5.2.2.11 reflects the difference in survival with respect to tumor histology of cervical cancer patients. We found no difference in overall survival with respect to tumor histology (p=0.562). The five year overall survival for those patients diagnosed with squamous histology and those diagnosed with histology other than squamous were found to be 81.5% and 88.6% respectively (Figure 5.2.2.11).

Table No.5.2.2.11: Observed Survival rate (%) of early stage cervical cancer according to tumor histology

Tumor Histology	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Squamous	157	97.9	92.5	85.9	83.3	81.5	0.562
Non-Squamous	31	96.7	96.7	96.7	92.6	88.6	

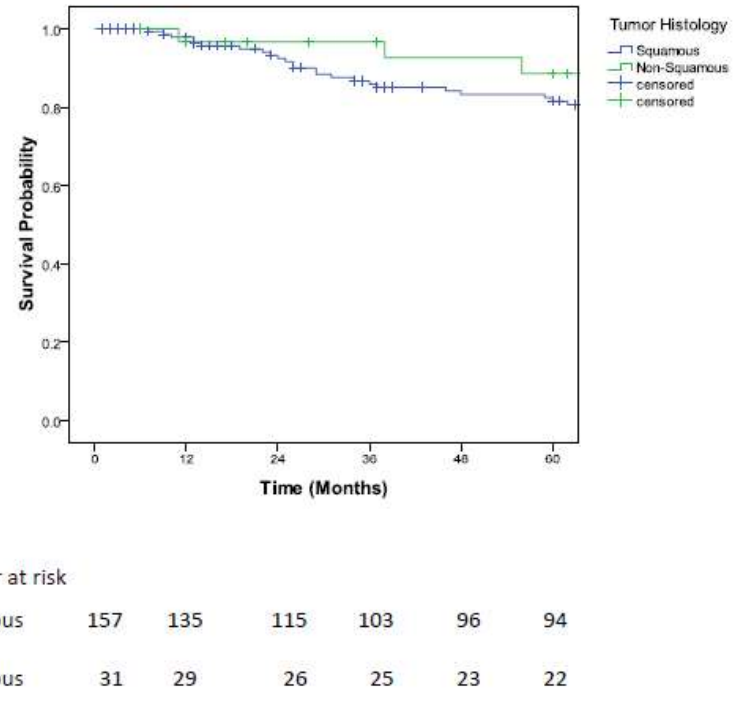


Figure 5.2.2.11: Survival rate (%) of early stage cervical cancer patients according to tumor histology

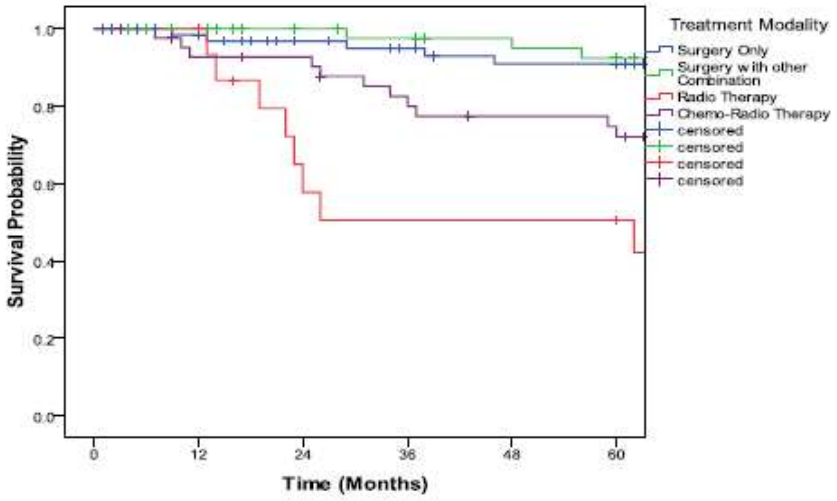
5.2.2.12 Survival according to treatment modality

Table 5.2.2.12 reflects the difference in survival with respect to treatment modality of early satge cervical cancer patients. We found significant difference in overall survival with respect to treatment modality (p<0.001). The five year overall survival for those patients treated with surgery only, surgery with radio &/ chemotherapy, radiotherapy only and radiotherapy with chemotherapy were found to be 90.9%, 92.4%, 50.6% and 72.1% respectively (Figure 5.2.2.12). Further it shows hazard ratio for different treatment modalities, taking surgery treated cases as reference category. There was no statistically significant difference between survival of those patients treated with surgery alone and those patients treated with surgery &/ chemo radiotherapy. However, we found hazard ratio of 7.5 times more for those patients treated with radiotherapy alone as compare to those treated with surgery alone (p<0.001). Hazard ratio was 2.8 times for those patients treated with chemo-radio therapy as compare to those treated with surgery alone. However this was marginally significant (p=0.042).

Table No.5.2.2.12: Observed Survival rate (%) of early stage cervical cancer according to Treatment

Treatment	Total Numb	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Surgery only	78	98.4	96.8	94.9	90.9	90.9	<0.001
Surgery with combination	51	100.0	100.0	97.6	95.0	92.4	
RT only	16	100.0	57.8	50.6	50.6	50.6	
RT + CT	43	92.7	92.7	80.0	77.4	72.1	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Surgery only	1						
Surgerywith	0.629(0.157-2.514)						0.512
Radiotherapy only	7.580(2.620-21.928)						<0.001
RT + CT	2.809(1.039-7.597)						0.042

**Calculated using Log Rank Test*



Number at risk						
S	78	62	53	49	45	45
S+Others	51	48	42	40	38	36
RT	16	16	9	7	7	7
RT+CT	43	38	37	32	29	28

Figure 5.2.2.12: Survival rate (%) of early stage cervical cancer patients according to treatment

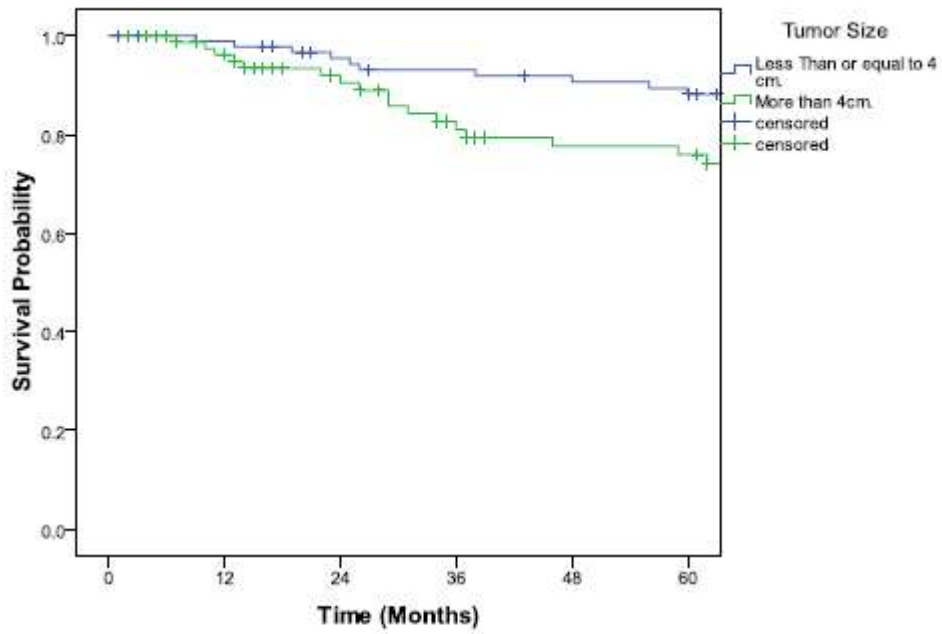
5.2.2.13 Survival according to tumor dimension

Table 5.2.2.13 reflects the difference in survival with respect to tumor dimension of early stage cervical cancer patients. We found significant difference in overall survival with respect to tumor dimension. The five year overall survival for those patients having largest tumor dimension less than or equal to 4 cm and those having tumor dimension of more than 4 cm. were found to be 88.2% and 76.0% respectively.

Figure 5.2.2.13 shows Kaplan Meier curve of overall survival according to tumor dimension taking a cut-off of 4 cm as largest tumor dimension of early stage cervical cancer patients.

Table No. 5.2.2.13: Observed Survival rate (%) of early stage cervical cancer according as per tumor dimension

Largest tumor	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
≤4 cms	101	98.9	95.5	93.1	90.6	88.2	0.015
> 4cms	87	96.1	90.5	81.1	77.7	76.0	
Univariate analysis (Cox- Proportional Hazard Model)							
	Hazard Ratio (95% CI)						**p Value**
≤4 cms	1						**0.019**
> 4cms	2.518 (1.161-5.462)						



Number at risk

≤4cm	101	90	80	77	75	73
>4cm	87	74	61	51	44	43

Figure 5.2.2.13: Survival rate (%) of early stage cervical cancer patients according to tumor dimension

5.2.2.14 Survival according to Performance Status

Table 5.2.2.14 reflects the difference in survival with respect to pretreatment performance status of cervical cancer patients. The five year overall survival for those patients fully active at the time of diagnosis and those who were restricted in physical activity at the time of diagnosis were found to be 82.2% and 86.2% respectively. There is very small difference in survival with respect to pretreatment performance status and this small difference was statistically highly non significant (p=0.557) (Figure 5.2.2.14).

Table No. 5.2.2.14: Observed Survival rate (%) of early stage cervical cancer according to Performance Status

Performance Status**	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
0**	161	95.8	93.5	87.2	84.7	82.2	0.557
≥1***	27	100.0	91.0	91.0	86.2	86.2	

***Performance Status:* 0 : able to carry out normal activity; ≥1 : Restricted in physical activity.

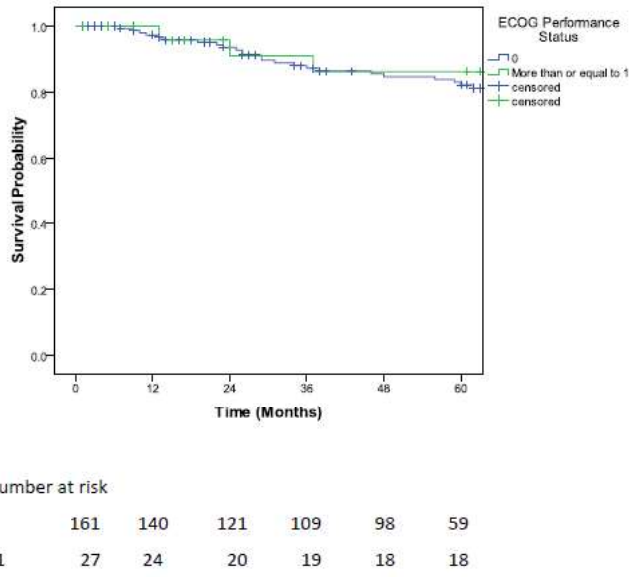


Figure 5.2.2.14: Survival rate (%) of early stage cervical cancer patients according to Performance status

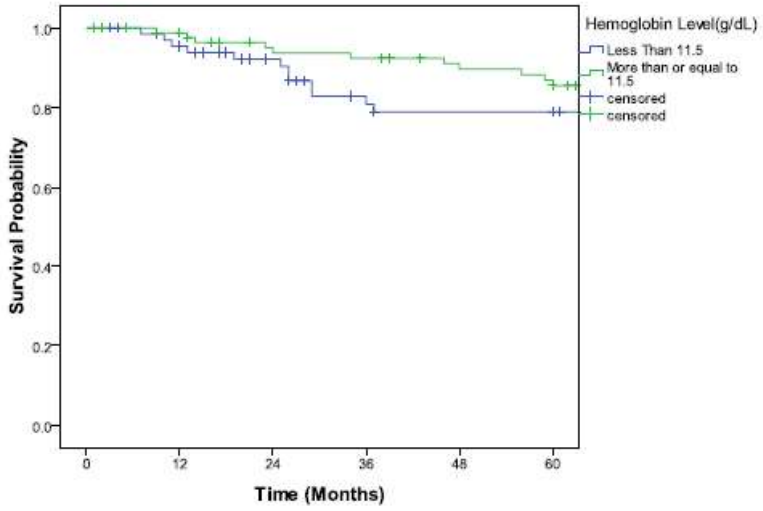
5.2.2.15 Survival according to Pre-treatment hemoglobin level

Table 5.2.2.15 reflects the difference in survival with respect to pretreatment hemoglobin level of early stage cervical cancer patients. On the basis of median value two groups were formed: those patients having pretreatment hemoglobin level of <11.5 g/dL and those patients having pretreatment hemoglobin level of ≥11.5 g/dL. We found no difference in overall survival with respect to pretreatment hemoglobin level. The five year overall survival for those patients diagnosed with pretreatment hemoglobin level of <11.5 g/dL and those patients having pretreatment hemoglobin level of ≥11.5 g/dL were found to be 78.9% and 85.5% respectively. There is almost 7% difference in five year overall survival with respect to pretreatment hemoglobin level. Although this was unable to achieve statistical significance (p=0.333).

Table 5.2.2.15: Observed Survival rate (%) of early stage cervical cancer according to Hemoglobin Level

Hemoglobin Level (g/dL)	**Total Number**	**Survival in percentage**					**p Value**
		1 Yr	**2 Yr**	**3 Yr**	**4Yr**	**5Yr**	
<11.5	74	95.4	92.2	80.9	78.9	78.9	0.333
≥11.5	92	98.8	93.8	92.4	89.7	85.5	

Figure 5.2.2.15 shows Kaplan Meier curve of overall survival according to pretreatment hemoglobin level of early stage cervical cancer patients. Curves are overlapping to each other upto 20months. After 20 months curves represented difference in survival at different point of times.



Number at risk

<11.5	74	62	51	42	39	39
≥11.5	92	83	72	70	66	63

Figure 5.2.2.15: Survival rate (%) of early stage cervical cancer patients according to pretreatment hemoglobin level

5.2.2.16 Survival according to pre-treatment WBC counts

Table 5.2.2.16 reflects the difference in survival with respect to pretreatment total WBC counts of early stage cervical cancer patients. On the basis of median value two groups were formed: those patients having total WBC counts of <8.39x 10^9/L and those patients having pretreatment WBC counts of ≥8.39x 10^9/L. We found no difference in overall survival with respect to pretreatment WBC counts. The five year overall survival for those patients diagnosed with pretreatment WBC counts of <8.39x 10^9/L and those patients having pretreatment WBC counts of ≥8.39x 10^9/L were found to be 82.4% and 83.2% respectively. Thus we found no difference in survival with respect to pretreatment WBC counts.

Table 5.2.2.16: Observed Survival rate (%) of early stage cervical cancer according to pretreatment WBC Counts

WBC Counts ($^10^9$/L)	Total Number	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<8.39	90	98.8	95.0	88.2	86.7	82.4	0.906
≥8.39	76	95.5	90.5	86.9	83.2	83.2	

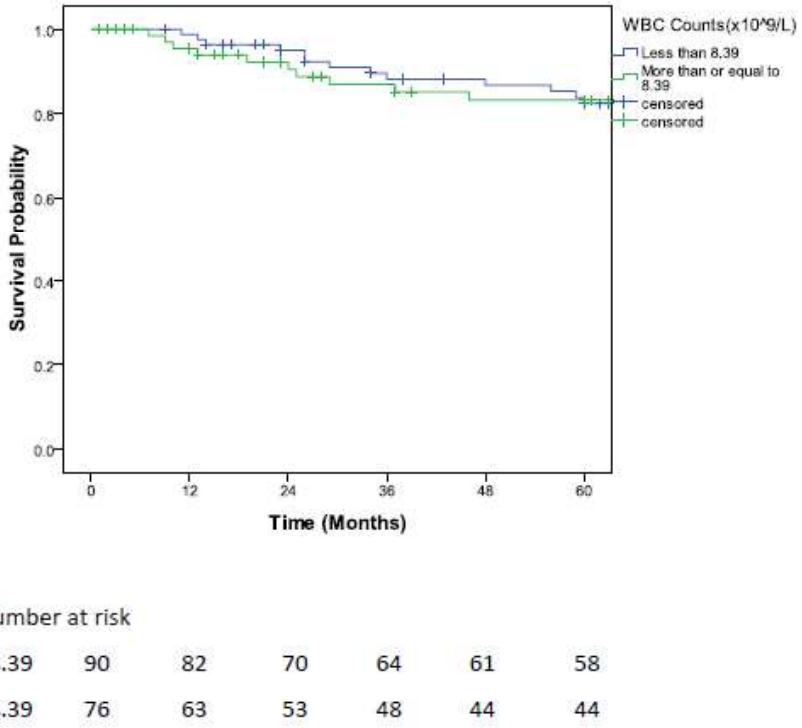


Figure 5.2.2.16: Survival rate (%) of early stage cervical cancer patients according to pretreatment WBC counts

Figure 5.2.2.16 shows Kaplan Meier curve of overall survival according to pretreatment WBC counts of early stage cervical cancer patients. Curves are overlapping to each other over a period of time.

5.2.2.17 Survival according to pre-treatment lymphocyte counts

Table 5.2.2.18 reflects the difference in survival with respect to pretreatment lymphocyte counts of early stage cervical cancer patients. On the basis of median value two groups were formed: those patients lymphocyte counts of <2.12x 10^9/L and those patients having pretreatment lymphocyte counts of ≥2.12x 10^9/L. We found no difference in overall survival with respect to pretreatment lymphocyte counts. The five year overall survival for those patients diagnosed with pretreatment lymphocyte counts of <2.12x 10^9/L and those patients having pretreatment lymphocyte counts of ≥2.12x 10^9/L were found to be 88.6% and 77.9% respectively (Figure 5.2.2.17).

Table 5.2.2.17: Observed Survival rate (%) of early stage cervical cancer according to pre-treatment Lymphocyte Counts

Lymphocyte Counts (x10^9/L)	Total Number	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<2.12	78	98.5	95.5	90.4	90.4	88.6	0.207
≥2.12	88	96.4	91.0	85.4	80.9	77.9	

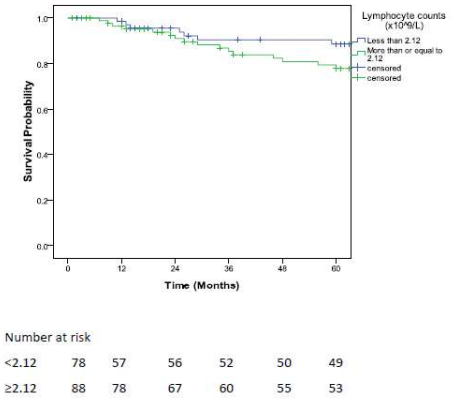


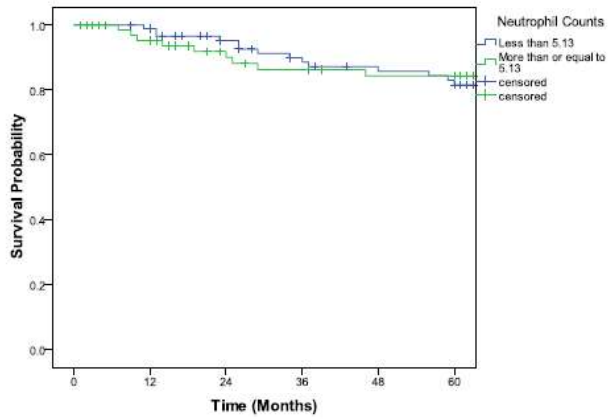
Figure 5.2.2.17: Survival rate (%) of early stage cervical cancer patients according to pretreatment lymphocyte counts

5.2.2.18 Survival according to pre-treatment neutrophil counts

Table 5.2.2.18 reflects the difference in survival with respect to pretreatment neutrophil counts of early stage cervical cancer patients. On the basis of median value two groups were formed: those patients neutrophil counts of <5.13x 10^9/L and those patients having pretreatment neutrophil counts of ≥5.13x 10^9/L. We found no difference in overall survival with respect to pretreatment neutrophil counts. Figure 5.2.2.18 shows Kaplan Meier curve of overall survival according to pretreatment neutrophil counts of early stage cervical cancer patients.

Table 5.2.2.18: Observed Survival rate (%) of early stage cervical cancer according to pre treatment Neutrophil Counts (x 10^9/L**)**

Neutrophil Counts	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<5.13	93	98.8	95.2	88.5	85.8	81.6	0.720
≥5.13	73	95.2	90.0	86.3	84.3	84.3	



Number at risk

<5.13	93	85	73	66	62	59
≥5.13	73	60	50	46	43	43

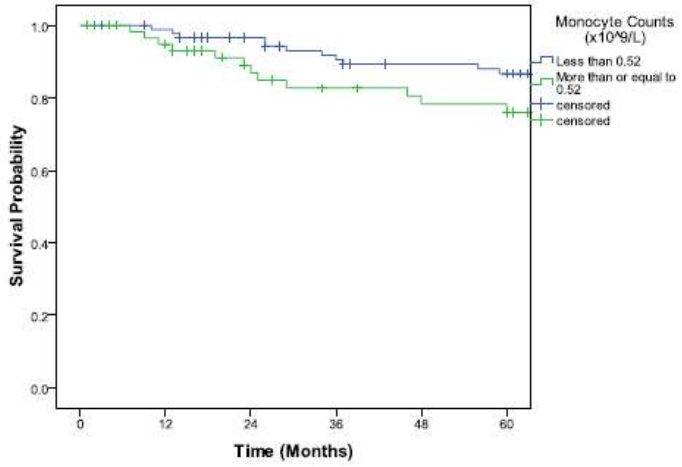
Figure 5.2.2.18: Survival rate (%) of early stage survival of cervical cancer patients according to pretreatment neutrophil counts

5.2.2.19 Survival according to pre treatment monocyte counts

Table 5.2.2.19 reflects the difference in survival with respect to pretreatment monocyte counts of early stage cervical cancer patients. On the basis of median value two groups were formed: those patients monocyte counts of <0.52x 10^9/L and those patients having pretreatment monocyte counts of ≥0.52x 10^9/L. However there is 10% difference in survival of high and low monocyte groups, this difference was unable to achieve statistical significance (p=0.136) (Figure 5.2.2.19).

Table 5.2.2.19: Observed Survival rate (%) of early stage cervical cancer according to Monocyte Counts (x 10^9/L)

Monocyte Counts	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<0.52	100	98.9	96.7	90.6	89.3	86.7	0.136
≥0.52	66	94.8	87.0	82.8	78.3	76.1	



Number at risk

<0.52	100	90	80	74	69	67
≥0.52	66	55	43	38	36	35

Figure 5.2.2.19: Survival rate (%) of early stage cervical cancer patients according to pretreatment monocyte counts

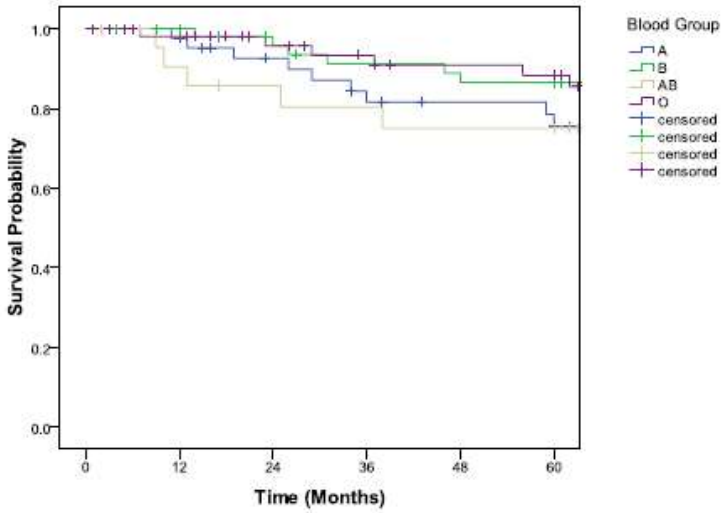
5.2.2.20 Survival according to blood group

Table 5.2.2.20 reflects the difference in survival with respect to blood group of early stage cervical cancer patients. There were total 8 patients not recorded information on blood group and labeled as unknown. We found no difference in overall survival with respect to different blood group. The five year overall survival for those patients having blood group A, B, AB and O were found to be 75.5%, 86.5%, 75.0% and 88.3% respectively. However these observed difference in survival were unable to achieve statistical significance (p=0.432).

Figure 5.2.2.20 shows Kaplan Meier curve of overall survival according to blood group of early stage cervical cancer patients.

Table No.5.2.2.20: Observed Survival rate (%) of early stage cervical cancer according to Blood Group

Blood Group	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
A	44	97.6	92.5	81.6	81.6	75.5	0.432
B	54	100.0	95.7	91.2	86.5	86.5	
AB	25	90.5	85.7	80.4	75.0	75.0	
O	57	98.0	95.7	93.3	90.9	88.3	



Number at risk						
A	44	41	34	30	27	26
B	54	49	44	40	38	37
AB	25	19	16	15	14	14
O	57	49	42	38	35	34

Figure 5.2.2.20: Survival rate (%) of early stage cervical cancer patients according to blood group

5.2.2.21 Univariate and Multifactorial analysis for OS in early stage cervical cancer patients

Table 5.2.2.21 shows multi-factorial analysis for early stage (FIGO stage I to IIA) cervical cancer patients. In univariate analysis only largest tumor dimension and treatment modality were found to be statistically significant. To study independent effect of these factors on overall survival, we kept both variables in to multifactorial cox regression model using backward selection method. Results of multi-factorial analysis shows that both largest tumor dimension and treatment modality were independent predictors of overall survival in early stage cervical cancer patients. The analysis revealed that those patients have largest tumor dimension of more than 4cm. have 2.402 times hazard ratio (95% CI=1.095 – 5.267; p=0.029) as compare to those having largest tumor dimension ≤4cms. We also found patients treated with radiotherapy only have 7.4 times hazard ratio (95% CI=2.554-21.483; p<0.001) as compare to those treated with surgery alone. However there was no statistically significant difference in survival of patients treated with surgery alone and those treated with surgery & radio/& chemo therapy (HR=0.584, 95% CI=0.146-2.388; P=0.447). Similar results was found for patients treated with surgery alone and patients treated with chemo-radio therapy (HR=2.380, 95% CI=0.872-6.500; p=0.091).

Table No. 5.2.2.21: Univariate and Multifactorial Analysis for OS in Early stage cervical cancer patients

Parameter	No. of cases	Univariate		Multifactorial	
		HR (95% CI)	p value	HR (95% CI)	p value
Tumor Size					
≤4cms	101	1	**0.019***	1	**0.029***
>4cms	87	2.518 (1.161-5.462)		2.402 (1.095-5.267)	
Treatment Modality					
Surgery only	78	1		1	
Surgery with other combination	51	0.629(0.157-2.514)	0.512	0.584 (0.146-2.338)	0.447
RT only	16	7.580(2.620-21.928)	**<0.001***	7.408 (2.554-21.483)	**<0.001***
RT + CT	43	2.809(1.039-7.597)	**0.042***	2.380 (0.872-6.500)	0.091

***p<0.05 Statistically Significant**

5.2.3: Advance stage IIB

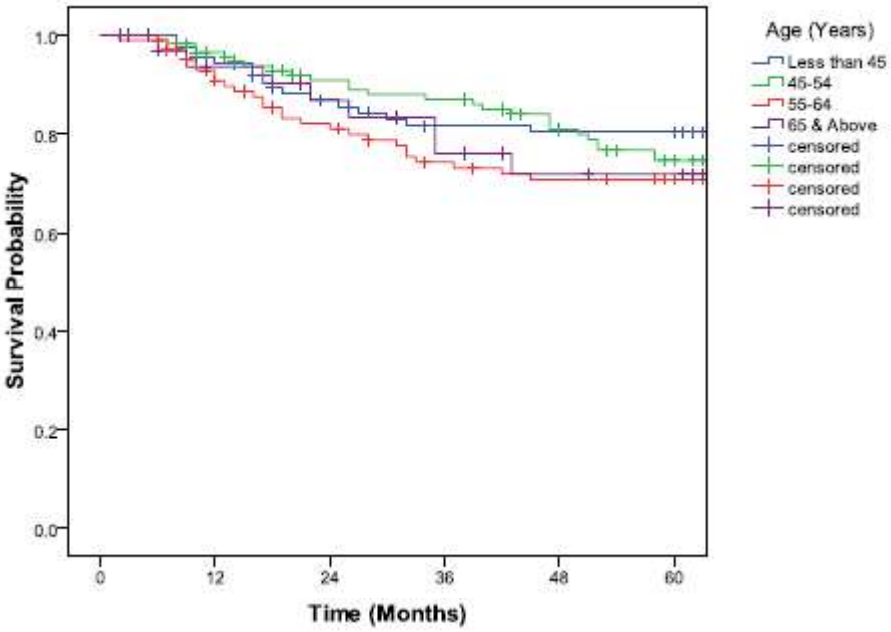
In this study we found 341 cervical cancer patients diagnosed with FIGO stage IIB. The median follow-up period for this cohort was 66 months, ranging from 2 to 96 months. There were 82 (24.0%) death occurred in stage IIB cervical cancer patients. The 3 year and 5 year overall survival of stage IIB cervical cancer patients were 80.8% and 74.8% respectively (Table 5.2.1.4).

5.2.3.1 Survival according to Age

Table 5.2.3.1 shows five year observed survival rate according to age of patients at the time of diagnosis. Overall survival was not found to be statistically significant according to age (p=0.395). Five year overall survival for patients aged less than or equal to 44 years, aged 45-54 years, 55-64 years and more than 64 years were found to be 80.4%, 74.7%, 70.8% and 71.9% respectively (Figure 5.2.3.1).

Table 5.2.3.1: Observed Survival rate (%) according to age of stage IIB cervical cancer patients

Age (Years)	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
≤44	87	94.2	86.9	81.7	80.4	80.4	0.395
45-54	117	96.5	90.9	87.0	81.0	74.7	
55-64	101	90.8	81.0	74.3	70.8	70.8	
≥65	36	93.6	86.8	76.1	71.9	71.9	



Number at risk						
≤44	87	80	69	61	60	60
45-54	117	107	93	89	79	69
54-64	101	88	75	65	61	58
5≥65	36	28	25	21	17	16

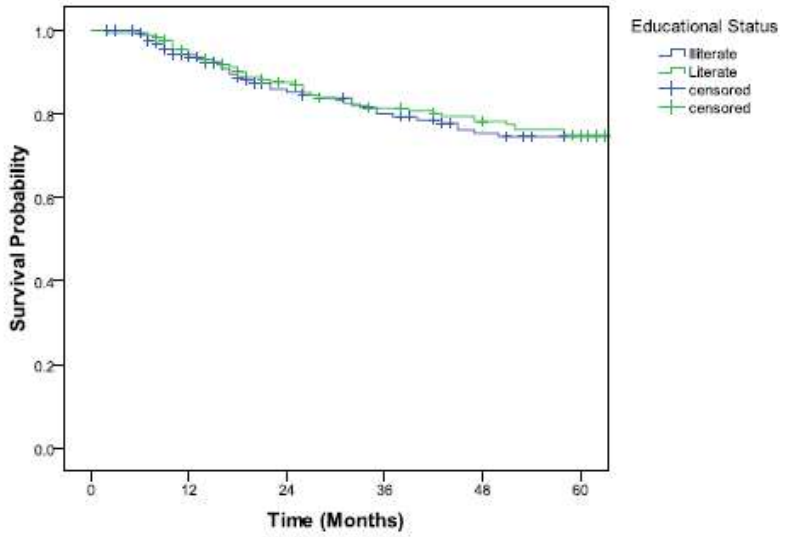
Figure 5.2.3.1: Survival rate (%) of stage IIB cervical cancer patients according to age

5.2.3.2 Survival according to Educational Status

Table 5.2.3.2 shows five year observed survival rate according to educational status of patients. Overall survival was not found to be statistically significant according to educational status (p=0.738). Five year overall survival for illiterate and literate patients were found to be 74.6% and 75.0% respectively (Figure 5.2.3.2).

Table No.5.2.3.2: Observed Survival rate (%) of stage IIB cervical cancer patients according to Education Status

Education Status	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Illiterate	165	93.6	85.3	80.1	75.4	74.6	0.738
Literate	176	94.2	87.6	81.4	78.2	75.0	



Number at risk						
Illiterate	165	141	120	107	95	89
Literate	176	162	142	129	122	114

Figure 5.2.3.2: Survival rate (%) of stage IIB of cervical cancer patients according to educational status

5.2.3.3 Survival according to Marital Status

Table 5.2.3.3 shows five year observed survival rate according to marital status of patients. Overall survival was not found to be statistically significant according to marital status (p=0.994). Five year overall survival for married and widow patients were found to be 74.8% and 73.6% respectively (Figure 5.2.3.3).

Table No.5.2.3.3: Observed Survival rate (%) of stage IIB cervical cancer patients according to Marital Status

Marital Status	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Married	258	94.1	87.3	81.2	77.6	74.8	0.994
Widow	79	93.3	83.3	78.6	73.6	73.6	

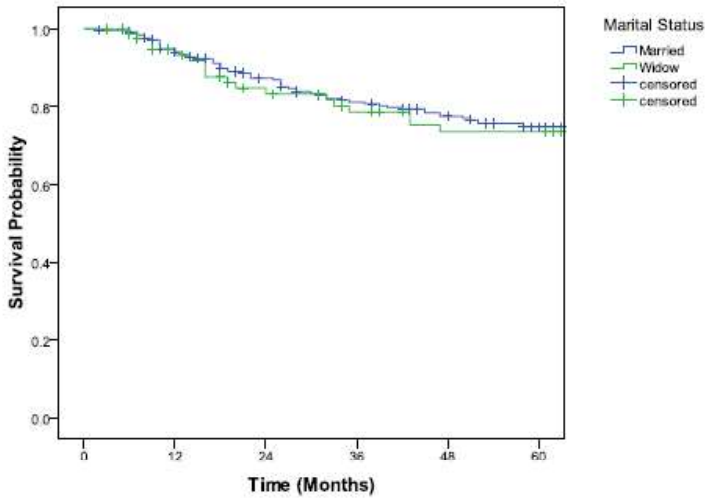


Figure 5.2.3.3: Survival rate (%) of stage IIB of cervical cancer patients according to marital status

5.2.3.4 Survival according to Place of Residence

Table 5.2.3.4 shows five year observed survival rate according to place of residence of patients. Overall survival was not found to be statistically significant according to place of residence (p=0.477). Five year overall survival for patients residing in Mumbai and outside Mumbai were found to be 80.7% and 73.2% respectively (Figure 5.2.3.4).

Table No.5.2.3.4: Observed Survival rate (%) of stage IIB cervical cancer patients according to Place of Residence

Place of Residence	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Mumbai	80	93.6	85.3	82.3	80.7	80.7	0.477
Non-Mumbai	261	94.1	86.9	80.4	75.9	73.2	

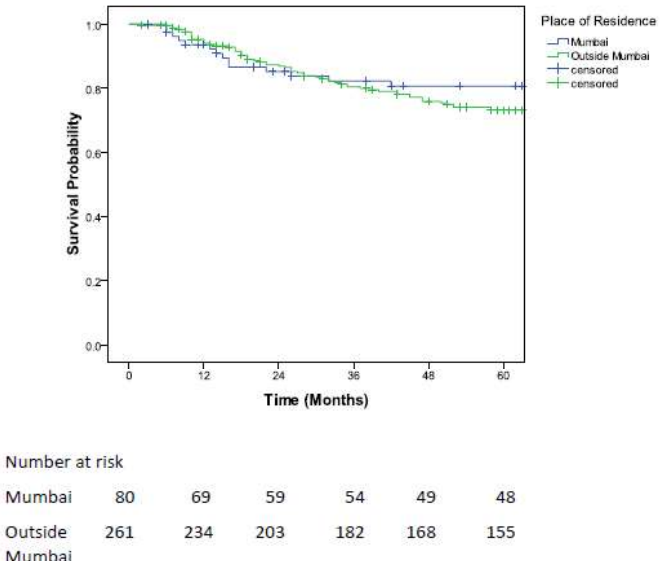


Figure 5.2.3.4: Survival rate (%) of stage IIB of cervical cancer patients according to place of residence

5.2.3.5 Survival according to religion

Table 5.2.3.5 shows five year observed survival rate according to religion of patients. Overall survival was not found to be statistically significant according to religion (p=0.580). Five year overall survival for Hindu and Non-Hindu patients were found to be 74.2% and 77.6% respectively (Figure 5.2.3.5).

Table No.5.2.3.5: Observed Survival rate (%) of stage IIB cervical cancer patients according to Religion

Religion	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Hindu	277	94.1	85.1	78.9	75.9	74.2	0.580
Non-Hindu	64	98.3	93.0	89.2	81.5	77.6	

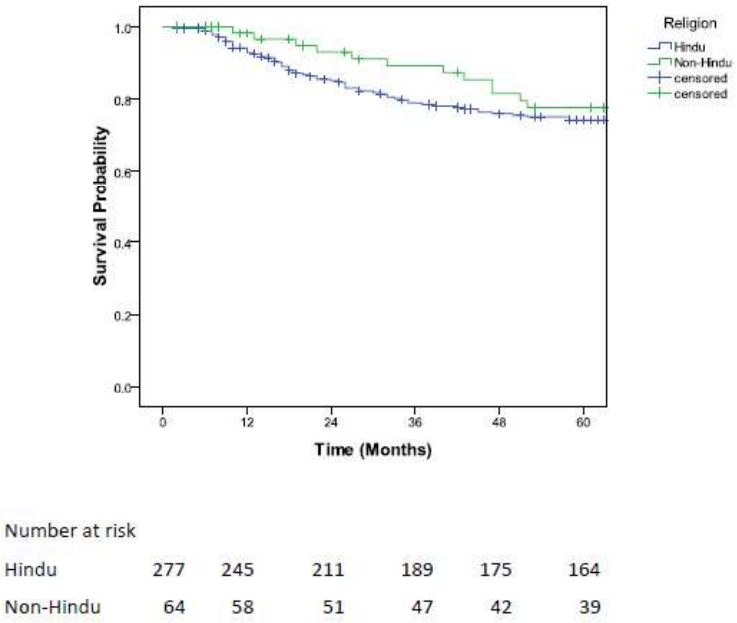


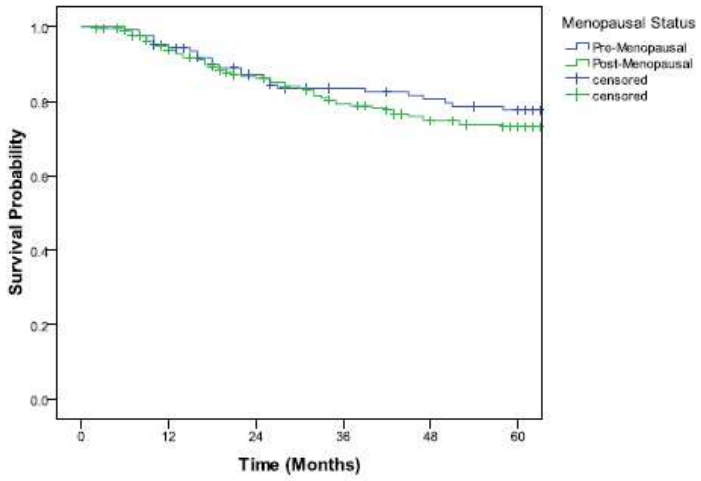
Figure 5.2.3.5: Survival rate (%) of stage IIB of cervical cancer patients according to religion

5.2.3.6 Survival according to menopausal status

Table 5.2.3.6 shows five year observed survival rate according to menopausal status of patients. Overall survival was not found to be statistically significant according to menopausal status (p=0.323). Five year overall survival for premenopausal and post menopausal patients were found to be 77.7% and 73.2% respectively (Figure 5.2.3.6).

Table No. 5.2.3.6: Observed Survival rate (%) of stage IIB cervical cancer patients according to Menopausal Status

Menopausal Status	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Pre-Menopausal	125	94.3	87.2	83.5	80.6	77.7	.323
Post-Menopausal	216	93.7	86.2	79.3	74.9	73.2	



Number at risk						
PreMenopausal	125	112	95	87	83	79
Post Menopausal	216	191	167	149	134	124

Figure 5.2.3.6: Survival rate (%) of stage IIB of cervical cancer patients according to menopausal status

5.2.3.7 Survival according to parity

Table 5.2.3.7 shows five year observed survival rate according parity of patients. Overall survival was not found to be statistically significant according to parity (p=0.062). Five year overall survival for women having parity of less than or equal to 2 and women having parity more than 2 were found to be 80.7% and 69.1% respectively.

Figure 5.2.3.7 shows Kaplan Meier curve of overall survival according to parity of FIGO stage IIB cervical cancer patients.

Table No.5.2.3.7: Observed Survival rate (%) of stage IIB cervical cancer patients according to Parity

Parity	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
≤2	57	96.3	90.6	84.8	80.7	80.7	0.062
≥3	209	91.7	82.3	76.7	72.1	69.1	

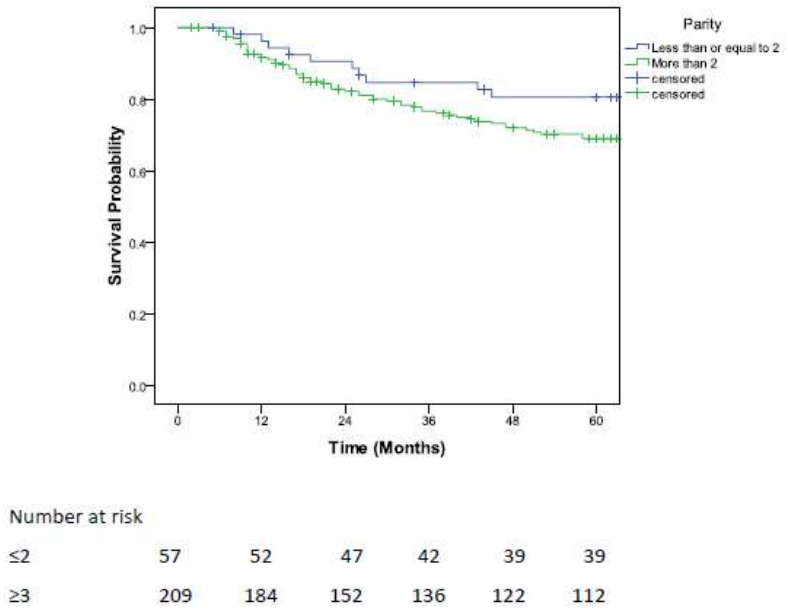


Figure 5.2.3.7: Survival rate (%) of stage IIB of cervical cancer patients according to parity

5.2.3.8 Survival according to Number of Abortions

Table 5.2.3.8 shows five year observed survival rate according to number of abortion done by cervical cancer patients. Overall survival was not found to be statistically significant according to number of abortion (p=0.120). Five year overall survival for women did not have any abortion in their life time and women have had abortion were found to be 74.1% and 61.2% respectively (Figure 5.2.3.8).

Table No.5.2.3.8: Observed Survival rate (%) of stage IIB cervical cancer patients according to number of abortion

Abortion	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
0	214	92.8	84.6	79.3	75.9	74.1	0.120
≥1	52	92.2	81.6	74.8	65.7	61.2	

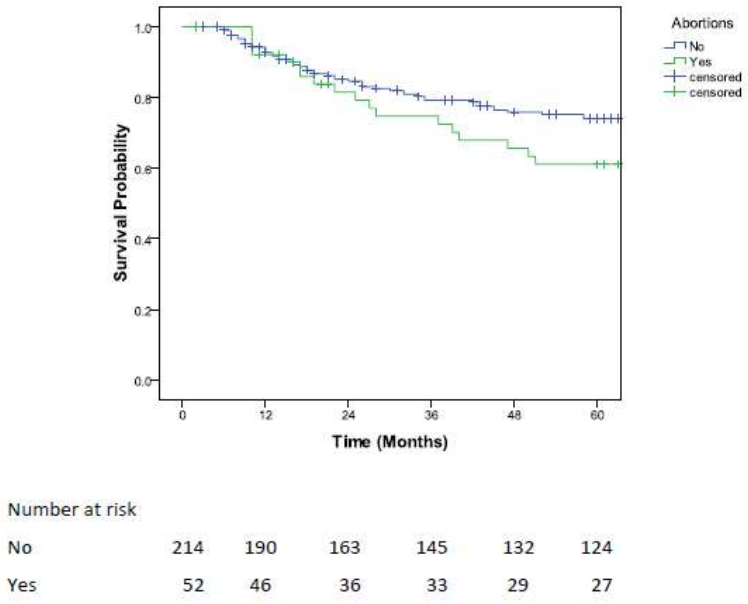


Figure 5.2.3.8: Survival rate (%) of stage IIB of cervical cancer patients according to number of abortions

5.2.3.9 Survival according to tumor grade

Table 5.2.3.9 shows five year observed survival rate according to tumor differentiation of patients. Five year overall survival for women diagnosed with low grade and high grade tumors were found to be 78.1% and 65.1% respectively (Figure 5.2.3.9). Further cox uni variate analysis showed that high grade tumors were associated with poor overall survival (HR=1.951; 95% C.I.= 1.118-3.405; p=0.019).

Table No. 5.2.3.9: Observed Survival rate (%) of stage IIB cervical cancer patients according to tumor differentiation

Tumor Differentiation	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Low Grade	89	96.6	90.8	86.2	78.1	78.1	0.016
High Grade	108	90.5	79.9	70.9	67.4	65.1	
Univariate Cox regression							
	Hazard Ratio						p-value
Low Grade	1						
High Grade	1.951(1.118-3.405)						0.019

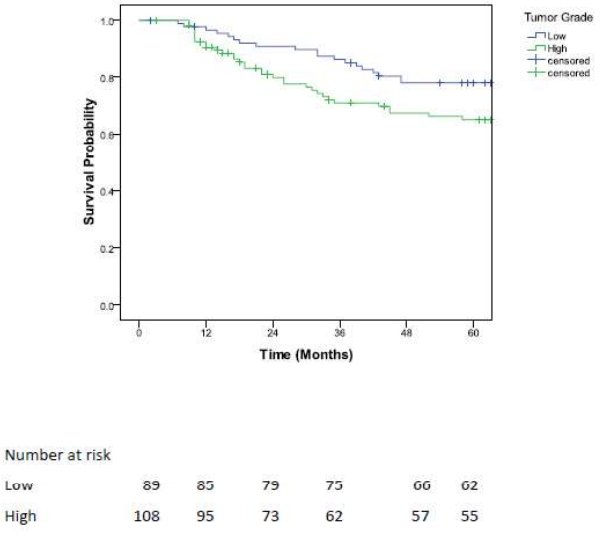


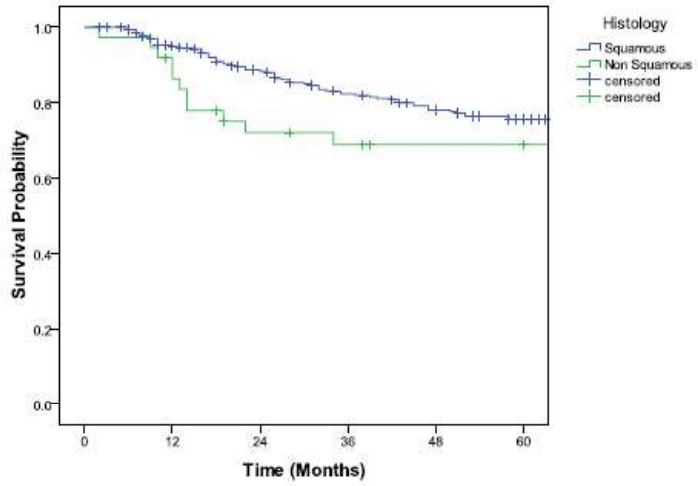
Figure 5.2.3.9: Survival rate (%) of stage IIB of cervical cancer patients according to tumor grade

5.2.3.10 Survival according to tumor histology

Table 5.2.3.10 shows five year observed survival rate according to tumor histology of cervical cancer patients. Overall survival was not found to be statistically significant according to tumor histology (p=0.279). Five year overall survival for women diagnosed with squamous and non - squamous histology were found to be 75.6% and 68.9% respectively (Figure 5.2.3.10).

Table No. 5.2.3.10: Observed Survival rate (%) of stage IIB cervical cancer patients according to tumor histology

Tumor Histology	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Squamous	304	94.9	88.4	82.3	78.0	75.6	0.279
Non-Squamous	37	86.3	72.1	68.9	68.9	68.9	



Number at risk						
Squamous	304	270	238	214	197	183
Non-Squamous	37	33	24	22	20	20

Figure 5.2.3.10: Survival rate (%) of stage IIB cervical cancer patients according to histology

5.2.3.2 Survival according to tumor dimension

Table 5.2.3.11 shows five year observed survival rate according to tumor dimension of cervical cancer patients. Overall survival was not found to be statistically significant according to tumor dimension (p=0.686). Five year overall survival for women having largest tumor dimension ≤4cm and >4cm were found to be 76.8% and 72.0% respectively (Figure 5.2.3.11).

Table No. 5.2.3.11: Observed Survival rate (%) of stage IIB cervical cancer patients according to tumor dimension

Tumor dimension (cm.)	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
≤4	127	93.6	86.9	83.4	78.6	76.8	0.686
>4	184	93.2	84.9	78.0	74.7	72.0	

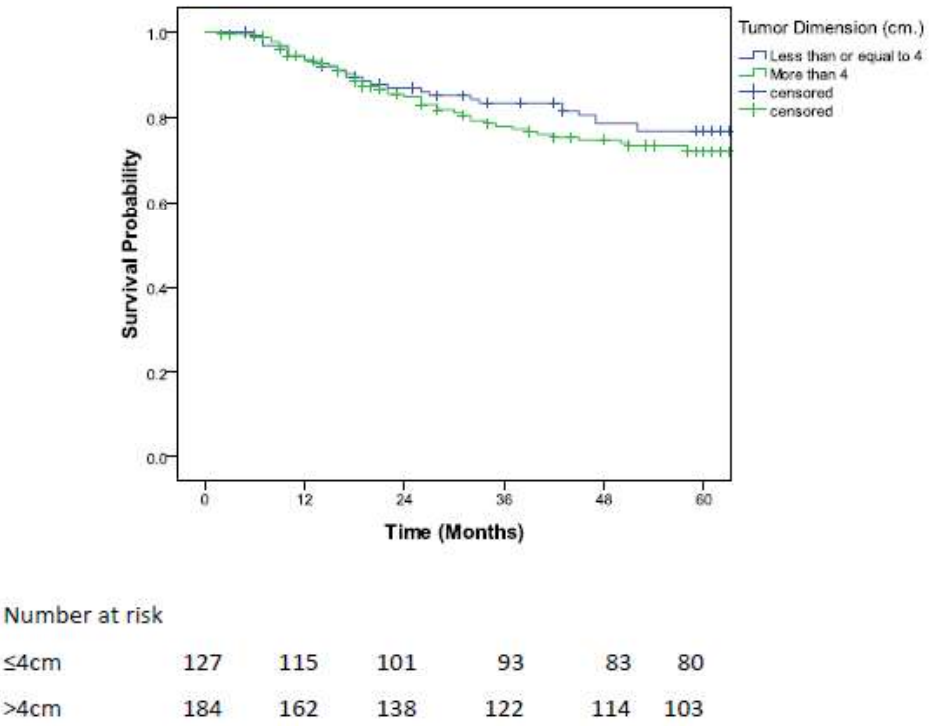


Figure 5.2.3.11: Survival rate (%) of stage IIB cervical cancer patients according to tumor dimension

5.2.3.12 Survival according to parametrium involvement

Table 5.2.3.12 shows five year observed survival rate according to laterality of involvement of parametrium of cervical cancer patients. We found significant difference in overall survival for women diagnosed with unilateral parametrium involvement and bilateral parametrium involvement (p<0.001) (Figure 5.2.3.12).

Table No. 5.2.3.12: Observed Survival rate (%) of stage IIB cervical cancer patients according to Parametrium Involvement

Parametrium	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Uni-lateral	198	96.4	91.4	87.3	84.4	82.6	<0.001
Bi-lateral	125	89.2	77.8	69.4	64.4	61.3	
Univariate Analysis							
	Hazard Ratio (95% C.I.)						p-value
Uni-lateral	1						
Bi-lateral	2.465 (1.574-3.860)						<0.001

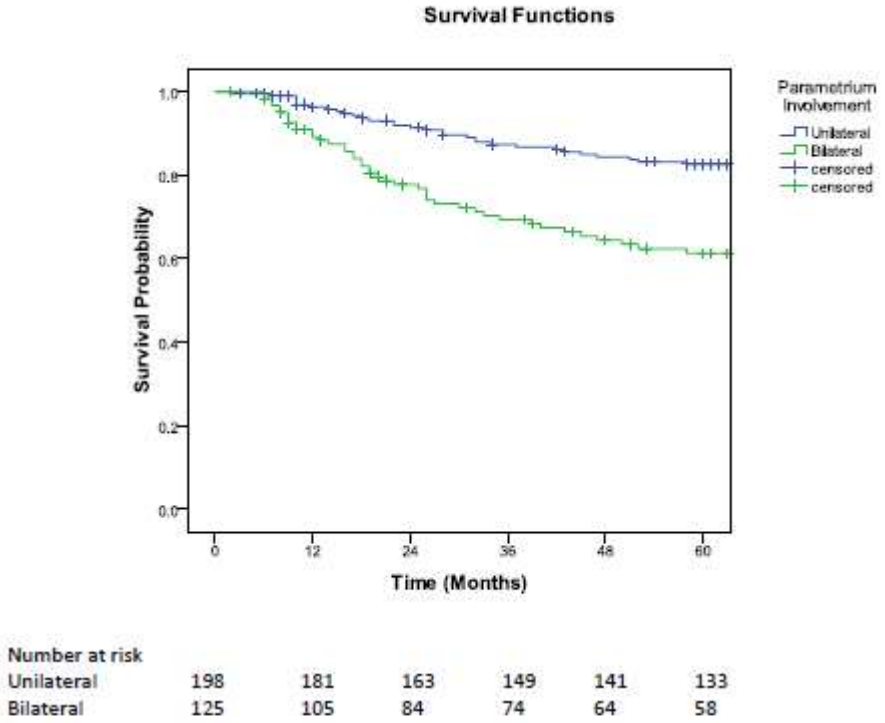


Figure 5.2.3.12: Survival rate (%) of stage IIB cervical cancer patients according to laterality of parametrium involvement

5.2.3.13 Survival according to treatment modality

Table 5.2.3.13 shows five year observed survival rate according to treatment modality of cervical cancer patients. Five year overall survival for women treated with radiotherapy only and treated with chemo-radiotherapy were found to be 64.7% and 79.9% respectively (p=0.001) (Figure 5.2.3.13). Further cox univariate analysis showed that patients treated with chemo-radio therapy were associated with higher overall survival (HR=0.488; 95% C.I.= 0.315-0.755; p<0.001) .

Table No. 5.2.3.13: Observed Survival rate (%) of stage IIB cervical cancer patients according to Treatment

Treatment	Total	Survival in percentage					p Value
		1	2 Yr	3 Yr	4Yr	5Yr	
Radiotherapy only	114	90.	79.9	72.4	66.9	64.7	0.001
Radiotherapy+ Chemotherapy	224	95.	89.7	85.2	82.0	79.9	
Univariate analysis							
	Hazard Ratio (95% CI)						p Value
Radiotherapy only	1						<0.001
RT + CT	0.488 (0.315-0.755)						

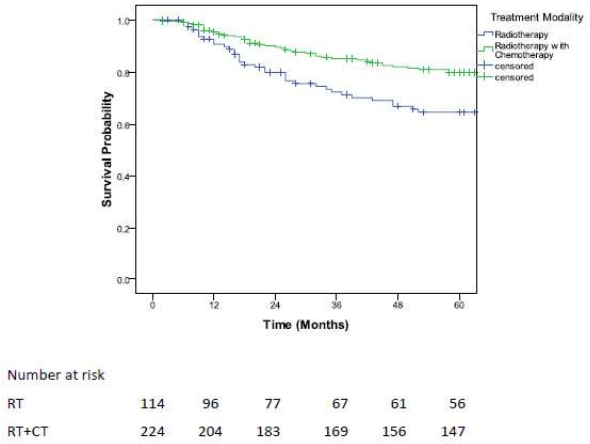


Figure 5.2.3.13: Survival rate (%) of stage IIB cervical cancer patients according to treatment modality

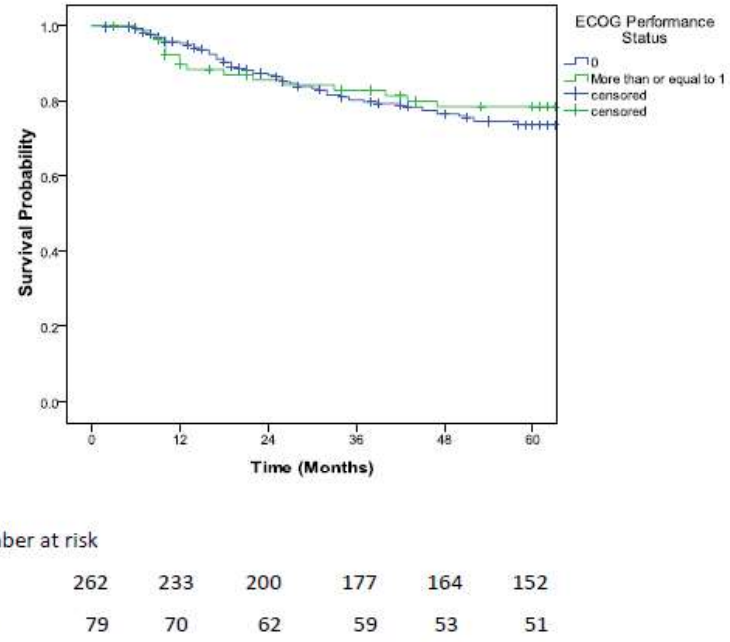
5.2.3.14 Survival according to pre-treatment performance status

Table 5.2.3.14 shows five year observed survival rate according to pretreatment performance status of cervical cancer patients. Overall survival was not found to be statistically significant according to pre treatment performance status (p=0.501). Five year overall survival for women fully active at the time of diagnosis and women restricted in physical activity (ECOG **≥1)** were found to be 73.6% and 78.4% respectively (Figure 5.2.3.14).

Table No. 5.2.3.14: Observed Survival rate (%) of stage IIB cervical cancer patients according to Performance Status

Performance Status**	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
0	262	95.3	86.8	80.2	76.5	73.6	0.501
≥1	79	89.6	85.5	82.8	78.4	78.4	

***Performance Status:* 0: able to carry out normal activity; ≥1: Restricted in physical activity.



Number at risk

0	262	233	200	177	164	152
≥1	79	70	62	59	53	51

Figure 5.2.3.14: Survival rate (%) of stage IIB cervical cancer patients according to pre-treatment performance status

5.2.3.15 Survival according to comorbid conditions

Table 5.2.3.15 shows five year observed survival rate according to presence of co-morbid condition in cervical cancer patients. Five year overall survival for women having presence of any co-morbid condition and women not having any co-morbid condition were found to be 66.4% and 78.3% respectively (p=0.010) (Figure 5.2.3.15). Further cox univariate analysis showed that presence of co-morbid condition was associated with poor prognosis in cervical cancer patients (HR=1.768; 95% C.I.= 1.139-2.744; p=0.011).

Table No. 5.2.3.15: Observed Survival rate (%) of stage IIB cervical cancer patients according to presence of comorbidity

Comorbidity	**Total**	**Survival in percentage**					**p Value**
		1 Yr	**2 Yr**	**3 Yr**	**4Yr**	**5Yr**	
Present	101	94.0	85.4	76.2	68.9	66.4	0.010
Absent	240	94.0	87.0	82.8	80.3	78.3	
Univariate Cox regression							
	Hazard Ratio						p-value
Absent	1						0.011
Present	1.768(1.139-2.744)						

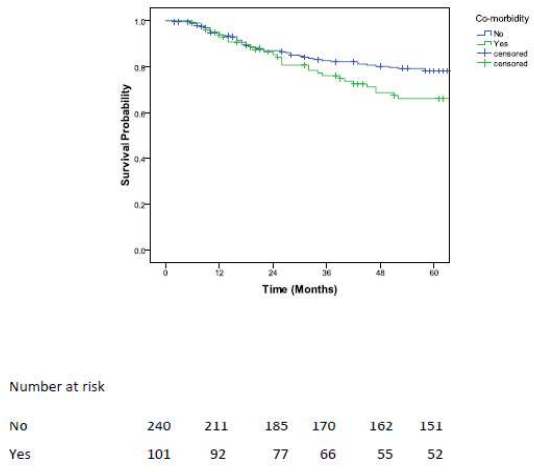


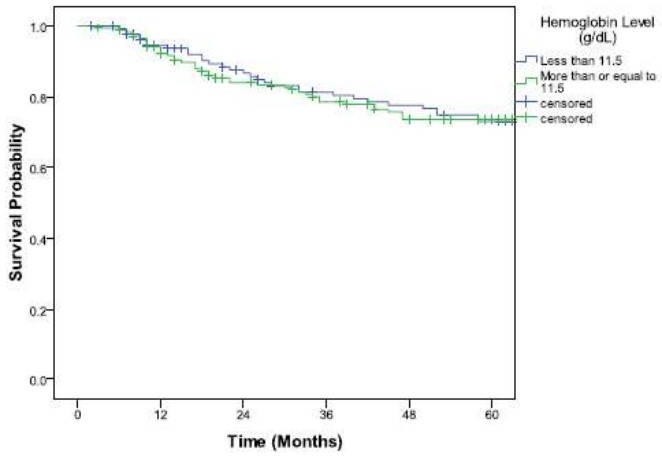
Figure 5.2.3.15: Survival rate (%) of stage IIB cervical cancer patients according to comorbid conditions

5.2.3.16 Survival according to pre-treatment hemoglobin level

Table 5.2.3.16 shows five year observed survival rate according to pretreatment hemoglobin level of cervical cancer patients. Overall survival was not found to be statistically significant according to pre treatment hemoglobin level (p=0.954). Five year overall survival for women having hemoglobin level <11.5 g/dL and women having hemoglobin level ≥11.5 g/dL were found to be 73.1% and 73.6% respectively (Figure 5.2.3.16).

Table No. 5.2.3.16: Observed Survival rate (%) of stage IIB cervical cancer patients according to hemoglobin level (g/dL)

Hemoglobin Level	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<11.5	132	94.5	86.7	81.3	77.7	73.1	0.954
≥11.5	172	92.2	84.0	78.6	73.6	73.6	



Number at risk

<11.5	132	113	99	89	85	79
≥11.5	172	153	128	115	102	95

Figure 5.2.3.16: Survival rate (%) of stage IIB cervical cancer patients according to hemoglobin level

5.2.3.17 Survival according to pre treatment WBC counts

Table 5.2.3.17 shows five year observed survival rate according to pretreatment WBC counts of cervical cancer patients. Overall survival was not found to be statistically significant according to pre treatment total WBC counts (p=0.088). Five year overall survival for women having total WBC counts <8.39(x10^9/L) and women having total WBC counts ≥8.39 (x10^9/L)were found to be 76.7% and 69.6% respectively (Figure 5.2.3.17).

Table No. 5.2.3.17: Observed Survival rate (%) of stage IIB cervical cancer patients according to total WBC counts

WBC Counts (x10^9/L)	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<8.39	158	96.1	89.3	83.5	78.2	76.7	0.088
≥8.39	146	89.9	80.5	75.6	72.2	69.6	

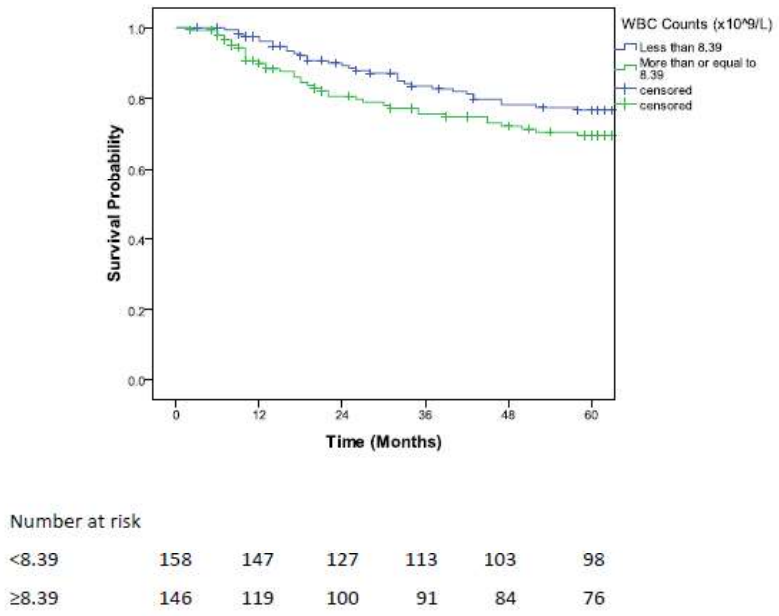


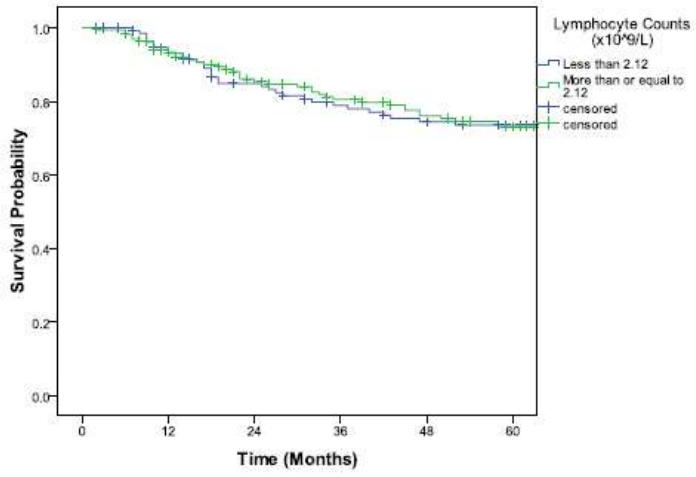
Figure 5.2.3.17: Survival rate (%) of stage IIB cervical cancer patients according to total WBC counts

5.2.3.18 Survival according to pre treatment lymphocyte counts

Table 5.2.3.18 shows five year observed survival rate according to pretreatment lymphocyte counts of cervical cancer patients. Overall survival was not found to be statistically significant according to pre treatment lymphocyte counts (p=0.677) (Figure 5.2.3.18). Five year overall survival for women having pretreatment lymphocyte counts <2.12(x10^9/L) and women having pretreatment lymphocyte counts ≥2.12 (x10^9/L) were found to be 73.6% and 73.1% respectively.

Table No. 5.2.3.18: Observed Survival rate (%) of stage IIB cervical cancer patients according to absolute lymphocyte counts(x10^9/L)

Lymphocyte	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
< 2.12	135	93.1	84.9	78.9	74.5	73.6	0.677
≥2.12	169	93.3	85.4	80.5	76.1	73.1	



Number at risk

<2.12	135	119	100	90	84	79
≥2.12	169	147	127	114	103	95

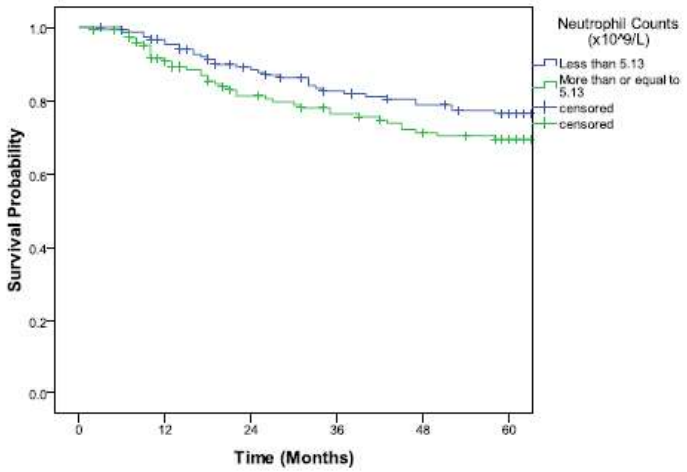
Figure 5.2.3.18: Survival rate (%) of stage IIB cervical cancer patients according absolute lymphocyte counts

5.2.3.19 Survival according to pre treatment neutrophil counts

Table 5.2.3.19 shows five year observed survival rate according to pretreatment neutrophil counts of cervical cancer patients. Overall survival was not found to be statistically significant according to pre treatment neutrophil counts (p=0.112). Five year overall survival for women having pretreatment neutrophil counts <5.13($x10^9$/L) and women having pretreatment neutrophil counts ≥5.13 ($x10^9$/L) were found to be 76.7% and 69.7% respectively (Figure 5.2.3.19).

Table No. 5.2.3.19: Observed Survival rate (%) of stage IIB cervical cancer patients according to absolute neutrophil counts($x10^9$/L)

Neutrophil	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<5.13	156	95.4	88.5	82.7	79.0	76.7	0.112
≥5.13	148	90.8	81.4	76.5	71.4	69.7	



Number at risk

<5.13	156	144	126	112	104	97
≥5.13	148	122	101	92	83	77

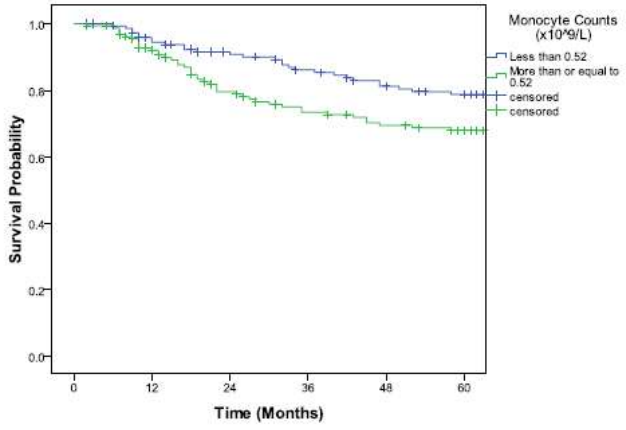
Figure 5.2.3.19: Survival rate (%) of stage IIB cervical cancer patients according to absolute neutrophil counts

5.2.3.20 Survival according to pre treatment monocyte counts

Table 5.2.3.20 shows five year observed survival rate according to pretreatment monocyte counts of cervical cancer patients. Overall survival was found to be statistically significant according to pre treatment monocyte counts (p=0.022) (Figure 5.2.3.20). Further cox univariate analysis showed that women having pretreatment monocyte counts ≥0.52 ($x10^9$/L) was associated with poor prognosis in cervical cancer patients (HR=1.707; 95% C.I.= 1.072-2.717; p=0.024).

Table No. 5.2.3.20: Observed Survival rate (%) of stage IIB cervical cancer patients according to absolute monocyte counts($x10^9$/L)

Monocyte	**Total**	**Survival in percentage**					**p Value**
		1 Yr	**2 Yr**	**3 Yr**	**4Yr**	**5Yr**	
<0.52	149	94.4	90.8	86.1	81.3	78.8	0.022
≥0.52	155	92.0	79.6	73.5	69.6	68.0	
Univariate Analysis							
	Hazard Ratio						p-value
<0.52	1						
≥0.52	1.707 (1.072-2.717)						0.024



Number at risk

<0.52	149	135	120	109	99	93
≥0.52	155	131	107	95	88	44

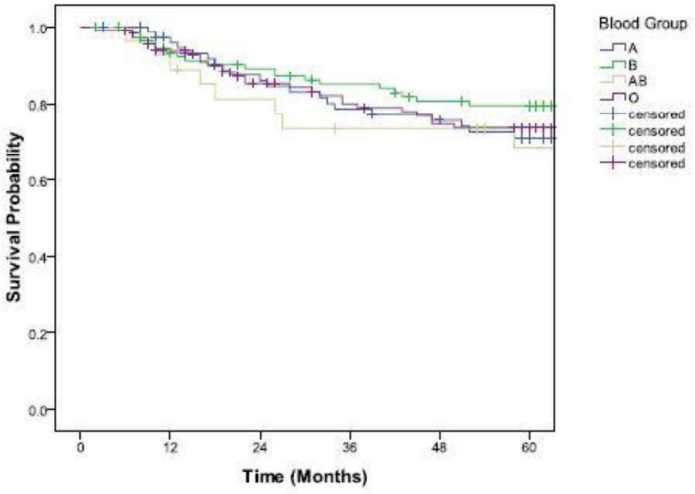
Figure 5.2.3.20: Survival rate (%) of stage IIB cervical cancer patients according to absolute monocyte counts

5.2.3.21 Survival according to blood group

Table 5.2.3.21 shows five year observed survival rate according to blood group of cervical cancer patients. Overall survival was not found to be statistically significant according to blood group (p=0.775). Five year overall survival for women having blood group A, B, AB and O were found to be 71.0%, 79.5%, 68.5% and 73.7% respectively (Figure 5.2.3.21).

Table No. 5.2.3.21: Observed Survival rate (%) of stage IIB cervical cancer patients according to blood group

Blood Group (n=328)	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
A	77	95.9	85.9	78.6	75.6	71.0	0.775
B	110	93.3	89.2	85.0	80.6	79.5	
AB	27	88.9	81.2	73.4	73.4	68.5	
O	114	93.8	85.1	80.0	74.7	73.7	



Number at risk

A	77	70	60	54	50	45
B	110	93	86	79	72	70
AB	27	25	21	17	17	14
O	114	102	85	77	71	68

Figure 5.2.3.21: Survival rate (%) of stage IIB cervical cancer patients according to blood group

5.2.3.22 Univariate and Multifactorial Analysis of OS of locally advance stage IIB

Table 5.2.3.22 shows multi-factorial analysis for stage IIB cervical cancer patients. In univariate analysis co-morbidity, tumor grade, laterality of parametrium involvement, pretreatment absolute monocyte counts and treatment modality were found to be statistically significant. To study independent effect of these factors on overall survival, we kept all the variables significant in univariate analysis in to multivariate cox regression model using backward selection method. Results of multi-factorial analysis shows that tumor grade was not longer found to be associated with prognosis of stage IIB cervical cancer patients. However, presence of co-morbidity, laterality of parametrium involvement, pretreatment absolute monocyte counts and treatment modality were independent predictors of overall survival in stage IIB cervical cancer patients. The analysis revealed that presence of co-morbid condition, bilateral parametrium involvement, elevated pretreatment monocyte counts were associated with poor prognosis of stage IIB cervical cancer patients. Patients treated with chemo-radio therapy were associated with better overall survival as compare to those treated with radiotherapy alone.

Table 5.2.3.22: Univariate and Multifactorial analysis for Overall Survival of Locally Advanced stage IIB cervical cancer patients

	No. of	Univariate		Multifactorial	
Parameter	**cases**	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Comorbidity					
Absent	240	1		1	
Present	101	1.768 (1.139-2.744)	0.011*	1.879 (1.202-2.937)	0.006*
Tumor Grade					
Low Grade	89	1		---	0.266
High Grade	108	1.951 (1.118-3.405)	0.019*		
Laterality of Parametrium Involvement					
Unilateral	198	1		1	
Bilateral	125	2.465 (1.574-3.860)	<0.001*	2.312 (1.464-3.651)	<0.001*
Monocyte Counts (x10^9/L)					
<0.52	149	1		1	
≥0.52	155	1.707 (1.072-2.717)	0.024*	1.814 (1.133-2.905)	0.013*
Treatment Modality					
RT only	114	1		1	
RT with CT	224	0.488(0.315-0.755)	<0.001*	0.554 (0.356-0.861)	0.009*

*p<0.05(StatisticallySignificant)

5.2.4: Advanced Stage (III-IVA) received curative treatment

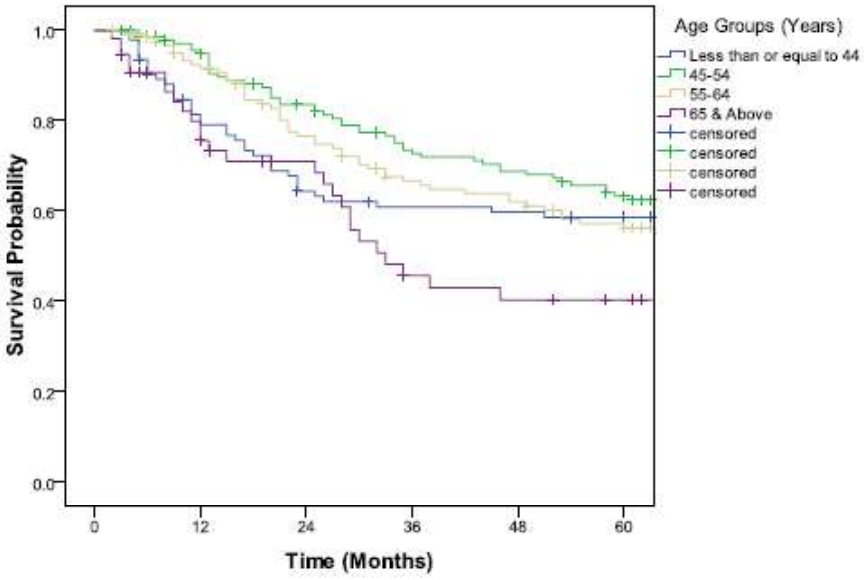
In this study we found 424 cervical cancer patients diagnosed with FIGO stage IIIA to IVA received curative treatment only. The median follow-up period for this cohort was 53 months, ranging from 2 to 96 months. There were 170 (40.09%) death occurred in stage III-IVA patients received curative treatment. The 3 year and 5 year overall survival of stage III-IVA cervical cancer patients received curative treatment were 65.0% and 57.5% respectively (Table 5.2.1.4).

5.2.4.1 Survival according to Age

Table 5.2.4.1 reflects the difference in survival with respect to age of cervical cancer patients. The five year overall survival for patients having age group ≤ 44 years, 45-54 years, 55-64 years and ≥ 65 years were found to be 58.6%, 63.3%, 56.2% and 40.3% respectively. We found age was associated with overall survival of cervical cancer patients (p=0.007). Further this table shows that this difference in survival is due to patients aged 65 years or older (HR=1.691; 95% C.I.=1.039-2.751; p= 0.034). Figure 5.2.4.1 shows Kaplan Meier curve of overall survival of stage III-IVA cervical cancer patients received curative treatment.

Table 5.2.4.1: Observed Survival rate (%) of stage III to IVA cervical cancer patients according to age

Age (Years)	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
≤44	94	79.1	64.4	60.9	59.7	58.6	0.007
45-54	145	94.9	83.6	72.7	68.8	63.3	
55-64	129	91.5	76.5	66.6	62.0	56.2	
≥65	56	75.6	71.0	45.6	40.3	40.3	
Univariate Analysis							
	Hazard Ratio						p-value
≤44	1						
45-54	0.763 (0.504-1.156)						0.202
55-64	0.935 (0.616-1.419)						0.752
≥65	1.691 (1.039-2.751)						0.034



Number at risk						
≤44	94	72	56	52	51	49
45-54	145	129	109	94	88	79
54-64	129	107	86	72	67	59
≥65	56	37	28	17	15	13

Figure 5.2.4.1: Survival rate (%) of stage III-IVA cervical cancer patients according to age

5.2.4.2 Survival according to educational status

Table 5.2.4.2 reflects the difference in survival with respect to educational status of cervical cancer patients. Further this table shows that literate patients have good prognosis as compare to illiterate patients (HR=0.707; 95% C.I.=0.520-0.961; p=0.027). The five year overall survival for illiterate and literate patients were found to be 51.8% and 64.0% respectively. We found educational status was associated with overall survival of cervical cancer patients (p=0.025) (Figure 5.2.4.2).

Table 5.2.4.2 Observed Survival rate (%) of stage III to IVA cervical cancer patients according to educational status

Education Status	**Total**	**Survival in percentage**					**p Value**
		1 Yr	**2 Yr**	**3 Yr**	**4Yr**	**5Yr**	
Illiterate	233	86.1	72.4	58.7	54.5	51.8	0.025
Literate	191	89.9	79.0	72.5	69.5	64.0	
Univariate Analysis							
	Hazard Ratio						p-value
Illiterate	1						
Literate	0.707 (0.520-0.961)						0.027

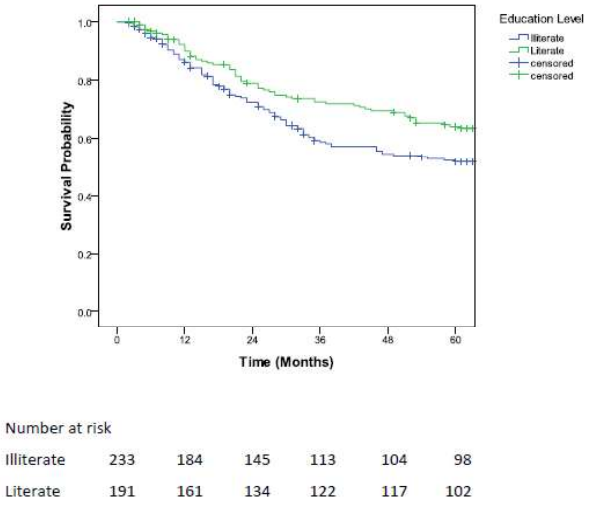


Figure 5.2.4.2: Survival rate (%) of stage III-IVA cervical cancer patients according to educational level

5.2.4.3 Survival according to marital status

Table 5.2.4.3 reflects the difference in survival with respect to marital status of cervical cancer patients. We found no difference in overall survival with respect to marital status (p=0.245) . The five year overall survival for currently married and widow patients were found to be 58.2% and 55.8% respectively (Figure 5.2.4.3).

Table No.5.2.4.3: Observed Survival rate (%) of stage III to IVA cervical cancer patients according to Marital Status

Marital Status	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Married	302	89.1	75.7	65.0	62.0	58.2	0.245
Widow	120	84.4	74.0	64.4	59.1	55.8	

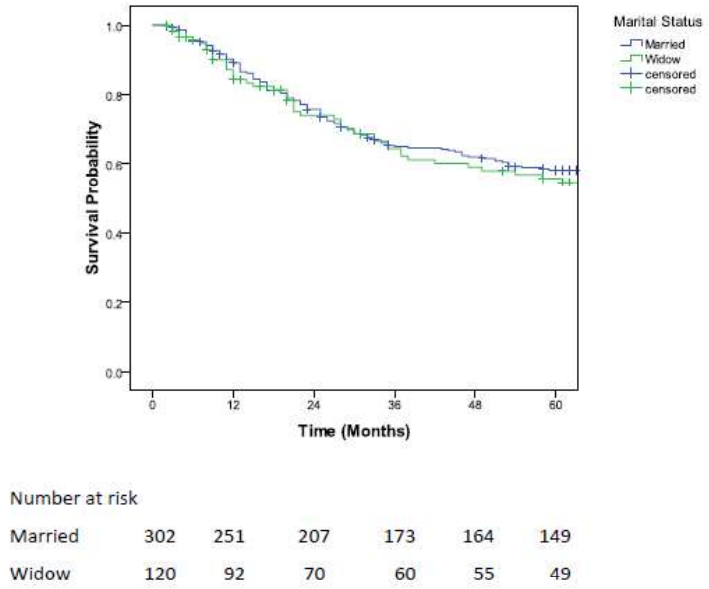


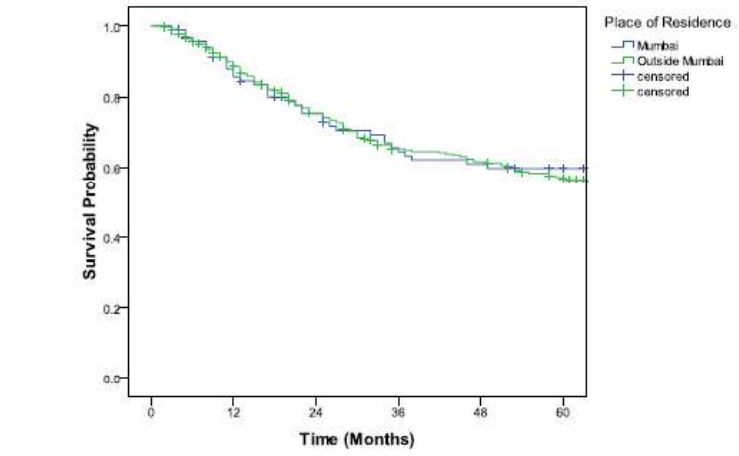
Figure 5.2.4.3: Survival rate (%) of stage III-IVA cervical cancer patients according to marital status

5.2.4.4 Survival according to place of residence

Table 5.2.4.4 reflects the difference in survival with respect to place of residence of cervical cancer patients. We found no difference in overall survival with respect to place of residence (p=0.981). The five year overall survival for patients residing in Mumbai and residing outside Mumbai were found to be 60.0% and 59.8% respectively (Figure 5.2.4.4).

Table No.5.2.4.4: Observed Survival rate (%) of stage III to IVA cervical cancer patients according to place of residence

Place of Residence	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Mumbai	95	85.6	75.2	64.5	60.9	60.0	0.981
Outside Mumbai	329	88.6	75.5	65.2	61.6	59.8	



Number at risk

Mumbai	95	78	64	55	51	47
Outside Mumbai	329	267	215	180	170	153

Figure 5.2.4.4: Survival rate (%) of stage III-IVA cervical cancer patients according to place of residence

5.2.4.5 Survival according to religion

Table 5.2.4.5 reflects the difference in survival with respect to religion of cervical cancer patients. We found no difference in overall survival with respect to religion (p=0.559). The five year overall survival for Hindu and Non-Hindu patients were found to be 58.1% and 53.1% respectively (Figure 5.2.4.5).

Table No.5.2.4.5: Observed Survival rate (%) of stage III to IVA cervical cancer patients according to religion

Religion	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Hindu	371	87.9	75.1	65.4	62.0	58.1	0.559
Non Hindu	53	87.9	77.4	62.0	57.5	53.1	

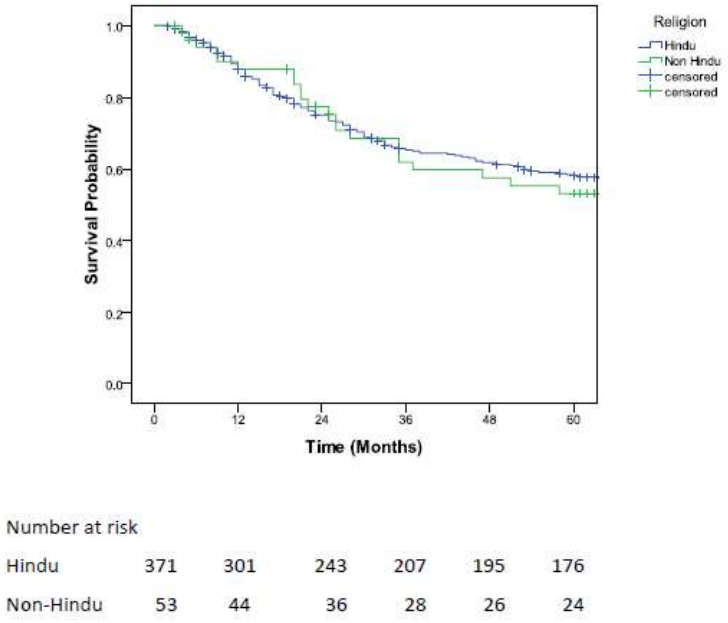


Figure 5.2.4.5: Survival rate (%) of stage III-IVA cervical cancer patients according to religion

5.2.4.6 Survival according to menopausal status

Table 5.2.4.6 reflects the difference in survival with respect to menopausal status of cervical cancer patients. We found no difference in overall survival with respect to menopausal status. The five year overall survival for pre-menopausal and post-menopausal patients were found to be 58.7% and 56.8% respectively (Figure 5.2.4.6).

Table No. 5.2.4.6: Observed Survival rate (%) of stage III to IVA cervical cancer patients according to Menopausal Status

Menopausal Status	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Pre-Menopausal	118	85.9	69.7	63.3	60.5	58.7	.866
Post-Menopausal	306	89.4	77.8	65.7	61.7	56.8	

**Calculated using Log Rank Test*

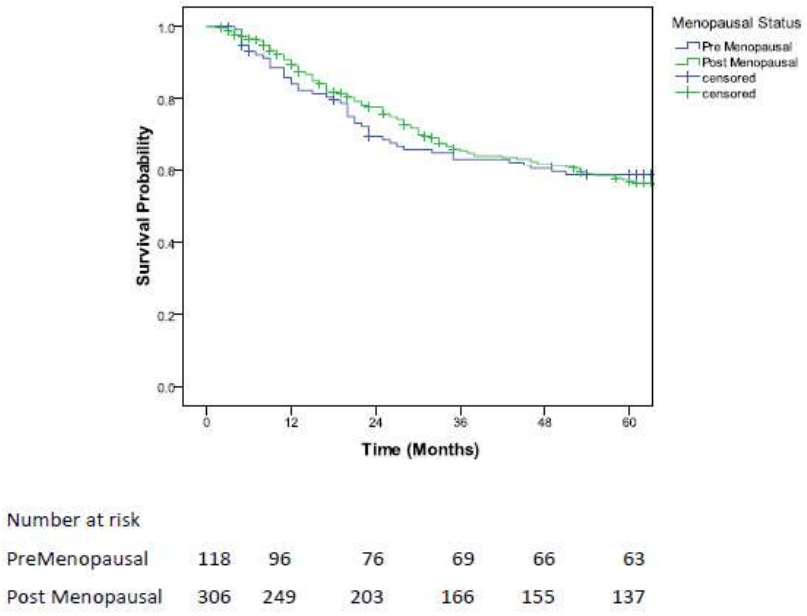


Figure 5.2.4.6: Survival rate (%) of stage III-IVA cervical cancer patients according to menopausal status

5.2.4.7 Survival according toParity

Table 5.2.4.7 reflects the difference in survival with respect to parity of cervical cancer patients. We found no difference in overall survival with respect to parity (p=0.475). The five year overall survival for patients having parity less than or equal to two children and patients having parity more than two children were found to be 62.0% and 54.6% respectively (Figure 5.2.4.7).

Table No.5.2.4.7: Observed Survival rate (%) of stage III to IVA cervical cancer patients according to Parity

Parity	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
≤2	93	91.8	79.3	68.8	66.1	62.0	0.475
≥3	282	87.1	73.2	63.0	58.4	54.6	

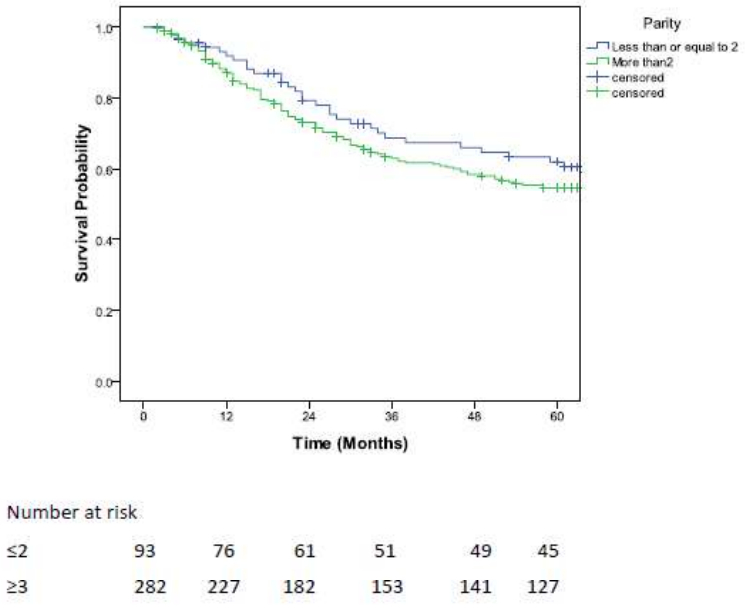


Figure 5.2.4.7: Survival rate (%) of stage III-IVA cervical cancer patients according to parity

5.2.4.8 Survival according to number of abortion

Table 5.2.4.8 reflects the difference in survival with respect to abortion history of cervical cancer patients. We found no difference in overall survival with respect to abortion history (p=0.176). The five year overall survival of the patients, do not have abortion and patients have atleast one abortion were found to be 58.0% and 48.1% respectively (Figure 5.2.4.8).

Table No.5.2.4.8: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to number of abortion

Abortion	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
0	319	87.7	75.2	64.8	61.8	58.0	0.176
≥1	56	91.0	71.9	62.2	52.2	48.1	

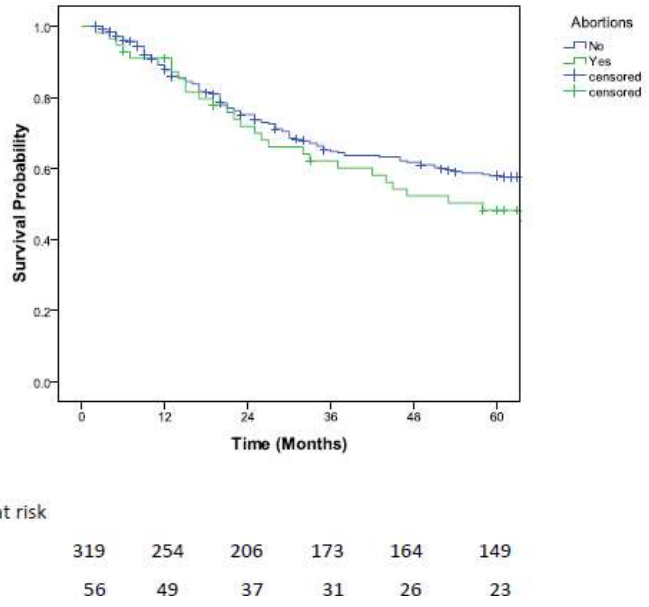


Figure 5.2.4.8: Survival rate (%) of stage III-IVA cervical cancer patients according to number of abortions

5.2.4.9 Survival according to tumor dimension

Table 5.2.4.9 shows that largest tumor dimension of more than 4 cm (HR=1.762; 95% C.I.=1.166-2.663; p=0.007) was associated with poor prognosis of stage III-IVA cervical cancer patients received curative treatment. The five year overall survival for patients having largest dimension ≤ 4 cm. and patients having largest dimension >4cm. were found to be 70.7% and 52.9% respectively (p<0.001) (Figure 5.2.4.9) .

Table No. 5.2.4.9: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to largest tumor dimension

Largest Tumor	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
≤4 cms	96	96.6	83.9	76.8	74.4	70.7	0.006
> 4cms	270	84.8	72.2	60.9	56.5	52.9	
Univariate analysis (Cox- Proportional Hazard Model)							
	Hazard Ratio (95% CI)						**p Value**
≤4 cms	1						
> 4cms	1.762 (1.166-2.663)						0.007

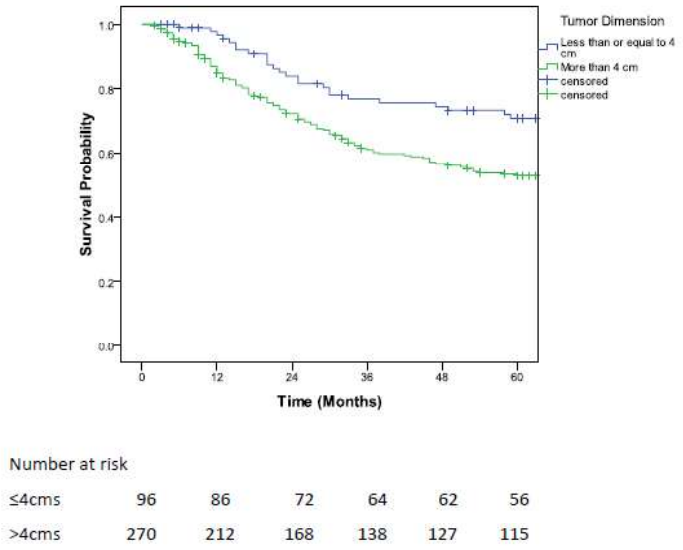


Figure 5.2.4.9: Survival rate (%) of stage III-IVA cervical cancer patients according to largest tumor dimension

5.2.4.10 Survival according to tumor grade

Table 5.2.4.10 shows that high grade tumor (HR=2.067; 95% C.I.=1.309-3.264; p=0.002) was associated with poor prognosis of stage III-IVA cervical cancer patients. The five year overall survival for low grade and higher grade patients were found to be 69.5% and 45.6% respectively (Figure 5.2.4.10).

Table No. 5.2.4.10: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to tumor differentiation

Tumor Differentiation	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Low Grade	90	92.7	81.3	76.1	73.6	69.5	0.001
High Grade	109	85.5	70.7	56.7	50.7	45.6	
Univariate Cox Analysis							
	Hazard Ratio						p-value
Low Grade	1						
High Grade	2.067 (1.309-3.264)						0.002

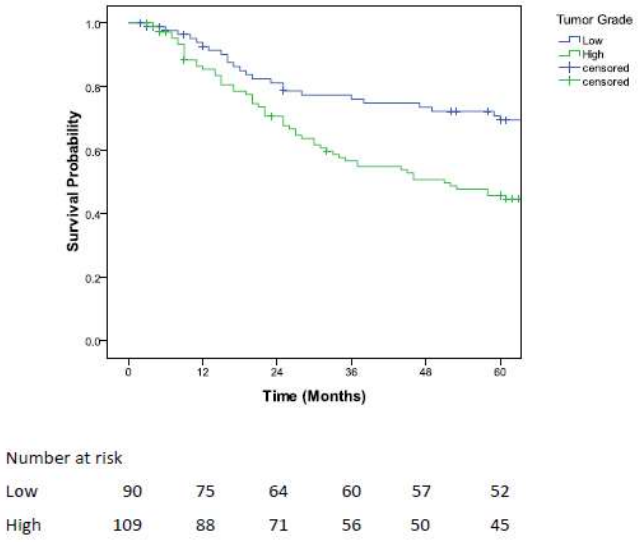


Figure 5.2.4.10: Survival rate (%) of stage III-IVA cervical cancer patients according to tumor grade

5.2.4.11 Survival according to tumor histology

Table 5.2.4.11 shows that non-squamous histology (HR=2.269; 95% C.I.=1.229-4.189; p=0.009) was associated with poor prognosis of stage III-IVA cervical cancer patients. The five year overall survival for patients diagnosed with squamous and non-squamous histology were found to be 58.4% and 38% respectively (Figure 5.2.4.11).

Table No. 5.2.4.11: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to tumor histology

Tumor Histology	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Squamous	403	89.1	76.9	66.4	62.6	58.4	0.007
Non-Squamous	21	63.2	45.6	38.0	38.0	38.0	
Univariate Cox Analysis							
	Hazard Ratio						p-value
Squamous	1						0.009
Non-Squamous	2.269 (1.229-4.189)						

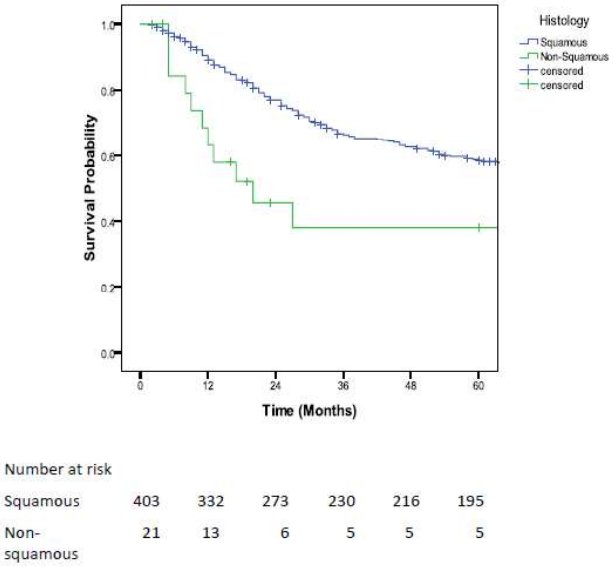


Figure 5.2.4.11: Survival rate (%) of stage III-IVA cervical cancer patients according to tumor histology

5.2.4.12 Survival according to treatment modality

Table 5.2.4.12 shows that patients treated with chemo-radiotherapy (HR=0.613; 95% C.I.=0.452-0.832; p=0.002) was associated with better prognosis of stage III-IVA cervical cancer patients. The five year overall survival for patients treated with radiotherapy only and those treated with chemo-radio therapy were found to be 49.7% and 64.3% respectively (Figure 5.2.4.12).

Table No.5.2.4.12: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to treatment modality

Treatment	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
RT only	182	82.5	66.6	55.6	52.3	49.7	0.001
RT+ CT	235	91.9	82.1	72.9	69.4	64.3	
Univariate analysis							
	Hazard Ratio (95% CI)						p Value
RT only	1						0.002
RT + CT	0.613 (0.452-0.832)						

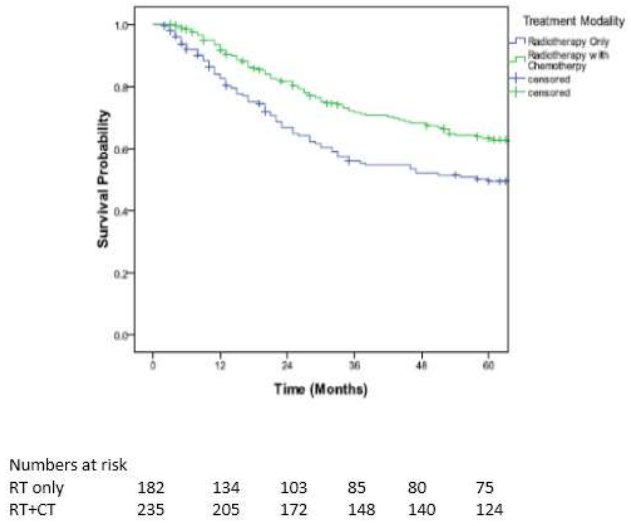


Figure 5.2.4.12: Survival rate (%) of stage III-IVA cervical cancer patients according to treatment modality

5.2.4.13 Survival according to pre-treatment performance status

Table 5.2.4.13 reflects no difference in overall survival with respect to pre-treatment performance status (p=0.360). The five year overall survival for patients fully active at time of diagnosis and patients restricted in physical activity were found to be 58.1% and 55.4% respectively (Figure 5.2.4.13).

Table No.5.2.4.13: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to Performance Status

Performance Status**	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
0	313	89.1	75.7	66.3	62.6	58.1	0.360
≥1	111	84.2	74.6	61.3	57.8	55.4	

***Performance Status:* 0 : able to carry out normal activity; ≥1 : Restricted in physical activity.

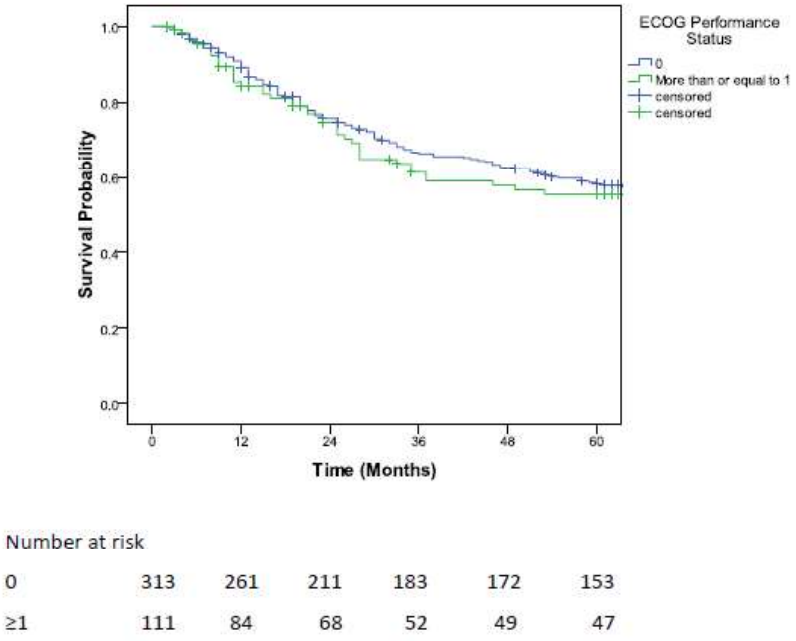


Figure 5.2.4.13: Survival rate (%) of stage III-IVA cervical cancer patients according to pretreatment performance status

5.2.4.14 Survival according to parametrium involvement

Table 5.2.4.14 reflects no difference in overall survival with respect to parametrium involvement (p=0.759). The five year overall survival for patients diagnosed with uni-lateral and bi-lateral parametrium involvement were found to be 57.8% and 57.8% respectively (Figure 5.2.4.14).

Table No. 5.2.4.14: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to parametrium involvement

Parametrium	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Uni-lateral	136	93.5	80.2	69.2	63.0	57.8	0.759
Bi-lateral	224	83.4	73.5	64.2	61.0	57.8	

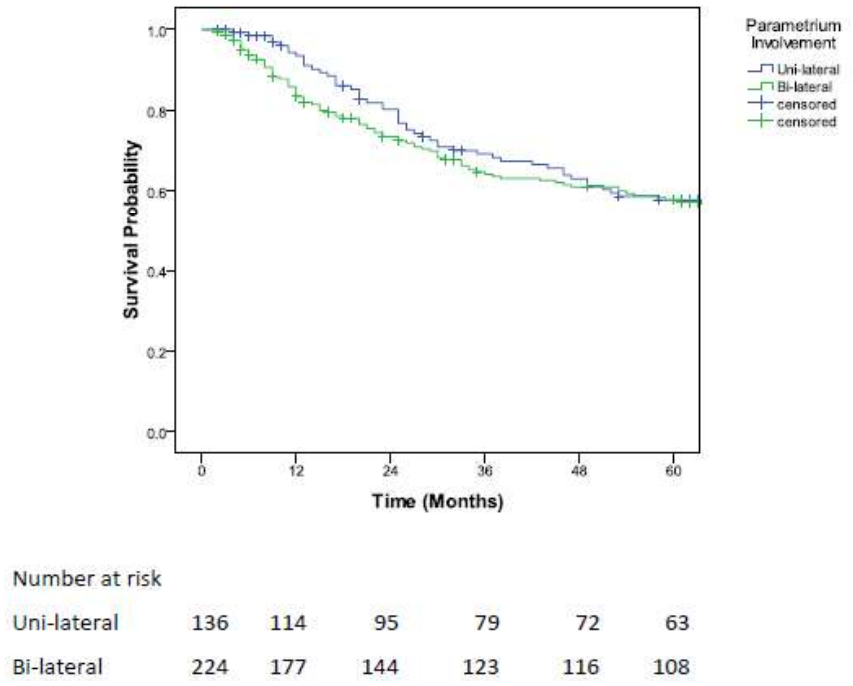


Figure 5.2.4.14: Survival rate (%) of stage III-IVA cervical cancer patients according to laterality of parametrium involvement

5.2.4.15 Survival according to comorbid condition

Table 5.2.4.15 shows that presence of co-morbid condition was associated with poor prognosis in cervical cancer patients (HR=1.584; 95% C.I.= 1.137-2.209; p=0.007). Five year overall survival for women having presence of any co-morbid condition and women not having any co-morbid condition were found to be 47.3% and 60.4% respectively (Figure 5.2.4.15).

Table No. 5.2.4.15: Observed Survival rate (%) of stage III to IVA cervical cancer patients according to presence of comorbidity

Comorbidity	**Total Number**	**Survival in percentage**					**p Value**
		1 Yr	**2 Yr**	**3 Yr**	**4Yr**	**5Yr**	
Present	93	77.7	65.2	55.8	51.1	47.3	0.006
Absent	331	90.8	78.4	67.7	64.5	60.4	
Univariate Cox regression							
	Hazard Ratio						p-value
Absent	1						0.007
Present	1.584(1.137-2.209)						

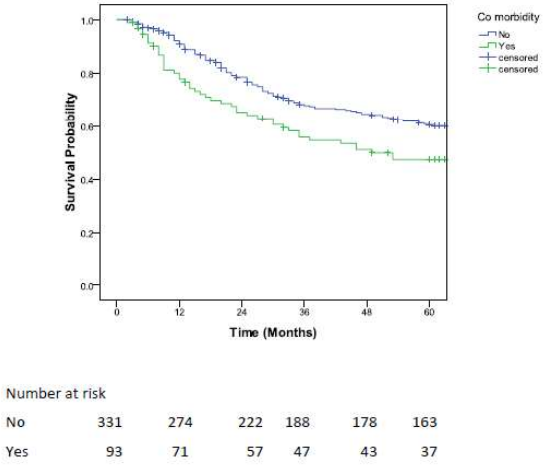


Figure 5.2.4.15: Survival rate (%) of stage III-IVA cervical cancer patients according to presence of comorbid condition

5.2.4.16 Survival according to hydronephrosis

Table 5.2.4.16 shows that patients diagnosed with bi-lateral hydronephrosis (HR=3.264; 95% C.I.=1.907-5.588; p<0.001) was associated with poor prognosis of stage III-IVA cervical cancer patients The five year overall survival for patients had no hydronephrosis, uni-lateral hydronephrosis and bi-lateral hydronephrosis were found to be 60.7%, 53.0% and 12.5% respectively (Figure 5.2.4.16).

Table No. 5.2.4.16: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to Hydronephrosis

Hydronephorosis	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
No	339	90.1	79.0	68.0	64.5	60.7	<0.001
Uni-lateral	64	81.6	62.6	56.9	53.0	53.0	
Bi-lateral	21	66.7	50.0	37.5	31.3	12.5	
Univariate Cox regression							
	Hazard Ratio						p-value
No	1						
Uni-lateral	1.371 (0.905-2.077)						0.136
Bi-lateral	3.264 (1.907-5.588)						<0.001

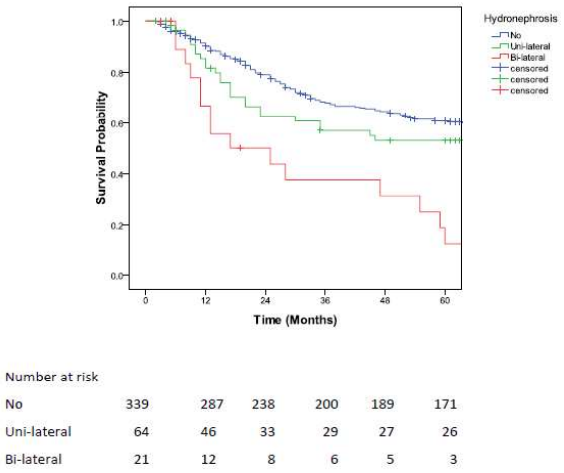


Figure 5.2.4.16: Survival rate (%) of stage III-IVA cervical cancer patients according to presence of hydronephrosis

5.2.4.17 Survival according to pre treatment hemoglobin level

Table 5.2.4.17 shows five year observed survival rate according to pretreatment hemoglobin level of cervical cancer patients. Overall survival was not found to be statistically significant according to pre treatment hemoglobin level (p=0.221). Five year overall survival for women having hemoglobin level <11.5 g/dL and women having hemoglobin level ≥11.5 g/dL were found to be 55.0% and 61.0% respectively (Figure 5.2.4.17).

Table No.5.2.4.17: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to pretreatment hemoglobin level (g/dL)

Hemoglobin Level	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<11.5	216	85.2	70.6	62.0	58.6	55.0	0.221
≥11.5	169	88.8	78.3	65.1	63.8	61.0	

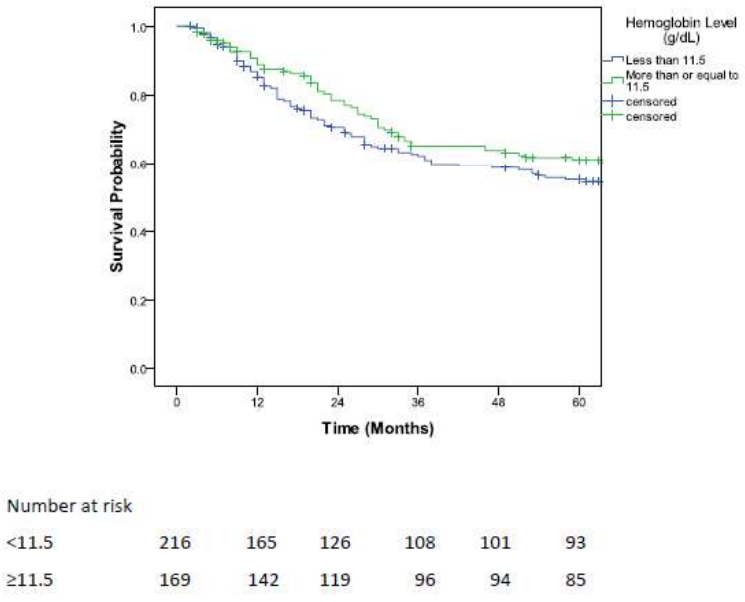


Figure 5.2.4.17: Survival rate (%) of stage III-IVA cervical cancer patients according to pretreatment hemoglobin level

5.2.4.18 Survival according to pre treatment WBC counts

Table 5.2.4.18 shows five year observed survival rate according to pretreatment WBC counts of cervical cancer patients. Five year overall survival for women having total WBC counts <8.39(x10^9/L) and women having total WBC counts ≥8.39 (x10^9/L) were found to be 56.4% and 58.7% respectively (Figure 5.2.4.18).

Table No.5.2.4.18: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to pretreatment total WBC counts(x10^9/L)

WBC Counts	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<8.39	176	86.2	71.7	61.5	60.1	56.4	0.622
≥8.39	209	87.3	76.0	64.9	61.5	58.7	

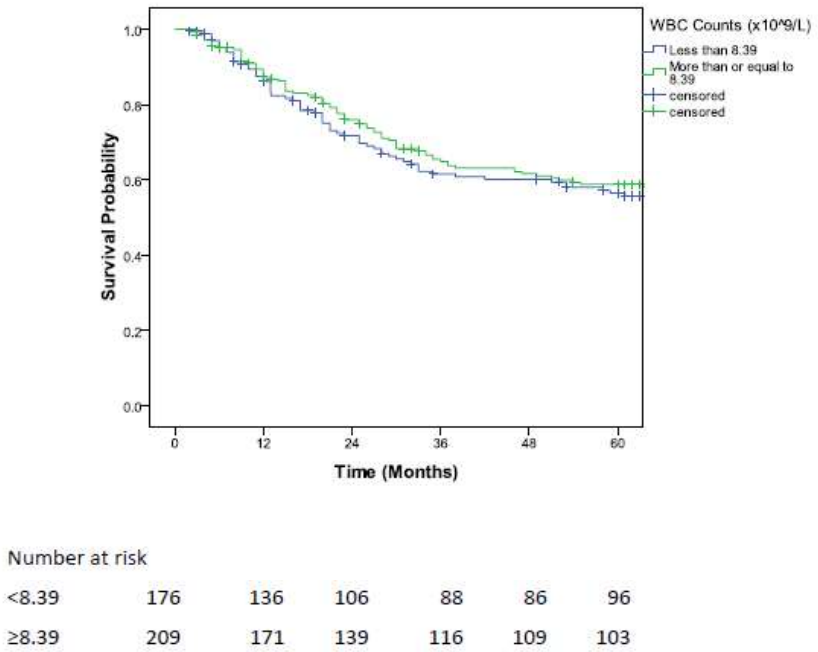


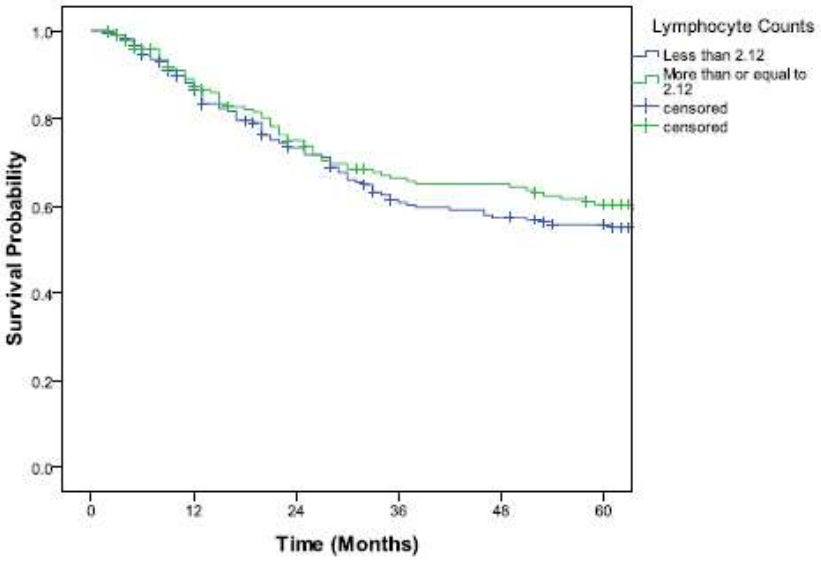
Figure 5.2.4.18: Survival rate (%) of stage III-IVA cervical cancer patients according to pretreatment absolute WBC counts

5.2.4.19 Survival according to pre treatment lymphocyte counts

Table 5.2.4.19 shows five year observed survival rate according to pretreatment lymphocyte counts of cervical cancer patients. Five year overall survival for women having pretreatment lymphocyte counts <2.12($x10^9$/L) and women having pretreatment lymphocyte counts ≥2.12 ($x10^9$/L) were found to be 55.5% and 60.3% respectively (Figure 5.2.4.19).

Table No.5.2.4.19: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to pretreatment lymphocyte counts($x10^9$/L)

Lymphocyte Counts	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<2.12	210	86.5	73.4	60.8	57.3	55.5	0.402
≥2.12	175	87.2	74.9	66.4	65.0	60.3	



Number at risk

<2.12	210	165	130	105	98	90
≥2.12	175	142	115	99	97	88

Figure 5.2.4.19: Survival rate (%) of stage III-IVA cervical cancer patients according to pretreatment absolute lymphocyte counts

5.2.4.20 Survival according to pre treatment neutrophil counts

Overall survival was not found to be statistically significant according to pre treatment neutrophil counts (p=0.970) (Table 5.2.4.20). Five year overall survival for women having pretreatment neutrophil counts <5.13($x10^9$/L) and women having pretreatment neutrophil counts ≥5.13 ($x10^9$/L) were found to be 57.9% and 57.5% respectively (Figure 5.2.4.20).

Table No.5.2.4.20: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to pretreatment neutrophil counts($x10^9$/L)

Neutrophil Counts	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<5.13	177	89.0	74.4	62.7	61.4	57.9	0.970
≥5.13	208	85.0	73.8	64.0	60.5	57.5	

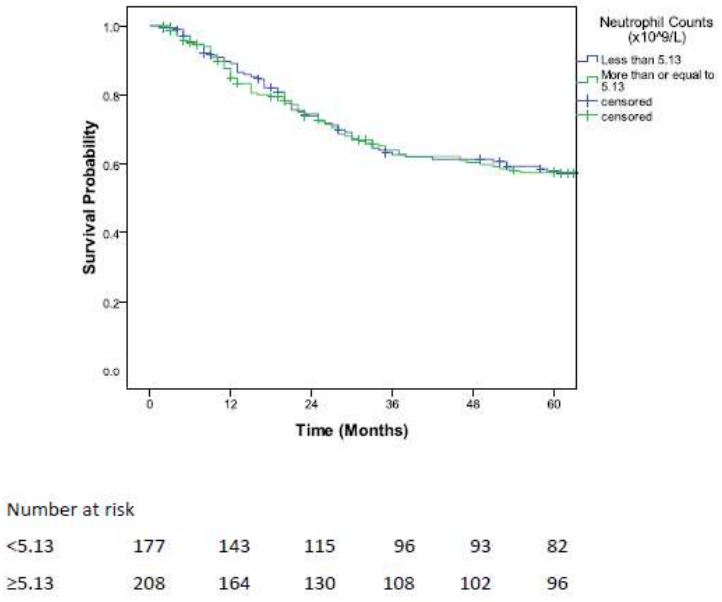


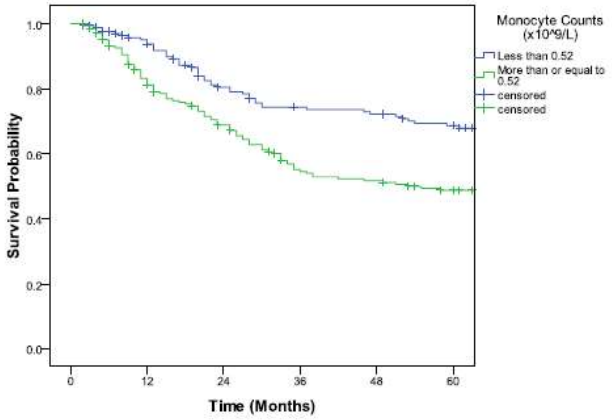
Figure 5.2.4.20: Survival rate (%) of stage III-IVA cervical cancer patients according to pretreatment absolute neutrophil counts

5.2.4.21 Survival according to pre treatment monocyte counts

Cox univariate analysis showed that women having pretreatment monocyte counts ≥0.52 ($x10^9$/L) was associated with poor prognosis in cervical cancer patients (HR=1.720; 95% C.I.= 1.233-2.398; p=0.001) (Table 5.2.4.21). Five year overall survival for women having pretreatment monocyte counts <0.52 ($x10^9$/L) and women having pretreatment monocyte counts ≥ 0.52 ($x10^9$/L) were found to be 68.7% and 48.8% respectively (Figure 5.2.4.21).

Table No.5.2.4.21: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to pretreatment monocyte counts($x10^9$/L)

Monocyte Counts	**Total**	**Survival in percentage**					**p Value**
		1 Yr	**2 Yr**	**3 Yr**	**4Yr**	**5Yr**	
<0.52	176	93.8	80.5	74.4	72.3	68.7	0.001
≥0.52	209	81.2	68.9	54.5	51.7	48.8	
Univariate Analysis							
	Hazard Ratio						p-value
<0.52	1						
≥0.52	1.720 (1.233-2.398)						0.001



Number at risk

<0.52	176	147	118	107	104	96
≥0.52	209	160	127	97	91	82

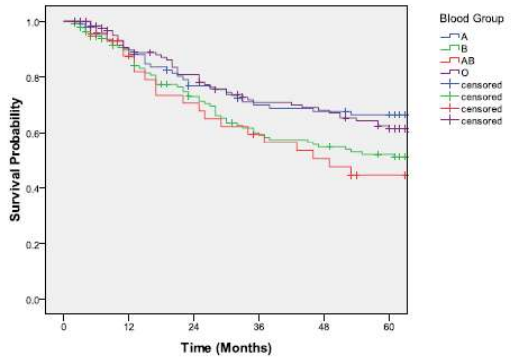
Figure 5.2.4.21: Survival rate (%) of stage III-IVA cervical cancer patients according to pretreatment absolute monocyte counts

5.2.4.22 Survival according to blood group

Table 5.2.3.22 shows five year observed survival rate according to blood group of cervical cancer patients. Overall survival was not found to be statistically significant according to blood group (p=0.088). Five year overall survival for women having blood group A, B, AB and O were found to be 66.4%, 51.9%, 44.5% and 61.5% respectively (Figure 5.2.4.22).

Table No.5.2.4.22: Observed Survival rate (%) of stage III to IVA cervical cancer patients received curative treatment according to blood group

Blood Counts (n=401)	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
A	98	88.0	76.8	69.9	67.6	66.4	0.088
B	133	87.2	73.0	59.0	54.6	51.9	
AB	43	87.5	70.6	59.3	50.4	44.5	
O	127	89.7	80.8	70.8	68.0	61.5	



Number at risk

A	98	82	67	60	58	56
B	133	109	84	68	62	56
AB	43	33	25	20	17	13
O	127	104	91	76	73	65

Figure 5.2.4.22: Survival rate (%) of stage III-IVA cervical cancer patients according to blood group

5.2.4.23 Univariate and Multifactorial analysis for locally advance stage III-IVA patients received curative treatment

Table 5.2.4.23 shows multi-factorial analysis for stage III-IVA cervical cancer patients received curative treatment. In univariate analysis co-morbidity, tumor grade, tumor histology, pretreatment absolute monocyte counts, treatment modality, largest tumor dimension, age, educational status and bi-lateral hydronephrosis were found to be statistically significant. To study independent effect of these factors on overall survival, we kept all the variables significant in univariate analysis in to multivariate cox regression model using backward selection method. Results of multi-factorial analysis shows that age and educational status (p= 0.141 and 0.294 respectively) were no longer found to be associated with prognosis of stage III-IVA cervical cancer patients received curative treatment. Although, presence of co-morbidity, high tumor grade, non-squamous histology, elevated pretreatment absolute monocyte counts, treatment modality, largest tumor dimension of >4cm. and bi-lateral hydronephrosis were independent predictors of overall survival in stage III-IVA cervical cancer patients received curative treatment.

Table 5.2.4.23 : Univariate & Multifactorial analysis for Locally Advanced stage III-IVA cervical cancer patients received curative treatment

Parameter	No. of	Univariate		Multifactorial*	
		HR (95% CI)	p value	HR (95% CI)	p value
Comorbidity					
Absent/ Present	331/ 93	1.584 (1.137-2.209)	0.007*	1.672(1.177-2.374)	0.004*
Tumor Grade					
Low/High	90/ 109	2.067 (1.309-3.264)	0.002*	1.892 (1.181-3.030)	0.008*
Tumor Histology					
Squamous/ Non-squamous	403/21	2.269 (1.229-4.189)	0.009*	3.389 (1.811-6.342)	<0.001*
Monocyte Counts (x10^9/L)					
Low/High	176/ 209	1.720 (1.233-2.398)	0.001*	1.727 (1.223-2.440)	0.002*
Treatment Modality					
RT / RT+CT	182/ 235	0.613 (0.452-0.832)	0.002*	0.707 (0.516-0.969)	0.031*
Tumor dimension (cm)					
≤4cm / >4cm	96/ 270	1.762 (1.166-2.663)	0.007*	1.742 (1.143-2.654)	0.010*
Age Groups					
≤44	94	1		----	0.141
45-54	145	0.763 (0.504-1.156)	0.202		
55-64	129	0.935 (0.616-1.419)	0.752		
≥65	56	1.691 (1.039-2.751)	0.034*		
Educational Status					
Illiterate / Literate	233/191	0.707 (0.520-0.961)	0.027*		0.294
Hydronephrosis					
No	339	1		1	
Uni-lateral	64	1.371 (0.905-2.077)	0.136	1.076 (0.701-1.651)	0.738
Bi-lateral	21	3.264 (1.907-5.588)	<0.001*	3.819 (2.140-6.817)	<0.001*

***p<0.05 (Statistically Significant)**

5.3: Effect of Timelines on Overall Survival

Effect of timelines on overall survival of cervical cancer patients were studied in three steps: timelines between registration and diagnosis, timelines between diagnosis and commencement of treatment and timelines between treatment commencement and treatment completion. This section was based on only on those patients received curative treatment. Analysis for each step was carried out separately in the following sections:

5.3.1: Time lines between registration and diagnosis

This section was evaluating the effect of time gap between registration and diagnosis of cervical cancer patients on overall survival. Table 5.3.1.1 shows that median time between registration and diagnosis of cervical cancer patients were 3 days. Approximately 92% of patients were registered and diagnosed between 1 to 10 days. Only a negligible cases taken more than or equal to 21 days between registration and diagnosis.

Table 5.3.1.2 shows that five year overall survival for patients taken less than or equal to 2 days and more than 2 days time lag between registration and diagnosis were found to be 70.2% and 67.8% respectively. This difference in survival was found to be statistically non-significant ($p=0.502$).

Figure 5.3.1.1 shows Kaplan-Meier curve for overall survival with respect to time lag between registration and diagnosis of cervical cancer patients.

Table No.5.3.1.1: Descriptive Statistics for time lines between registration and diagnosis

Time(Days)	Number (%)
≤2	287(30.1)
3-5	451(47.3)
6-10	148(15.5)
11-15	44 (4.6)
16-20	9(0.9)
≥21	14(1.5)
Total	**953(100.0)**
Median	**3 days**

Table No. 5.3.1.2: Observed Survival rate (%) according to time lag between registration and diagnosis

Time	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<3 days	287	90.5	80.9	76.4	73.4	70.2	0.502
≥3 days	666	92.6	83.7	74.5	70.7	67.8	

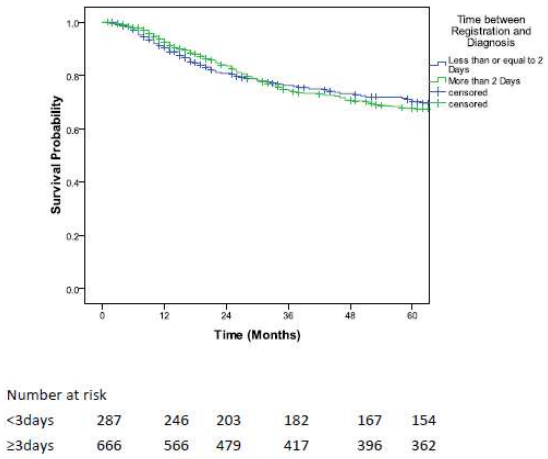


Figure 5.3.1.1: Survival rate (%) with respect to time lag between registration and diagnosis of cervical cancer patients

5.3.2: Time lines between diagnosis and treatment commencement

This section was evaluating the effect of time gap between diagnosis and treatment commencement of cervical cancer patients on overall survival. Table 5.3.2.1 shows that median time between diagnosis and treatment commencement of cervical cancer patients were 27 days ranging from 1 to 205 days. Approximately 90% of patients were start taken treatment within 60 days from diagnosis. Only 3.4% of patients taken more than or equal to 91 days between diagnosis and treatment commencement.

Table No.5.3.2.1: Descriptive Statistics for time lines between diagnosis and commencement of treatment

Time(Days)	**Number (%)**
≤30	549(57.6)
31-60	300(31.5)
61-90	72(7.6)
≥91	32(3.4)
Total	**953(100.0)**
Median	**27 days**

Table 5.3.2.2 shows that five year overall survival for patients taken less than or equal to 26 days and more than 26 days between diagnosis and treatment commencement were found to be 67.2% and 69.8% respectively. This difference in survival was found to be statistically non-significant (p=0.535).

Figure 5.3.2.1 shows Kaplan-Meier curve for overall survival with respect to time lag between diagnosis and treatment commencement of cervical cancer patients.

Table No. 5.3.2.2: Observed Survival rate (%) according to time lag between diagnosis and commencement of treatment

Time	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<27 days	463	92.2	82.4	74.8	70.9	67.2	0.535
≥27 days	490	91.7	83.3	75.4	72.1	69.8	

**Calculated using Log Rank Test*

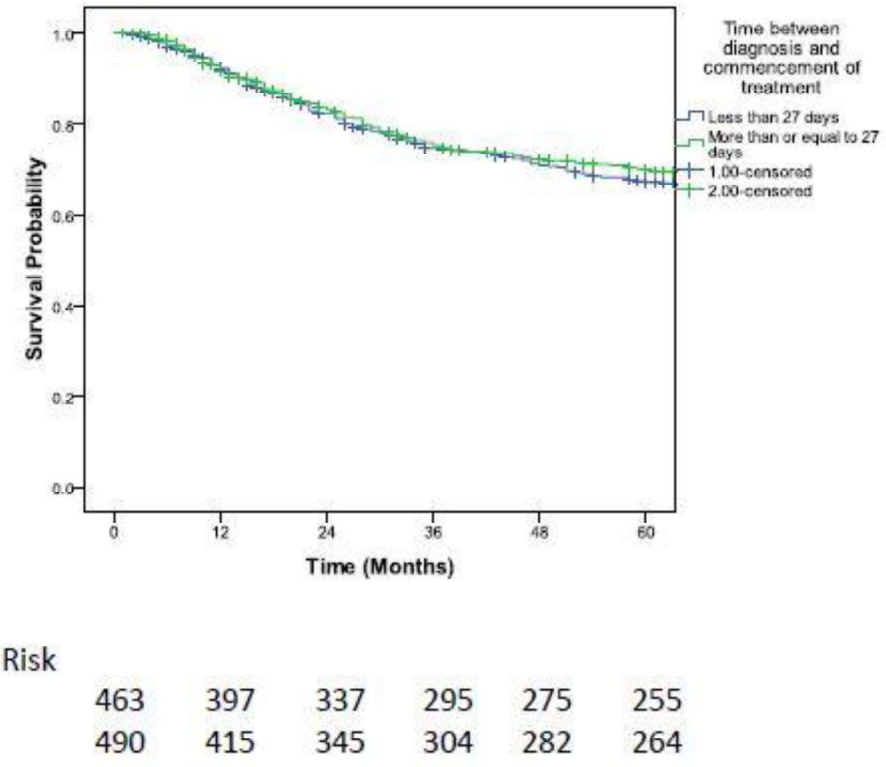


Figure 5.3.2.1: Survival rate (%) with respect to time lag between diagnosis and commencement of treatment

5.3.3: Time lines between treatment commencement and treatment completion

This section emphasize on effect of time taken between treatment commencement and treatment completion on overall survival. Since treatment completion depend upon type of treatment taken, here we analyze the effect of time between treatment commencement and treatment completion on overall survival according to the type of treatment.

Table 5.3.3.1 shows median survival time between treatment commencement and treatment completion for surgically treated cases was found to be 8 days. In this study, date of discharge from hospital was taken as date of treatment completion for surgically treated cases only.

Table No.5.3.3.1: Descriptive Statistics for time lines between commencement of treatment and treatment completion for surgically treated cases only

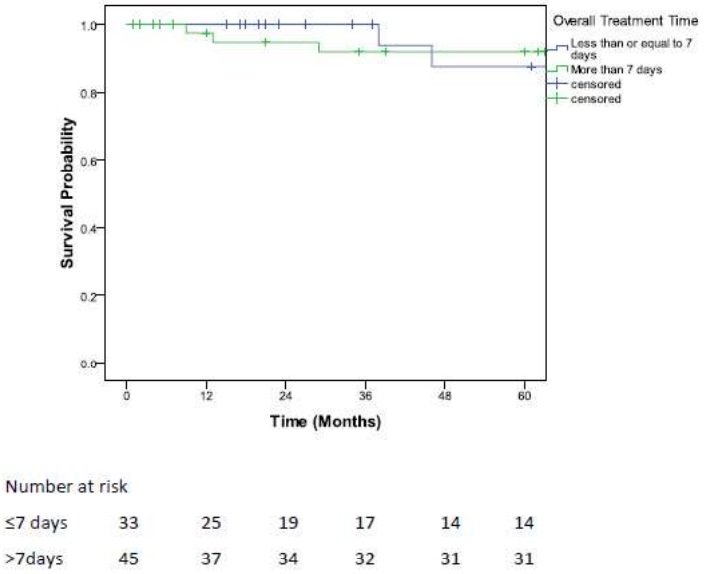
Time(Days)	Number (%)
≤5	17 (21.8)
6-7	16 (20.5)
8-11	25 (32.1)
≥12	20 (25.6)
Total	**78(100.0)**
Median	**8 days**

Table 5.3.3.2 shows overall all survival with respect to taken between treatment commencement and treatment completion for cervical cancer cases treated with surgery only. Five year overall survival for patients taken less than 8 days and patients taken more than or equal to 8 days for treatment completion were found to be 87.5% and 91.9% respectively. There was no difference in survival with respect to time lines between commencement of treatment and treatment completion for patients treated with Surgery only (p=0.883).

Table No. 5.3.3.2: Observed Survival rate (%) according to time lines between commencement of treatment and treatment completion for surgically treated cases only

Time (days)	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<8	33	100.0	100.0	100.0	87.5	87.5	0.883
≥8	45	97.4	94.7	91.9	91.9	91.9	

Figure 5.3.3.1 shows_Kaplan-Meier curve for overall survival with respect to time lag between treatment commencement and treatment completion of cervical cancer patients treated by surgery only. Two curves were crossed to each other at 41 months.



Number at risk

≤7 days	33	25	19	17	14	14
>7days	45	37	34	32	31	31

Figure 5.3.3.1: Survival rate (%) with respect to time lag between treatment commencement and treatment completion of cervical cancer patients treated by surgery only

Table No.5.3.3.3: Descriptive Statistics for time lines between commencement of treatment and treatment completion for patients treated with Surgery and adjuvant or neo-adjuvant chemo/radiotherapy

Time(Days)	Number (%)
≤69	13 (24.1)
70-91	14 (25.9)
92-112	14 (25.9)
≥113	13 (24.1)
Total	**54 (100.0)**
Median	**92 days**

Table 5.3.3.3 shows median survival time between treatment commencement and treatment completion for patients treated with Surgery and adjuvant or neo-adjuvant chemo/radiotherapy was found to be 92 days.

Table 5.3.3.4 shows overall all survival with respect to taken between treatment commencement and treatment completion for cervical cancer cases treated by surgery and other therapies. Five year overall survival for patients taken less than 92 days and patients taken more than or equal to 92 days for treatment completion were found to be 91.3% and 88.9% respectively. There was no difference in survival with respect to time lines between commencement of treatment and treatment completion for patients treated with Surgery and adjuvant or neo-adjuvant chemo/radiotherapy (p=0.900). Figure 5.3.3.2 shows Kaplan-Meier curve for overall survival with respect to time lag between treatment commencement and treatment completion of cervical cancer patients treated by surgery and other therapies.

Table No. 5.3.3.4: Observed Survival rate (%) according to overall treatment time for patients treated with Surgery and adjuvant or neo-adjuvant chemo/radiotherapy

Time (days)	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<92	27	100.0	100.0	91.3	91.3	91.3	0.900
≥92	27	100.0	100.0	100.0	94.4	88.9	

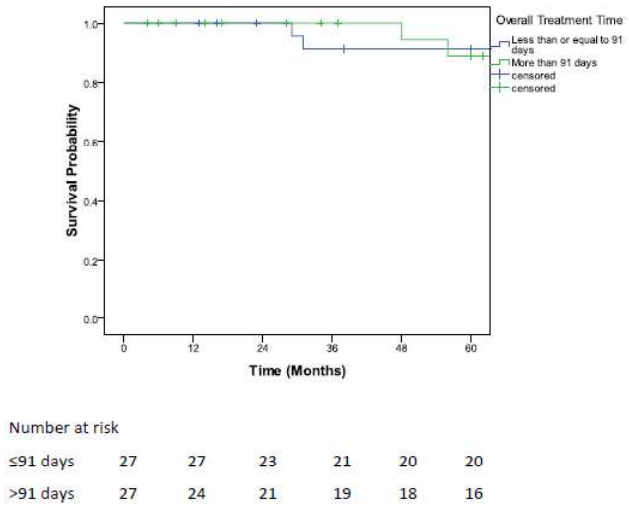


Figure 5.3.3.2: Survival rate (%) with respect to time lag between treatment commencement and treatment completion of cervical cancer patients treated by surgery and other therapies

Table5.3.3.5 shows median survival time between treatment commencement and treatment completion for radio therapy or chemo-radio therapy treated cases was found to be 48 days.

Table No.5.3.3.5: Descriptive Statistics for time lines between commencement of treatment and treatment completion for Radiotherapy or Chemo-Radiotherapy treated cases

Time(Days)	Number (%)
≤60	624(76.7)
61-90	141(17.3)
≥91	49(6.0)
Total	**814(100.0)**
Median	**48 days**

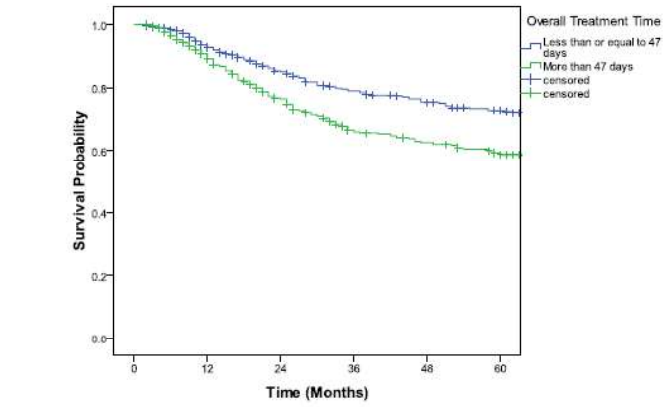
Table 5.3.3.6 shows overall all survival with respect to taken between treatment commencement and treatment completion for cervical cancer cases treated with radio therapy or chemo-radiotherapy. Five year overall survival for patients taken less than 48 days and patients taken more than or equal to 48 days for treatment completion were found to be 72.7% and 58.6% respectively. Further it shows that patients taken more than or equal to 48 days were associated with poor prognosis (HR=1.610; 95%C.I.=1.261-2.056; p<0.001).

Table No. 5.3.3.6: Observed Survival rate (%) according to overall treatment time for Radiotherapy or Chemo-Radiotherapy treated cases

Time (days)	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
<48 days	401	92.8	85.0	78.9	75.3	72.7	<0.001
≥48days	413	89.1	76.4	65.9	62.6	58.6	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
<48 days	1						<0.001
≥48 days	1.610 (1.261-2.056)						

**Calculated using Log Rank Test*

Figure 5.3.3.3 shows Kaplan-Meier curve for overall survival with respect to time lag between treatment commencement and treatment completion of cervical cancer patients treated by radio therapy or chemo-radiotherapy.



Number at risk

≤47 days	401	354	313	284	265	246
>47 days	413	339	268	224	208	191

Figure 5.3.3.3: Survival rate (%) with respect to time lag between treatment commencement and treatment completion of cervical cancer patients treated by radiotherapy or chemo-radiotherapy

Table 5.3.3.7 shows overall all survival with respect to taken between treatment commencement and treatment completion for cervical cancer cases treated with radio therapy or chemo-radiotherapy. Five year overall survival for patients taken less than or equal to 56 days and patients taken more than 56 days for treatment completion were found to be 70.2% and 53.9% respectively. Further it shows that patients taken more than 56 days were associated with poor prognosis (HR=1.767; 95%C.I.=1.375-2.271; $p<0.001$).

Table No. 5.3.3.7: Observed Survival rate (%) according to overall treatment time for Radiotherapy or Chemo-Radiotherapy treated cases (taking a cut off of 56 days)

Time (days)	Total	Survival in percentage					p Value
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
≤56 days	586	92.8	83.8	76.5	73.4	70.2	<0.001
≥57 days	228	86.1	72.5	61.8	57.3	53.9	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
≤56 days	1						<0.001
≥57 days	1.767 (1.375-2.271)						

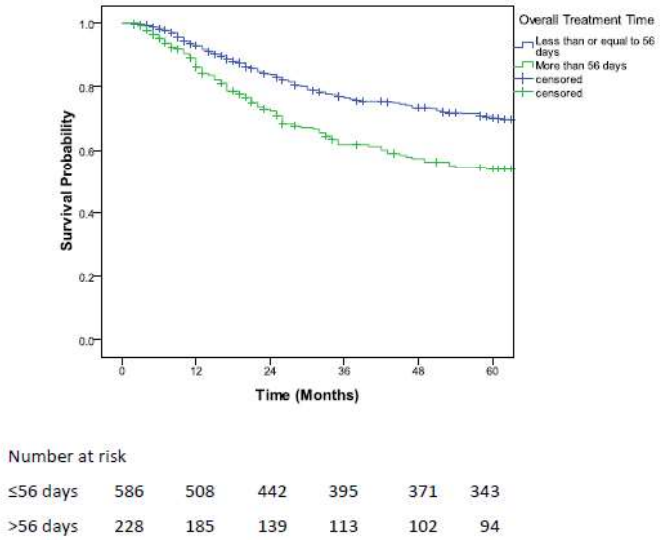


Figure 5.3.3.4: Survival rate (%) with respect to time lag between treatment commencement and treatment completion of cervical cancer patients treated by radiotherapy or chemo-radiotherapy (taking a cut off of 56 days)

5.4: Loss Adjusted Survival Rates

Loss adjusted survival method developed by Ganesh (1995) was applied to obtain the loss corrected survival rate. This method takes into account the losses into different strata by adjustment to obtain the corrected survival rates. Estimated deaths were obtained in those with complete follow up and then subsequently these estimates were applied to those with incomplete follow up.

Information on the association between prognostic factors and loss to follow-up can be used to reduce the bias in estimates of survival (Ganesh, 1995; Mathew, 1996). In this study we have adjusted for age and stage of disease for obtaining Loss adjusted Overall Survival rate. Table 5.4.1 shows the risk of death and loss to follow-up with respect to factors studied. The proportion of patients loss to follow up during the five year period was 21.5% and of dying was 28.4%. The risk of death increased 1.36 fold for patients age 50 years or above as compare to those aged less than 50 years. Similarly risk of death for those diagnosed at stage IIB & III-IV were 1.63 fold & 3.46 fold respectively as compare to those diagnosed at an early stage (I-IIA) of disease. Table 5.4.2 shows the year wise percentage of loss to follow up and dead. Table 5.4.3 portrays year wise loss adjusted rates after adjusting for age and stage of disease.

Table 5.4.1: Risk of death and loss to follow-up at 5-years and 95% confidence interval

	Loss to follow-up			Dead		
Factors	**HR[a]**	**95%CI**	**p-value**	**HR[b]**	**95% CI**	**p-value**
Age Group						
<50 years	1			1		
≥50 years	1.399	1.065-1.838	**0.016**	1.363	1.077-1.727	**0.010**
Stage of Disease						
I-IIA	1			1		
IIB	0.671	0.458-0.983	**0.040**	1.626	1.035-2.553	**0.035**
III-IV	1.030	0.732-1.449	0.865	3.457	2.277-5.248	**<0.001**

[a]HRs of each factor adjusted for other factors in the table. [b]Estimated among those with complete follow up.

Table 5.4.2: Number of cases, proportion loss to follow up and death at varying intervals of time

	1st Year		2nd Year		3rd -5th Year	
All Cases	Loss	Dead	Loss	Dead	Loss	Dead
1036	12.07	8.5	4.73	8.9	4.7	11.0

Table 5.4.3: Loss adjusted overall survival rates for cervical cancer patients

Method	1st Year	2nd Year	3rd Year	4th Year	5th Year
Actuarial	91	80	73	69	67
Loss Adjusted	90.05	79.20	71.53	67.94	65.11

CHAPTER-6

DISCUSSION

Tata Memorial Hospital (TMH), Mumbai, is a pioneer cancer centre in India engaged in cancer diagnosis, treatment, research and education since more than seven decades. There are few studies describing the pattern of survival in cervical cancer patients, and the few studies published focus on one more specific variable which was of interest to their study. Thus, literature with respect to cervical cancer survival in India is deficient and incomprehensive. Therefore, this study seeks to provide a holistic picture of overall survival and to also, identify the impact of patient's characteristics and tumor related characteristics on survival of cervical cancer patients.

6.1 Overall Survival

Indian studies reporting survival statistics specifically on cervical cancer are sparse. Few Indian authors who have studied exclusively cervical cancer have focused on one or more specific variable which was of interest to their study rather than providing holistic picture of cervical cancer survival. The five year overall survival of cervical cancer patients in our study was found to be 67%. Yeole et al. (19) in his study reported a five year absolute survival rates for cervical cancer as 42.2%, which is much lower than our study. Few other Indian studies, enrolled cervical cancer patients diagnosed before year 2000, reported 5-year overall survival of cervical cancer patients as 34.4%, 44.0% & 47.4% respectively [(20), (21), (22)]. All these studies had a high proportion of advance & unknown stage patients as compare to our study. Also these studies included both treated and untreated cases, while we have taken only those patients completed surgery or radiotherapy. Another explanation of such differences in survival as compare to our

study may be explained with respect to time frame. Shrivastava, et al. 2013 analyzed the disease outcome of cervical cancer patients in relation to time periods. They found significant (p = 0.000) improvement in DFS from 35% for 1979-1983 and 45% for 1984-1987 to 55% at 8 years for 1988-1994 not only for the whole group, but also for individual stages (251). This significant improvement is also reflected in the change in treatment protocols, continuous advancements in treatment over time and this might be partially explained due to improved services quality. Recently, Saptarshi Ghosh etal. (23) conducted a study and reported two year OS of 81.2%, which is comparable to 2 year OS observed in our study (80%). However, Radha Munagala et al.2010 reported five year OS of 81.4% which is much higher than our study. This difference could be because of high proportion of advanced stage (stage III & IV-48.9%) cases in our study as compared to only 33.7% advanced stage (Stage III) cases in study conducted by Radha Munagala et al (24).

6.2 Differences in Survival with respect to patient and tumor related characteristics

Prognostic factors of clinical outcomes in patients with cancer are a useful tool in the practice of medicine, especially in the field of oncology. Prognostic factors in cancer patients provide information about possible clinical outcomes and help classify patients into different risk groups. Treatment and clinical management decisions are often challenging, thus the availability of reliable and accessible prognostic markers is vital when designing treatment plans and discussing them with patients (252). In this study we evaluate prognostic effect of patient and tumor related factors on overall survival of cervical cancer patients. These includes demographic variables, tumor related factors, clinical presentation at the time of diagnosis, treatment modalities and

some baseline laboratory parameters. Discussion for each of the factor is discussed separately in the sections below:

6.2.1 Staging and Survival

In our study, 12.5% cases had early stage disease (stage I) and 48.9% patients had presented with advanced stage disease (Stage III & IV). Till date there are sufficient publications on role of clinical stage as a prognostic factor for cervical cancer survival [(24) (31) (113) (114) (115) (116) (117) (118) (121) (253)]. In this study, we also found stage is significantly predicting survival of cervical cancer patients. Also pair wise analysis was showed significant difference in survival of patients except for stage I & II, which is similar to Nurana et al. 2014 (133). Further we found no difference in survival of stage I & IIA patients which is similar to studies reported by other authors (150), thus we regrouped these two into one category. However regrouped FIGO staged I-IIA, IIB and III-IVA patients received curative treatment showed highly significant difference in survival of cervical cancer patients and is well reported in the literature. Stage is well known & widely used prognostic factor, but several studies also showed limitation of FIGO staging in terms of huge variability in survival probability within each stage and this variability reduces the accuracy of individual outcome predictions [(146) (254)]. Keeping this in mind we studied difference in survival with respect to patient and tumor related characteristics for early stage (I-IIA), IIB & III-IVA patients received curative treatment separately.

6.2.2 Age

Median age of all cases was found to be 50 years ranging from 21-85 years. However when the patients were grouped age-wise majority of them belonged to 45-54 years followed by 55-64 years age groups. Similar age wise distribution has been reported by many researchers [(42)(255)(62)(20)(256) (257)]. Stage wise median age were found to be 47 years, 50 years and 51 years for stage I-IIA, IIB and III-IVA patients treated with curative intent. Late diagnosis of cervical cancer can be the likely explanation of higher median age of patients with advanced stage disease. Further, it is also likely that the findings reflect differences in awareness of cervical cancer symptoms in older women and/ or differences in health care seeking behavior (258). This suggests that equipping older women with the knowledge, skills and confidence to present promptly with cervical cancer symptoms might help downstage cervical cancer in older women and thereby improve their survival. Landoni et al. 1997 also reported cut-off of 50 year and non-significant effect on early stage cervical cancer survival (150). Nurana et al. 2014 also reported non sig effect of age groups on survival (133). In present study, we found no difference in survival of cervical cancer patients with respect to age for early stage I-IIA & IIB cervical cancer patients, while in advance stage III-IVA patients we found significant difference in univariate analysis but after adjusting for important factors age was not remained significant in multivariate analysis. This finding of our study is in line with many studies showed no effect of age on overall survival or disease free survival of cervical cancer patients [(20), (22),(32),(33), (34),(35), (133), (150)].

6.2.3 Place of Residence

Place of residence is very well known risk factor for cervical cancer incidence. Rural - urban differences in cancer incidence and mortality is reported by several authors (36)(37). In this study we tried to investigate the role of place of residence in OS of cervical cancer patients. Numerous studies have suggested a strong association between place of residence and overall survival in different cancer sites (38) including cervical cancer [(38) (36)]. However we found controversial results in this study as we did not found any association between place of residence and OS. The likely reason for such finding is this may be because it was a single institution study and all the patient were treated as per same protocol regardless of place of residence. Finding of our study is similar to several studies that showed place of residence is independent of survival. Michelle Kaku et al.(2008) found that district of patient is independent of late stage diagnosis (p=0.12) (40). Radha Munagala et al.(2010) reports that they did not found any association between rural and urban residence and event free survival & overall survival (24).

6.2.4 Educational Status

Illiteracy is a common factor that not only lowers the age at marriage and encourages high parity but also influences genital hygiene, menstrual hygiene, dietary deficiencies, and utilization of health services. Education can be taken as an indirect and important indicator of social class. Thus role of educational status is crucial in cervical cancer. Although, illiteracy or low socio-economic status is well known risk factor for cervical cancer incidence and mortality [(42), (43)], it's role as a prognostic factor remains unclear. In this study, we investigated the prognostic role of education in cervical cancer survival. We found 51.4% of patients were illiterate (Table 5.1.3). This finding is in consonance with many studies which has found illiteracy as a risk factor for cervical cancer (259). Thus improving educational status of women in our country is an essential

component of holistic approach for cervical cancer control in India. However, we did not found educational status as an independent predictor of cervical cancer survival. Our finding are similar to some studies [(24), (260)] while contradictory to other studies [(60), (261)]. The possible explanation of non-significant findings in our study may be because it was a single institution study and all the patient were treated as per same protocol regardless of educational level.

6.2.5 Marital Status

Marriage is a social institution that affects individuals' lives in many aspects. Marriage is associated with family life, wellbeing, and mutual support in times of hardship. In a past some studies reported marital status as independent predictor (57), (58) while others reported it's not associated with survival of cervical cancer patients [(24), (59), (60)]. In this study we examined the role of marital status as a prognostic factor on cervical cancer survival. In this study we found 74% patients as married which is slightly lower than Mungala et al. 2010 (86%), comparable to Franceschi et al. 2003 (70%). We did not found any significant difference in survival which is comparable to studies reported by other authors [(24), (59), (60)]. The possible explanation of non-significant findings in this study may be because it was a single institution study and all the patient were treated as per same protocol regardless of marital status.

6.2.6 Religion

Religion in India is characterized by a diversity of religious beliefs and practices. In past studies incidence of Cancer of uterine cervix has been reported to be very low amongst Muslims as compared to Hindu females [(61), (62), (65)]; which is similar to our study as we found only 8.7% Muslims as compare to 85% Hindus in our study (Table 5.1.2). However there are many studies reported incidence and prevalence according to religion, there are very few reported the

effect of religious affiliation on cervical cancer survival. In this study we examined the prognostic role of religion on cervical cancer survival. In this study, we found no association between religious group of patients and cervical cancer survival. This finding of our study is comparable to A NandKumar et al.(1995) as he did not found any difference in survival on the basis of religion in Bangalore. He reported 5 year survival for Hindus, Muslims & Christians were 34.4%, 34.0% and 34.5% respectively (p=0.52) (20). Similar results was found by a hospital based study in Mysuru conducted by Vishma B. Kaverappa et al (2015) (60). The possible explanation of non-significant findings in our study may be because it was a single institution study and all the patient were treated as per same protocol regardless of marital status.

6.2.7 Menopausal Status

Menopause does not cause cancer, but the risk of developing cancer increases as a woman ages. (68). In addition to aging another risk factor for development of cervical cancer in postmenopausal women is that they are prone to have persistent human papilloma virus (HPV) infection (69). Up to the date, there are very few studies reported the prognostic effect of menopausal status on cervical cancer survival. Munagala et al.(2010) reported that there is no difference in event free survival and overall survival among patients attained menopause and not attained menopause (24). Another study also reported the same finding that menstrual status had no impact on cervical cancer patient's survival (70). In this study, we also did not find any effect of menopausal status on Overall Survival.

6.2.8 Parity

Parity is probably a good marker of hormonal environment throughout the fertile years of women, as well as a marker of repeated cervical trauma predisposing to infection (262). Differences in reproductive habits may have contributed to differences in cervical cancer

incidence between developed and developing countries (27). High Parity (having three or more children) is well known factor for cervical carcinogenesis (72). In our study approximately 63% of cervical cancer patients had parity of three or more. There are several studies showing odds of having cervical cancer to high parity women is much more higher than those having less children [(73) (74) (75)]. In order to explore the effect of parity on survival, L. Flores-Luna et al. (2001) reported that median number of pregnancies was associated with clinical stage (p=0.001) (31) and clinical staging is a well known strong prognostic factor for cervical cancer survival. However there is no strong evidence suggesting association of cervical cancer survival and parity. Munagala et al.(2010) (24) & Lukaszuk K et al.(2007) (76) reported that they did not found parity as a independent prognostic factor in cervical cancer patients. In this study, we also did not find parity as independent predictor of survival.

6.2.9 Abortions

There are very few studies reported the role of abortion on cervical cancer survival. In this study we found almost 70% patients never had abortion in their life time as compare to 13.8% had abortion in their life (Table 5.1.8). This distribution of our study patients is similar to Mungala et al. 2010 (24). Literature suggest that number of abortion is not a prognostic factor for cervical cancer survival. Munagala et al.(2010) reported that there is no difference in event free survival and overall survival among patients do not did any abortion and those had a abortion (24). Another study by Lukaszuk K et al.(2007) also reported the same finding that they did not discovered statistical significance as regards abortion in relation to survival (76). In this study, we also did not find significant difference in survival of cervical cancer patients.

6.2.10 Co-morbidity

Co-morbidity may influence the clinical management of cancer patients during or after treatment. For example, patients with severe chronic obstructive pulmonary disease are not good candidates for resection of a lung malignancy and therefore there chance of cure is decreased (84,85). Similarly a diagnosis of congestive heart failure precludes some cancer treatments (86,87). Co-morbidity is also competing cause of death, particularly for older patients with cancer. Numerous studies have shown poor survival outcome among cancer patients with co-morbidity (88–97). In case of cervical cancer there are very few studies reported the prognostic effect of co-morbidity on survival outcome. In this study we tried to investigate the role of co-morbidity on prognosis of cervical cancer. In stage I-IIA, we did not found any difference in OS with respect to presence or absence of co-morbidity. Jeong-Yeol Park 2012 also reported the similar findings for early stage cervical cancer(263) . Jeong In Choi et al. 2015; evaluated the impact of diabetes mellitus on the prognosis of stage I-IV (64% patients of stage I alone) cervical cancer and found that diabetes mellitus was not a poor prognostic factor for such patients (101), while Ingporn Jiamset et al. 2016 reported significant difference in Overall Survival of early stage cervical cancer patients & marginally non-significant on Recurrence Free Survival (RFS). Their study also evaluate the prognostic effect of diabetes mellitus with in 5 year of diagnosis and after 5 years of diagnosis and they found significant difference in RFS with respect to DM only after 5 year of diagnosis (102). Thus it might be possible in our study that presence of co-morbidity play role on OS after 5 years of diagnosis, but this was not the matter of concern in the present study. Another reason of non-significant effect of co-morbidity on OS in early stage may be because we consider only presence or absence of co-morbid condition and not number of co-morbid conditions. Leigh G. Seamon et al also reported that in stage I-IV cervical cancer patients

presence of one co-morbid condition as compare to no co-morbid condition does not play any role in survival differences, however more than or equal to 2 co-morbid condition had a significant hazard ratio (98). Also early stage patients in our study were very few in number (188 patients). Analysis of stage IIB & III-IVA was based upon relatively larger sample size of 341 & 424 respectively. There are several reasons why comorbidity impacts survival. The most obvious is the direct independent impact of concomitant diseases on non cancer mortality. Also, presence of comorbidities might affect the renal function which can affect the administration of Cisplatin based chemotherapy(30). For patients with FIGO stage IB2, IIB-IVA, age affected the choice of chemo-radiation significantly . There is reliable evidence that those with comorbidity receive less active treatment than those without, and this impacts their survival probabilities (30) and older patients received less radiation (264).Co-morbidity is age dependent. In stage IIB and III-IVA patients received curative treatment, we found presence of co-morbidity is associated with poor prognosis of cervical cancer patients. Results of our study are supported by many authors [(100), (98), (30)]. However different co-morbid condition can affect survival in different ways, the underlying mechanism is not known till yet, but likely reason for diabetes mellitus and HIV was reported by several authors [(102) (100)]. Due to limited documentation in our study, we are unable to determine with confidence that access to and tolerability of cisplatin was affected by co-morbid conditions. Also in the present study to evaluate the effect of co-morbid condition we had not taken some important factors into consideration like duration of co-morbid condition, any treatment taken for co-morbidity. The major drawback of this comparison is bias in including co-morbid condition. We was able to take only those conditions reported in patient records. We also have not taken into account symptoms to evaluate the prognostic role of composite symptom co-morbidity scale on cervical cancer as it was done by L. Flores-Luna2001

(31) and Peipert JF 1994 (103). Thus we suggest prospective studies to evaluate the role of co-morbid condition on survival of cervical cancer patients by taking detail history of co-morbidity and symptoms.

6.2.11 Performance Status

A number of studies have examined the prognostic impact of patients' "performance status" at the time of cancer diagnosis. In this study we also tried to examine the prognostic role of pre-treatment performance status on OS. Out of total 1036 cases, only 20.5% patients were scored as ECOG score of 1 and 4.2% patients were scored as ECOG score of 2 or 3. None of the patients was scored 4 (Table 5.1.15). Since there are very small percentage of patients with ECOG score of 2 or 3, we merged these patients with those patients having ECOG score of 1. Thus effect of performance status on OS was examined by making two categories of performance status i.e. 0 (fully active) versus ≥1 (restricted in physical activity). We found no difference in OS with respect to performance status in each FIGO regrouped stages separately. This non-significant finding of our study is similar to Hyunsoo Jang et al. 2013 (110) and Jeung Eun Lee etal.2004 (111). On the other side there are some studies found contradictory results and found performance status was an independent predictor of OS (106), (107). Jin-hong Park et al. 2010; found that ECOG performance status (0,1vs 2) was independent prognostic factor for 5 year OS while it looses its prognostic effect to determine cancer specific survival(CSS) (108). Most of the studies reflecting significant effect of performance status on survival by comparing ECOG score of 0,1 vs 2,3. In this study we merge score 1 with score 2 & score 3 due to small percentage of patients in later two categories. Survival is supposed to be better for performance status 1 as compare to 2 or 3. Thus this merging might dilutes the effect of this comparison. The likely reason for getting very low percentage of patients scored 2 or 3 in our retrospective study design

may be due to the fact that performance status scales are subjective, subject to bias and high inter observer variability (265), thus status recorded in a retrospective study design may not be very reliable.

6.2.12 Tumor grade

Tumor grade is an indicator of how quickly a tumor is likely to grow and spread. Role of tumor grade as a prognostic factor had investigated by several authors with controversial findings in different cancer sites included colon cancer, breast cancer and oral cavity cancer (122–128). There are several studies reported the prognostic role of tumor grade in cervical cancer patients, reflecting controversial views [(129) (130) (131) (133)]. In this study, we found only 4.7% patients well differentiated tumor grade, 20.3% had moderately differentiated tumor grade, 31.1% poorly differentiated and 43.9% patients were not graded (Table 5.1.11). This distribution is comparable to Srivastava et al.2013(251), C.-M. Ho et al 2004(132). We found no difference in survival with respect to tumor grade in early stage cervical cancer, which is similar to several studies (132). In stage IIB, tumor differentiation was significant in univariate analysis but losses it's statistical significance in multivariate analysis. However in stage III-IVA patients received curative treatment, we found tumor differentiation as an independent predictor of OS. In the existing literature there are contradictory views about prognostic role of tumor differentiation. Our study results are similar to many studies [(130) (131) & (133)]. M.P. Hopkins et al. 1991 (130) reported that for stage I to IV cervical cancer patients with a well differentiated tumor had an 85% survival rate while those with a poorly differentiated tumor had a 57% survival rate and tumor grade maintained significance in the multiple proportion hazard analysis. However a separate analysis was conducted for stage II patients and found a non-significant difference in survival (p=0.06). Carol L. Kosary 1994 also reported that tumor differentiation is independent

predictor of overall survival of stage I-IV cervical cancer patients. However stage wise analysis showed that in early stage survival was not very different. In stage IIB 48.4%, 55% and 47% relative survival for well, moderately and poorly differentiated tumor (131).Thus we concluded that tumor grade plays prognostic role in advance stage rather than early stage cervical cancer.

6.2.13 Tumor Histology

In this study, we investigate the role of tumor histology on OS. We found majority (91%) of the patients with squamous histology (Table 5.1.10). This is very well known finding in published research. In early stage and stage IIB we found no significant difference in survival of squamous or non-squamous cervical cancer patients. This finding is in accordance with some previous retrospective studies of early stage cervical cancer patients that were treated with radical surgery as they did not detect any survival differences between AC/ASC and SCC(134,135). There is little known about significance of histology in locally advance cervical cancer and reported results are conflicting(141–144). G. Ferrandina et al. reported that histology was found to be non significant for DFS and OS (99). S Polterauer et al. 2012 compared the OS of patients diagnosed with adenocarcinoma and other histological types with squamous cell as reference category and used histological type as predictor of OS to construct a nomogram (32). Asmis et al. 2017 reported no difference in survival according to histological subtype (93). J.M. de Rijke et al.2002 found marginally non-significant association between histological type and excess mortality [RR(95%C.I.= 1.4 (1.0–2.0); p=0.06] (145). S.-H. Shim et al. 2013 found histology as an independent predictor of overall survival of locally advanced cervical cancer [HR (95%C.I.) = 3.605 (1.674–7.764); p=0.001] (146). In our study, stage III-IVA patients received curative treatment, histology was found to be independent predictor of OS. Although in this stage (III-IVA) we get histology as an independent predictor of OS, this finding is based upon very small

number of cases as only 21 patients of this stage had non-squamous histology. We suggest further studies to be conducted to evaluate prognostic role of histology in cervical cancer patients.

6.2.14 Parametrial invasion

Parametrial invasion is an important criterion in FIGO staging, however, no distinction is made between unilateral parametrium involvement and bilateral parametrium involvement. In this study we tried to explore the prognostic effect of parametrium involvement on OS of locally advance stage IIB & III-IVA cervical cancer patients separately. In stage IIB, we found bilateral parametrium involvement as an independent predictor of poor OS. Coia et al. analyze the importance of unilateral *versus* bilateral parametrial involvement on 4 year actuarial survival and find marginally non-significant results with 57% actuarial survival for unilateral involvement and 48% actuarial survival for bi-lateral involvement (p=0.06). For patients with Stage IIb cancer, there was a trend toward decreased 4 year survival in patients with bilateral parametrial involvement compared with unilateral (67%vs 54% ; p=0.10) (161). Ciuseppe Sinistrero et al. also tried to investigate the role of bilateral parametrium involvement on OS. In their study the 5-year survival in patients with Stage IIb disease was 68% for unilateral parametrial infiltration and 52% for bilateral (163). However these studied found non-significant result in their study, they reported a trend of poor survival for bi-lateral parametrium involvement as compare to unilateral involvement which is similar to our study. Rachelle M. Lanciano et al. reported that in stage IIb cervical cancer patients bi-lateral parametrium involvement (as compare to unilateral involvement) is associated with poor 4 year survival rate (52% vs 70%, p=0.001) (164). This finding is in accordance with our study. Further we did not find any difference in OS of stage III-IVA patients received curative treatment. This finding of our study is similar to Coia et al as they

reported no difference in survival or in-field failure for unilateral *versus* bilateral parametrial involvement for stage III patients (161). The reason for non-significant effect of laterality of involvement in this study may be because of importance of sidewall involvement in stage III. In this study we have not included extent of sidewall involvement. However, Ciuseppe Sinistrero et al also reported that the 5-year survival in Stage IIIb with one parametrium fixed to the pelvic wall and limited (less than a half) involvement of the other side was 66% and with one parametrium fixed and the other with more than half involved, the survival was only 15% (P = 0.01)(163). Rachelle M. Lanciano et al. reported that for stage III patients, the separation by extent of pelvic disease used in their analysis had significant value with respect to infield pelvic control and survival. Lower third vaginal involvement is the least favorable pelvic extension and usually signifies massive disease. Bilateral sidewall involvement is intermediate in prognosis whereas unilateral sidewall involvement the most favorable (p=0.04) (164).

6.2.15 Tumor Dimension

Bulky tumors are found to be associated with survival of various cancer sites including cervical cancer. One major finding of our study is that we found largest tumor dimension of more than 4 cm. was associated with poor OS of early stage cervical cancer patients. This study is in accordance with S Polterauer et al. 2012. They compared the OS of stage I-IV cervical cancer patients on the basis of tumor size and found that tumor size of 2-4 cm and more than 4 cm had poor prognosis (32). Similarly other studies were also reported the role of tumor size in early stage cervical cancers [(34), (266), (267), (268), (269)]. For locally advance stage IIB cervical cancer patients we did not find any difference in survival. This finding of our study can be supported with reference to earlier studies that did not confirm tumor size as an independent risk factor and had more than 40% were composed of patients with stage IIb disease

[(173)(149)(270)]. Rose et al. 2015 reported tumor size as significant predictor of survival and used tumor size as one of factor to construct a nomogram for cervical cancer patients of which more than 50% patients had either stage I or III-IVA (107). Further we found in our study that tumor size of more than 4 cm was associated with poor OS in Stage III-IVA patients treated with curative intent. This finding of significant difference in OS with respect to tumor dimension of our study is similar to other previous studies [(107) (146) (147) (148)**].**

6.2.16 Hydronephrosis

Hydronephrosis is frequently encountered in advanced stage cervical cancers. Although, presence or absence of hydronephrosis is already taking in to account in FIGO stage IIIB of cervical cancer patients as it is one of the condition for stage III, prognostic role of hydronephrosis as a independent factor is not very clear. In this study, we tried to investigate the independent role of bi-lateral and unilateral hydronephrosis as compare to those not had hydronephrosis. S.-H. Shim et al. 2013 found that presence of hydronephrosis is not a significant prognostic factor for overall survival of locally advanced cervical cancer patients (146). Masateru Fujiwara et al. 2015 studied the prognostic factor for FIGO stage IB2 to IVA cervical cancer patients and found no association between presence or absence of hydronephrosis and PFS (165). These studies was based on small sample size and enrolled stage I to IVA patients. Results of these studies are contradictory to our findings, however we examine the effect of hydronephrosis only on stage III & IVA and also we have a comparatively larger sample of 424 patients. However finding of our study are in accordance with many studies. Peter G. Rose et al. 2010 conducted a study on FIGO stage IIIB reported that hydronephrosis at presentation is a significant but not independent prognostic factor associated with poor survival. Later they found

significant difference in survival of patient not had hydronephrosis, hydronephrosis with relief and hydronephrosis with out relief. They concluded that the presence of hydronephrosis is a clinical surrogate of poorer OS (106). Mehmet Rıfat Goklu et al. 2015 conducted a study on 165 patients of stage III & IV and reported that when compared to mean survival in patients who did not have hydronephrosis [71.52 months (58.24-84.81)], survival was significantly shortened in patients who had bilateral [29.93 months (21.80-38.05)] and unilateral hydronephrosis[42.21 months (32.14-52.27)] ($p < 0.05$) (166) .

Pradhan et al. 2011 found median time to death was significantly shorter for patients with unilateral HN (27 months; 95% confidence interval [CI]= 10-48) and bilateral HN (12 months; 95% CI= 6-23) versus patients without HN(68 months; 95%CI= 39-∞; $P < 0.001$). Unadjusted hazard ratio (HR) for HN (both unilateral and bilateral) was 2.4 (95% CI, 1.5-3.8); $p< 0.001$. Of potential covariates evaluated, performance status and sidewall involvement were significantly associated with HN ($P = 0.021$ and $P = 0.014$, respectively). Proportional hazards regression revealed that controlling for use of radiation, chemotherapy, and for performance status, HN was still significantly associated with poor prognosis (HR unilateral HN= 2.0, 95%CI=1.2-3.5; HR bilateral HN= 3.2, 95% CI= 1.7-6.0); $P \leq 0.001$) (168). Thus in our study we suggest that it's meaningful to consider absence or presence (unilateral & bilateral) hydronephrosis to predict OS of FIGO stage III-IVA patients received curative treatment.

6.2.17 Treatment Modality

Gynecologic malignancies may be treated either alone or with a combination of surgery, chemotherapy, or radiotherapy. Surgery and/or radiation are the primary treatment modalities used to treat cancers of the uterine cervix. In this study we tried to investigate the difference in OS with respect to treatment modality for stage I-IIA, IIB and III-IVA patients received curative treatment separately. In early stage I-IIA, we found significant difference with respect to treatment in both univariate and multivariate analysis, however in multivariate analysis significant difference in survival was observed only for radiotherapy treated cases when compared to surgically treated cases. This finding of our study is contradictory to Fabio Landoni et al. 1997 as they found no difference in survival between patients treated with surgery alone and patients treated with radio therapy (150). In our study among radiotherapy treated patients larger proportion were old aged or suffering from some co-morbid condition or largest tumor dimension of more than 4 cm as compare to those patients treated with surgery alone. Thus these difference in distribution of patients in both treatment groups can be responsible for observed differences in OS. Also it's important to note that in the present study only 16 patients were treated with radiotherapy alone, this sample size is too small to drawn any conclusion about importance of significance found in this study. Our finding of difference in survival of early stage cervical cancer patients treated with surgery alone and radiotherapy is similar to some recent studies. Maaike A et al. 2009; reported that there was a survival difference of early stage I to IIA cervical cancer patient treated with radical hysterectomy, radiotherapy and other treatment (76% vs 41% vs 49%; p=0.002) (152). We also found highest survival for surgically treated cases, lowest for radiotherapy treated cases and survival rate for patients other than above two treatment (i.e. surgery with other therapies/chemo-radio therapy) was in between the survival of

patients treated with surgery alone and patients treated with radiotherapy alone. *Kemi* M. Doll, et al. 2014 also found the same trend in difference in 5-year survival of patients treated with surgery alone and patients treated with radiotherapy (271). Also, in a multivariate analysis, we did not found any difference in survival for patients treated with surgery and other therapies and patients treated with chemo-radio therapy when compare with the survival of patients treated with surgery alone. Srivastava et al. 2013 reported no difference in DFS among patients treated with surgery alone, pre operative RT with surgery and RT alone (p=0.168)(251). Use of adjuvant/neo-adjuvant therapies with stratified risk factors have shown benefit in survivals and is the standard of care today (272). Our study finding is comparable to Srivastava et al. 2013 in a way that we also did not find any difference in survival of patients treated with surgery alone or in combination with other therapies. Jeong-Yeol Park et al. 2012 reported significant difference in survival of patients treated with surgery and chemo-radiotherapy may be because much older patients were treated with CRT(263) and their study was based on early stage but bulky tumor of >4cm. Ghanim Khatib et al 2016 (273) and Jiamset et al. 2016 (102) reported no difference in survival between patients treated with surgery alone and patients treated with adjuvant therapy after surgery. Oliver Zivanovic et al. 2008 reported both RH and definitive RT/CRT are adequate management strategies for patients with FIGO stage IB2 cervical cancer (274). Further in the present study, we found significant difference in OS for locally advance stage IIB and stage III-IVA patients received curative treatment in both univariate and multivariate analysis. These finding of our study is similar to results reported by several authors. A number of studies showed an absolute benefit in OS and PFS with CRT in patients with stage Ib2 to IVA disease as well as high risk patients after hysterectomy (153–157), (159). There was also some suggestions that the benefit is greater in stages I & II; there was benefit in both local and distant failure rates (153)

and trend in the relative effect of chemo-radiotherapy by tumor stage (p=0.017), with the benefit of chemo-radiotherapy decreasing with increasing stage (158).

6.2.18: Baseline Laboratory Parameters

In the recent past, there have been a number of publications suggesting the role of various hematological parameters in cancer survival. Therefore, in the present study we tried to access the role of pretreatment hemoglobin, total white blood cell count along with its individual cell components in cervical cancer survival. Since in this study, differences in survival was studied for stage I-IIA, IIB and III-IVA patients received curative treatment; hence median value of the baseline parameters were calculated only on those patients received curative treatment. This median value was used to study differences in OS for all the FIGO regrouped stages defined above.

6.2.18.1 Hemoglobin level

Anemia is one of the most common systemic symptoms accompanying cancer. Although the exact pathophysiologic mechanisms of cancer-related anemia are not fully understood, suggested reasons include changes in iron metabolism, suppression of erythroid progenitor cells by releasing tumor cytokines, impaired erythropoietin response on erythroid progenitor cells, and hemorrhage (275). Numerous retrospective studies suggested that there is strong correlation between hemoglobin level and cancer survival. However the optimal time point to measure hemoglobin level for studying its prognostic effect in cervical cancer varies throughout the literature including pretreatment, post treatment, nadir hemoglobin level or hemoglobin level at the time of recurrence [(35), (276)]. Also, optimal cutoff point for studying prognostic effect is

also not clear as it varies from one study to another and consider various number of categories ranging from 2 to 4 categories, ranging from cut-off of <7g/dL to >12.5g/dL.

In this study we tried to find out prognostic effect of pre-treatment hemoglobin level on OS by taking median value (11.5 g/dL) as cut-off. We did not found significant role of pre-treatment hemoglobin level to predict OS of early stage, IIB & III-IVA cervical cancer patients received curative treatment. This finding is in contradictory to several published literature [(149), (173), (170) & (174)]. However our study finding is similar to other studies [(34), (146), (148)]. Shim et al. 2013 tried to explore the effect of pretreatment hemoglobin level on overall survival of locally advanced cervical cancer and they found non significant effect of pretreatment hemoglobin level on overall (146). Daisuke Endo et al. 2014 also found non-significant effect of pretreatment hemoglobin level on overall survival (148). Na-Ri Shin, et al. 2014 shows non significant effect of pre-treatment hemoglobin level (<11.2 g/dL vs ≥11.2 g/dL) on OS in early stage(IB to IIA) cervical cancer patients (34). In our study non-significant effect of Hb level on OS can be explain in many ways- Firstly, Hemoglobin may be corrected during radiotherapy. It's suggested that Hb level is no longer a prognostic factor if anemia has been actively corrected using blood transfusion during radiotherapy (277); Secondly, a sufficient hemoglobin level might have been of no benefit in advance stage disease (148); Thirdly, it might be possible that instead of pretreatment Hb level, nadir Hb or post treatment Hb level affect survival [(35), (276)]. Since it's a retrospective data analysis we are unable to collect information on Hb level at different point of times and measuring it's prognostic effect; Fourthly, optimal cut-off point varies from one study to another, to study it's prognostic role. It might be possible to get different results while using different cut-off point. Hence future studies are needed to explore the prognostic impact of anemic condition before or during treatment in patients with cervical cancer.

6.2.18.2 WBC counts and it's components

There is ample evidence suggesting that outcome in cancer patients is greatly affected by immune response and pre-treatment measure of inflammatory immune response can be used to independently predict survival of cancer patients (278–280). Total and differential WBC count is one of the most easily accessible markers of inflammation and many recent studies in cancers provide evidence that there is an interconnection between pre-treatment WBC counts and overall (OS) and disease free cancer survival (DFS) [(178), (179), (180), (181)]. In this study, we investigated the prognostic role of WBC counts and its differentials within each stage separately. We found no association between total WBC counts and overall survival of cervical cancer patients in all FIGO regrouped stages (i.e. early stage (I-IIA), locally advance stage IIB and III-IVA patients received curative treatment). This finding of our study is in accordance with other published studies [(182) (183) (184)]. Also in the present study we did not find any association of neutrophil counts or lymphocyte counts on overall survival. These findings of our study were similar with other studies [(190), (184)]. The major finding of our study was that elevated monocyte counts ($\geq 0.52 \times 10^9$/L) was associated with poor OS of locally advance stage IIB-IVA patients received curative treatment. This result is with concordance of other published literature probing the role of monocyte count in prognostication of breast cancer (182), gastric cancer(197), Head and Neck cancer(184),(198), endometrial cancer (190) and cervical cancer patients (194). In this study we found no association of elevated monocyte count on early stage cancer which is similar to study reported by Yoo-Young Lee (194). Yoo-Young Lee et al. taken median value as a cut-off for making two groups (high monocyte counts vs low monocyte counts) and found no association of elevated monocyte counts on PFS and OS (p= 0.552 and 0.946 respectively) for early stage cancer. For advance stage cancer they found HR(95%

CI)=5.37(1.594-18.10; p=0.007 and 3.97(1.076-14.61); p=0.038. We also found elevated monocyte count was associated with poor OS in stage IIB-IVA patients received curative treatment. Recently, Sajadieh et al reported that a higher number of circulating monocytes can independently predict mortality (hazard ratio [HR], 1.13; 95% CI, 1.06-1.19) as well as incident cancer (HR, 1.12; 95% CI, 1.05-1.19) in a healthy population (196). All these studies provide evidence that monocytes are immunologically relevant host factors that can be routinely assessed through the CBC count to monitor patients' response to treatment and identify high-risk patients who are more likely to have adverse outcomes.

The exact underlying mechanism explaining the association between elevated number of monocyte and unfavorable cancer prognosis has not been elucidated. However, a possible explanation can be that monocytes secrete various pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-10 and tumor necrosis factor (TNF-α), which have been associated with shorter survival and worse prognosis in malignances (281,282). Moreover, monocytes upon stimulation are known to release monocyte chemo-attractant protein (MCP-1)-1 and mediate tumor associated macrophage infiltration in solid tumors, which could produce a variety of chemokines such as transforming growth factor (TGF-α) , IL-1 and IL-6 to promote tumorigenesis, angiogenesis and distant metastasis of malignant tumors (282,283). Further, studies have linked monocyte with an increased number of bone marrow-derived myelomonocytic cells, these cells infiltrate the tumor and differentiate into tumor-associated macrophages, which in turn release many angiogenic factors and have been shown to be associated with poor prognosis in cancer(282,284).

It's important to note that different studies included different cut-off points to investigate the effect of WBC counts and it's components. There is a need to define optimal cut-off point to

study such differences in survival. Also it is important to consider limitation of this analysis as WBC counts was measured only once; multiple measurements would have increased the precision of the results.

6.2.18.3 Blood Group

To determine the significance of blood group on cervical cancer prognosis, we evaluate the effect of blood group on OS. Distribution of ABO blood group in our study is almost similar with other studies, with major chunk of patients had blood group O or B. This is similar to other studies [(29), (75)]. However, in our study we found blood group A, B, AB and O are independent of five year OS. This finding is in contradictory to Marinaccio M et al. 1995. They showed that a little better 5-year survival is associated with O blood phenotype; but they also showed when a 10-year or longer survival is considered, a better survival is associated with A blood phenotype (215). Jitti Hanprasertpong et al. (29) tried to understand the exact impact of ABO blood group on cervical cancer prognosis. They first compared the 5-year OS of cervical cancer patients with the individual ABO blood type and did not found any statistically significant differences between the four ABO blood groups (A, B, AB and O) on RFS or OS. Further, in order to evaluate the possible favorable effect of blood type O on survival, they divided the whole group of patients into two subgroups, patients with blood group O and patients with blood group non-O and again did not found any statistically significant differences between the four ABO blood groups (A, B, AB and O) in RFS or OS. This finding of no association between blood group and OS is in accordance with the results of our study. Since there are dearth of studies reporting such a association, especially in cervical cancer. Hence there is a need of conducting more studies to evaluate prognostic effect of blood group on cervical cancer in future.

6.2.19 Summary of Independent predictors of overall survival of cervical cancer

Table 6.2.19.1 provides the summary of the identified independent predictors of survival of cervical cancer patients. Stage wise analysis showed that in stage (I-IIA) independent predictors of survival were largest tumor dimension and treatment modality. In stage IIB independent predictors of survival were presence of co-morbidity, parametrium involvement, elevated monocyte counts and treatment modality. In stage III-IVA patients independent predictors of survival were presence of co-morbidity, high grade tumors, pre-treatment monocyte counts, treatment modality, histology, largest tumor dimension and hydronephrosis.

Table 6.2.19.1: Summary of Independent predictors of overall survival of cervical cancer

Early Stage (I-IIA)	**Locally Advanced stage IIB**	**Locally advanced stage III-IVA (curative treatment)**
Largest Tumor Dimension	Co-morbidity	Co-morbidity
Treatment Modality	Laterality of Parametrium Involvement	Tumor Grade
	Pretreatment Monocyte Counts	Pretreatment Monocyte Counts
	Treatment Modality	Treatment Modality
		Hydronephrosis
		Tumor Histology
		Largest Tumor Dimension

6.3 Difference in Overall survival with respect to timelines

It is unclear whether more timely cancer diagnosis brings favorable outcomes, with much of the previous evidence, in some cancers, being equivocal. Time to diagnosis can be measure from timing of first symptom onset or first seen in primary care or first seen in specialist care. In our study we measured time to diagnosis as time between registration and diagnosis. We find very small (3 days) median time taken between registration and diagnosis and seen no effect of it on OS. However, there are very few studies reported effect of delay in diagnosis on cancer outcome [(219) (220–223)] and authors measured this time from different time points. This finding of no difference in OS is in accordance with other studies (285,286). Also since we found very small difference between registration and diagnosis at our institution, it seems reliable that we found no difference in survival. However, we need to acknowledge the limitation that due to the nature of our study we could only analyze the effect of time required for diagnosis in the hospital but could not account for the time period from onset of symptoms to patient reporting to first health care centre, which is likely to be longer than the time spent in the hospital for diagnosis.

The next question is whether a delay between the diagnosis of cancer and its treatment has a negative effect on the patient's clinical outcome has been examined in several malignancies, with conflicting results (225–232). In this study we examined such delay between diagnosis and treatment initiation on OS of cervical cancer patients. We found median of 27 days from diagnosis to treatment commencement. This time is lesser than the previous study on cervical cancer (224). Also Distribution of delay in treatment commencement shows less time taken for treatment initiation as compare to other study by Choan et al 2005 on cervical cancer patients (233). In this study we found no significant difference in survival due to delay in treatment. This finding is in accordance with Umeza et. Al. 2012 reported difference in OS (≤50 days vs

>50days) and reported 5-year OS of 96.7% vs 92.5% (p=0.653) (224). Also other study by Tamar Perri et al. 2014 (287) supports finding of our results. They reported that time from diagnosis to treatment initiation for cervical cancer, when analyzed as a continuous variable, was not a significant factor in survival. Further this association was tried to find out on the basis of categorical variable in 3 groups that differed in waiting time between diagnosis and treatment initiation: 30 days or less, 30 to 45 days, and more than 45 days. However, they still did not find any association between longer waiting time from diagnosis to treatment with worse survival.

This shorter median time of 27 days of our results indicate good access to services and good quality of care. Since we did not find any association between delay of 27 days in treatment initiation and overall survival, we therefore suggest that if patients desire fertility or ovarian preservation procedures before starting treatment, or if patient wants to obtain second opinion, it is acceptable to allow time to them. Now the question is how much delay in treatment can be tolerated well without any worse impact on OS? This question was tried to answer by A. Fortin et al.2002. They reported no poor prognosis when delay was upto 40 days and showed poor prognosis on early stage Head & Neck cancer patients when delay was above 40 days (235). Also Choan et al reported median time from biopsy to radiotherapy of cervical cancer patients was 42 days and revealed an adverse effect of treatment delay on survival outcomes (233).

However literature reports prognostic effect of OTT on other cancer sites [(234), (235)], in cervical cancer patients treated with surgery alone or in combination with other therapies adjuvant or neo-adjuvant chemotherapy plus surgery, we found only one study reporting the effect of overall treatment time (OTT) on PFS and OS. Jeongshim Lee et al. 2016 showed no difference in OS with respect to OTT (236). In our study we found median OTT for surgically treated cases and surgery with other therapy treated cases as 8 days and 92 days respectively and

not found any significant difference in OS with respect to OTT. Due to lag of literature on OTT for cervical cancer patients treated by surgery only, we are unable to compare results with other studies for surgically treated cases only. For patients treated with surgery and other therapies, Jeongshim Lee et al. 2016 reported median time for surgery and other therapies group as 83 days. Our study reported a bit higher OTT as compare to Jeongshim Lee et al. 2016. However Jeongshim Lee et al. 2016 test the prognostic effect of OTT for all IB-IIB patients irrespective of the treatment with median OTT of 65 days and does not find it as an independent predictor of OS, which is in accordance with our study. One likely reason for non-significance of OTT on OS of patients treated with surgery with other therapies may be that adjuvant or neo-adjuvant therapies were given to only those patients who had bulky tumors at the time of diagnosis or those had high or intermediate risk group after surgery (251). Thus other therapy is part of essential treatment for such cases and multi therapy takes time to complete. Hence it's obvious to take much time for patients treated with adjuvant or neoadjuvant therapies with surgery. However how much time is affordable in term of affect on OS is a question need to be investigated in future.

In our study we found median completion time for RT or CT RT for those patients received curative treatment was 48 days. However we don't have data on why few patients taken more than 60 days. The likely reason for long treatment completion time may be due to breakdown during EBRT, gap between EBRT and ICT, machine breakdown, holidays or patient's personal affairs (238). Further we found that prolong treatment time had poor effect on OS. This finding is in accordance with other studies [(237),(238),(239),(240),(241),(242)]. The likely explanation of prolong treatment time on poor OS was given by several authors [(288) (289) (290)] .

Thus we concluded that, in the treatment of patients with radiation therapy/chemo-radiotherapy, treatment time should be minimize and avoid any planned or unplanned interruptions or delays in patients with carcinoma of the uterine cervix.

6.4 Comparison of LAR with Actuarial Method

The vital step in carrying out a survival study is to promise good and complete follow up information. The actuarial method use information from all subjects, including those censored before five years of follow up or death. The actuarial survival rates gives an unbiased estimate of true survival only if censorship have the same distribution between the groups being compared and is independent of risk of the outcome studied. The magnitude of bias involved in the estimation of the survival probability is dependent on both the magnitude and nature of losses to follow up, and may be in either direction. For example, the true probability of death of patient loss to follow up may be greater than assumed if patients with poor prognosis are more likely to be lost. In these circumstances, the actuarial survival estimates are biased and too high. Similarly, if the true probability of death of patient loss to follow up may be lesser than assumed if patients with good prognosis are more likely to be lost. In these circumstances, the actuarial survival estimates are again biased and too low (216).

Socio-economic factors are in fact not directly linked to survival, but it is directly related to a person's general state of health, nutritional status, attitudes, beliefs and health behavior. It can affect the chances of being early detected, access to or completion of treatment and follow-up and perhaps survival is mediated by all these factors (33). Thus first step in deciding whether bias in the actuarial estimate of survival is likely is to examine whether loss to follow-up varies according to socio-demographic variables reflected prognostic effect. In this study we had adjusted for stage and age to obtain LAR. Computation of loss adjusted-survival (216), then

takes into consideration such differential losses by assuming the patients loss to follow-up within strata defined by these variables have the same probability of death as those still remaining under observation and belonging to the same stratum. It is reasonable to expect survival experience in patient's loss to follow-up and with complete follow-up to be more similar within a prognostic group, then when all patients are considered together. The difference between crude actuarial survival and the loss-adjusted rate indicates the value of the effect of differential loss to follow-up. In this study we found small difference (1.89%) between the absolute (actuarial) survival and LAR, which is much less than in other studies [(9), (216), (291)]. However Swaminathan et al. 2002 (292) conducted an international comparison of actuarial and loss adjusted survival of cervix cancer cases from different population based cancer registries in developing countries and found that the maximum difference was 4.1% with a loss to follow up of 44% and presence of non randomness. The observation was not confined to cancer of the cervix; differences for other sites like female breast (data from six registries from developing countries) and larynx (data from Chennai and Mumbai cancer registries) were of similar (small) size. S Sriamporn et al 2004 (218) reported only 2.1% difference between the loss-adjusted and observed survival at 5 years, which was very small and comparable to the small difference of 1.89% reported by us. Thus in this study, the assumption of independence of loss to follow up and death was seems to be reasonable, so that calculation of survival by the actuarial method without adjusting for losses to follow-up is likely to have resulted in no material bias in the estimates. Another reason to found small difference may be due to our selection of cases in this study. No treatment taken is one of the most important determinant of loss to follow up (218) and we have excluded not treated cases in this study.

6.5 Strength & Limitation of this study

The strength of the present study is, firstly that, information for large number of variables was retrieved from all possible resources such as medical case sheets, electronic medical records, reports and OPD data, for a large cohort of patients. Secondly, stage wise survival estimates are more relevant to individual patients than estimates based on large numbers of heterogeneous patients, and thus could be used as an aid for patient counseling. Thirdly, this study evaluates large no. of factors affecting survival, including certain hematological factors as well as timelines of different evolutions involved in patient care. In addition, loss adjusted survival rate to cater for patients lost in follow-up has also been computed and presented.

There were several limitations of our study which need to be acknowledged. The study was conducted was of retrospective nature and relies on clinical data not primarily meant for research. Thus we could only evaluate those factors which were recorded in the case sheets/ medical records. for example some important prognostic factors such as lymph node involvement & toxicities after treatment, nadir hemoglobin level were not included in present study because of non-availability of records. Additionally, only information about the presence of comorbid disease was available but details regarding time of onset, duration of disease, whether on medication were not obtainable from the medical records.

CHAPTER 7

SUMMARY & CONCLUSION

7.1 Summary

- The overall 5-year survival of cervical cancer was found to be 67%.
- In early stage (FIGO stage I-IIA) cervical cancer the independent predictor of survival were treatment modality and largest tumor dimension.
- In stage IIB the independent predictor of survival were co-morbidity, parametrium involvement, pre-treatment monocyte counts and treatment modality.
- In stage III-IVA patients received curative treatment the independent predictor of survival were co-morbidity, high grade tumors, pre treatment monocyte counts, treatment modality, non-squamous histology, largest tumor dimension and hydronephrosis.
- The median time from registration to diagnosis was 3 days, from diagnosis to treatment commencement was 27 days. We did not find any significant difference in survival for time lag between registration and diagnosis & diagnosis and treatment commencement for patients received curative treatment.
- Prolonged time taken between treatment commencement and treatment completion was associated with poor survival for patients treated with radio/chemo-radiotherapy but not for surgically (alone or in combination) treated patients.

- **A** small difference in 5-year overall survival was seen between loss-adjusted survival rates and actuarial survival of cervical cancer patients.

7.2 Conclusion

This present study is one of the few Indian studies to comprehensively analyze and present a holistic picture of cervical cancer survival. The 5-year survival rates were better in patients with the early stages of cervical cancer than in those with advance stages. There was no significant impact of various socio demographic factors on overall survival. There was no significant difference in survival for time lag between registration and diagnosis & diagnosis and commencement of treatment for patients received curative treatment. Further we found poor survival with prolonged time taken between treatment commencement and treatment completion in patients treated with radio/chemo-radiotherapy but not for surgically (alone or in combination) treated patients. Further analysis for secondary objectives showed small difference between LAR and actuarial survival of cervical cancer patients.

Utility of this study can be explain in several ways: **first**, stage wise survival estimates are more relevant to individual patients than estimates based on large numbers of heterogeneous patients, and thus could be used as an aid for patient counseling; **second**, there are few studies reporting prognostic effect of co-morbidity on OS of cervical cancer patients. In this study we found presence of co-morbid condition as an independent predictor of OS of stage IIB and III-IVA patients received curative treatment; **third**, there are very few studies reporting on prognostic effect of WBC count and it's component on cancer survival. In this study we investigated such an association and found that elevated monocyte counts were associated with poor prognosis of locally advanced cervical cancer. Since, Complete Blood Count test is cost effective, easily

accessible and reproducible, pretreatment monocyte counts can be used as a prognostic factor in clinical practices.

However, present study is limited by the fact that it is a retrospective review of a single-institution experience. Larger, prospective multi-centric studies are warranted to evaluate further.

CHAPTER-8

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