A Study of Survival in Oral Cavity Cancer Patients

By

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Tata Memorial Centre
Mumbai

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Recommendations of the Viva Voce Committee

As members of the Viva Voce Committee, we certify that we have read the dissertation prepared by **Dr Saurabh Bobdey** entitled **"A study of survival in oral cavity cancer patients"** and recommend that it may be accepted as fulfilling the thesis requirement for the award of Degree of Doctor of Philosophy.

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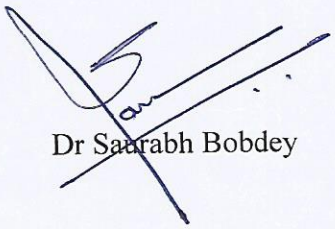

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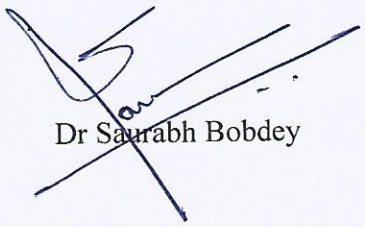
DECLARATION

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



Dr Saurabh Bobdey

List of Publications arising from the thesis

- Bobdey S, Ganesh B, PS Mishra. Nomogram prediction for survival of patients with oral cavity squamous cell carcinoma. Head Neck 2016; 38 (11): 1826-1831. DOI 10.1002/hed.2450.

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Other Publications:

- Bobdey S, Jain A, Ganesh B. Epidemiological review of laryngeal cancer: An Indian perspective. Indian J Med Paediatr Oncol 2015;36:154-60.

- Bobdey S, Jain A, Abhinendra K, Ganesh B. Cancer Screening: Should Cancer Screening be essential component of Primary Health Care in Developing countries?. Int J Prev Med. 2015 ;6: 56. doi: 10.4103/2008-7802.160053.

- Bobdey S, Sathwara J, Jain A, Balasubramaniam G. Burden of cervical cancer and role of screening in India. Indian J Med Paediatr Oncol 2016;37:278-85.

Conferences

- Presented "Pretreatment circulating monocyte count a progonostic marker for patients with oral cavity cancer" in 37th Annual Scientific Meeting of the International Association of Cancer Registries between 8 to 10 October 2015 at Mumbai.

- Presented "A quest for easily assessable prognostic marker for oral cancer: Is routine pretreatment WBC count an answer?" in XXXI National Conference of Marine Medical Society held in Mumbai from 6-8 Nov 2015.

- Presented "Nomogram for prediction of prognosis in patients with oral cavity squamous cell carcinoma" in TMC platinum jubilee conference entitled "A Conference of New Ideas in Cancer – Challenging Dogmas" held at Tata Theatre, National Centre for the Performing Arts (NCPA), Mumbai from 26th to 28th February, 2016.

Dr. Saurabh Bobdey
Date: 22/05/17

CERTIFICATE

I certify that the thesis titled '**A study of survival in oral cavity cancer patients**' submitted for the degree of Doctor of Philosophy by **Dr Saurabh Bobdey** is a record of the research carried out by him 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

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Date 22 May 17

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Teachers are like the candles, which consume themselves to brighten the lives of others.

- Author Unknown

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TABLE OF CONTENTS

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SYNOPSIS OF Ph. D. THESIS

1. Name of the Student:	Dr. Saurabh Bobdey
2. Name of the Constituent Institution:	Tata Memorial Hospital, Mumbai
3. Enrolment No. :	HLTH09201304003
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A study of survival in oral cavity cancer patients

Introduction

Oral cavity squamous cell carcinomas (OCSCC) are malignant lesions occurring in the oral cavity. The majority (84-97%) of OCs are squamous cell carcinomas which arise from pre-existing "potentially malignant" lesions or more often from normal appearing epithelium. (1,2) Oral cancer is one of the most fatal public health problems faced by many countries across the globe and more so by India. An estimated 300,400 new cases of OC (including lip cancer) occurred in 2012 worldwide. 36% (108,651) cases were reported from South Central Asia which is known to have high incidence of OCs. India alone accounted for a quarter (77000 cases) of total number of cases across the globe. (3,4) Thus, compared to global statistics where oral cavity cancer is the eleventh leading cancer, in Indian subcontinent oral cancer is a major public health problem and is the 2nd leading cause of cancer.(5) The relatively high incidence of oral cancer in India is mainly because of extremely popular use of the smokeless tobacco product called gutkha and betel quid chewing (with or without tobacco), which renders its population and especially its youth to a greater risk of developing oral submucous fibrosis, a premalignant disease resulting in increased incidence of oral cancer in younger patients.(6)

The World Health Organization (WHO) has estimated that oral cancer resulted in a total of 145,353 years of life lost globally during 2012. This translated to an estimated 97940 deaths in male and 47413 deaths in females worldwide during 2012. Thus, 2.1% of all cancer related deaths in males were due to OC's (4). In India, an estimated 52067 deaths occurred due to Oral cancers in 2012, with 6.7 deaths per 100,000 males and almost its half i.e 3 deaths per 100,000 in females (4). Inspite of such disturbingly high figures, there are no organized early detection programs by the government and health authorities for oral cancers in India. As a result, these

early detectable and treatable cancers usually present at late stage resulting in increased treatment morbidity and reduced survival rates.(7)

Long-term survival reflects cure and is a positive measure that can be used by planners and health professionals to discuss the outcome of cancer diagnosis and treatment. It is also the result of most interest to patients, their families and the general public. Survival estimates also provide key information about efficiency of cancer health services and are an indicator of progress in cancer control in a given region. The 5-year age specific relative survival rate for oral cancer in India is approximately 37% (26–45), which is much lower as compared to other Asian countries such as China, South Korea, and Singapore. (8) Furthermore, there is a dearth of studies pertaining specifically to Indian population. Most of the researchers have studied oral cancer survival in a fragmented approach, focusing on one or more specific variables which were of interest to their study.

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. On an average 3000 patients attend the hospital daily for various cancer related investigation, treatment and follow-up. It has a well organized digital medical record system which provides sufficient opportunity for research. This study seeks to provide a holistic picture of overall survival and to also, identify and evaluate the impact of patient characteristics and tumor related factors on survival of patients with oral cavity cancer (malignancy of Lip (C00.3/4), Tongue (C02), Gum (C03), Floor of mouth (C04), Hard Palate (C05.0), Cheek Mucosa (C06.0), Vestibule of mouth (C06.1) and Retromolar Area (C06.2))

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Hypothesis

Patient characteristics and tumor related factors impact survival of oral cavity cancer patients.

Aim

To determine and study factors affecting survival in oral cavity cancer patients.

Primary Objectives

1. To compute overall survival of oral cavity cancer patients.

2. To identify the difference in survival with regards to subsite, clinical extent and stage of the disease at diagnosis, Lymph node involvement including histopathological characteristics, treatment modalities and selected baseline laboratory parameters.

3. To evaluate the effect of demographic factors, Lifestyle factors (smoking, tobacco chewing, alcohol etc), major co-morbidities on overall survival of oral cavity cancer patients.

Secondary Objective

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

2. To study patterns and factors which contribute to loss to follow-up and to compute loss adjusted survival rates (LAR) for the associated factors.

Material and methods:

Study Design:

The study was a retrospective analysis of hospital records of oral cavity cancer patients from the Tata Memorial Hospital (TMH) Cancer Registry. All Oral cancer patients who were residents of Mumbai and registered in TMH from 01 January 2006 to 31 December 2008 and had completed at least one modality of cancer directed treatment at TMH were included in the study.

Inclusion Criteria:

- All newly diagnosed oral cavity cancer patients registered in TMH between 01st January 2006 to 31st December 2008.
- Oral cavity cancer patients who are residents of Mumbai (who have been residing in Mumbai for more than 1 year)
- 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

Sample Size:

Total 889 oral cavity cancer cases who residents of Mumbai, registered in TMH between 01st Jan 2006 to 31st Dec 2001, 163 cases were excluded (104 were prior treated cases and 59 cases were excluded due to incomplete treatment). A total of 726 oral cavity cancer patients were included in the study and their medical records were analyzed retrospectively. Oral cavity cases comprised of malignancy of Lip (C00.3/4) excluding skin of lip, Tongue (C02) excluding base of

tongue, Gum (C03), Floor of mouth (C04), Hard Palate (C05.0), Other and Unspecified parts of mouth (C06) (Cheek Mucosa (C06.0), Vestibule of mouth (C06.1) and Retromolar Area (C06.2))

Data Collection

Details regarding demographic characteristics, disease (tumor) related factors (including histological characteristic of the tumor), treatment received, baseline laboratory parameters, co-morbid conditions, lifestyle habits, 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:

- **Survival 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. The Overall survival was calculated by using actuarial method (9) and the difference in survival rates with regards to various factors were studied by Kaplan-Meier method (10) and compared using log-rank test (11). The Cox-regression model (12) was used to investigate the effect of these factors simultaneously on overall survival in a multifactorial setting. All statistical analyses were performed using the Statistical Package for Social Science program (SPSS for Windows, version 20, SPSS, Chicago, IL). A probability, p value < 0.05 was considered to be statistically significant.
- **Statistical Analysis for timelines:** Time periods in days were calculated from date of registration to diagnosis, diagnosis to treatment commencement, treatment

commencement to treatment completion and Overall Treatment Time (OTT) i.e time period from date of registration to treatment completion. These periods have been described in median, minimum and maximum period. The median time was taken as cut-off for categorization of time period and for analysis of its effect on overall survival.

- **Computation of Loss-adjusted survival (LAR):** Loss-Adjusted Survival Rate (LAR) a method proposed by Ganesh (13) was applied to obtain the corrected survival rates for various groups. Loss-adjusted survival is estimated under the assumption that survival of patients lost to follow-up is the same as that for patients with known follow-up time and have similar characteristics of different prognostic factors at first entry. Thus, using this method the estimated deaths in those with complete follow-up were calculated and then subsequently, these estimates were applied to those with incomplete follow-up to get expected deaths. A standard framework, such as the actuarial one, was then applied with the sum of observed and expected outcome events. The above methods alongwith mathematical derivations are described in detail elsewhere. (14)

Results and Discussion

Overall Survival: A total of 726 cases of oral cancer, comprising cancers of the lip, buccal mucosa, gingiva, retromolar trigone, floor of mouth, hard palate and anterior tongue, were included in the study. The closing date for recording the last follow-up was taken as 31st December 2014, vital status of the each case on the last date of follow-up, was retrieved from the patient's medical case file and hospital based electronic medical record system (EMR). Out of the 726 patients, at the end of follow-up (31st Dec 2014), 329 (45.3%) patients had expired, and 397 (54.7%) were censored. The overall 5 yr survival rates of all cases and subsets are presented

in table no.1. The observed 5 yr survival of the cohort was found to be 52%. Sankaranarayanan R et al. (2010) in his study of 25 population-based cancer registries in 12 countries in sub-Saharan Africa, Central America and Asia, found India to have the lowest survival rate in Asian countries and this difference was attributed to lack of established screening and early detection programmes, which in turn results in majority of cases presenting with advanced stage disease and lower survival. (8) Survival rates similar to our study were reported by Rogers SN et al. (2009) who in their study of 541 patients with oral squamous cell carcinoma found 5 yr overall survival of 56%. (15) A multicentric study of 2003 patients who had received treatment for oral cavity sqamous cell carcinoma (OCSCC) from 2000 to 2011 in 7 cancer centers worldwide, including TMH, reported an observed 5yr survival of 70% (16). The 5yr survival rate of 52% found in our study is much lower than this multicenteric study which is due to, firstly, 5 out of the 7 collaborating centers were from developed countries, contributing to more than 70% of the data/cases. Secondly, in our study, almost 70% (stage IV 54%; and stage III 15.3%) of cases had advanced stage disease at diagnosis as compared to only 55% in multicentric international collaborative study. This is further substantiated by the fact that 5yr survival of patients with early stage disease (TNM I & II) was found to be same in both the studies i.e 77%. However in our study, 5yr survival of patients with advanced stage disease (TNM III & IV) was found to be much lower i.e 40% as compared to 63% found in multicentric international collaborative study (16). Thus, higher percentage of advanced stage cases with lower survival rate can possibly explain the lower overall survival found in our study. The 5yr survival rate of 40% in advanced stage cases found in our study is comparable with similar rates reported from India by Sayed SI et al. (2013) in their study of 1,408 oral cavity cancer patients. (17)

Table No. 1: Overall Survival

Factor	Total Number	Survival in percentage				
		1 Yr	2 Yr	3 Yr	4Yr	5Yr
All cases	726	78	62	57	54	52
Early stage	223	91	82	79	77	77
Advanced Stage	503	70	53	47	43	40
Tongue Cancer Cases	245	76	58	52	51	50
Cheek Mucosa & others	481	79	64	60	55	52

Table 2 Summary of independent predictors of survival of oral cancer

All Cases (n=726)	Advanced Disease (n=503)	Early Disease (n=223)	Tongue Cancer (n=245)	Cheek mucosa and others (n=481)
• Age • Comorbidity • Poorly Differentiated • Tumor Size (histological) • Lymph node involvement • Advanced Stage • Perineural invasion • Extracapsualar Spread • Monocyte count • Neutrophil Lymphocyte ratio	• Age • Comorbidity • Poorly Differentiated • Tumor Size (histological) • Lymph node involvement (histological) • Perineural invasion • Extracapsualar spread • Monocyte count • Neutrophil Lymphocyte ratio	• Age • Poorly Differentiated • Tumor Size (histological) • Perineural invasion	• Comorbidity • Poorly Differentiated • Tumor Size (histological) • Lymph node involvement • Advanced Stage • Perineural invasion • Extracapsualar spread	• Age • Poorly Differentiated • Tumor Size (histological) • Lymph node involvement • Advanced Stage • Perineural invasion • Extracapsualar spread

Independent predictors of survival: Table 2 (given above) provides a summary of the identified independent predictors of overall survival in all cases as well as in various subset analysis. Age of more than 40 yrs was found to be an independent prognostic factor overall except tongue cancer cases, however in tongue cancer subset it was found to influence survival significantly in univariate analysis but failed to achieve statistical significance in multivariate model, this may be because very few patients were of age less than 40 years in this subset (59 cases). Similarly, though patients with comorbidity were found to have lower survival it failed to attain statistical significance in early stage and cheek mucosa subsets. Heamatological parameters namely monocyte and neutophil-lymphocyte ratio were found to be independent predictors of poor survival both in overall and in advanced stage disease, but failed to influence survival of cases with early stage disease. This is because in contrast to early stage, advanced stage is known to be associated with higher inflammatory state of the body and heamatological parameters are known to be marker of infection and inflammation. This effect was also seen when all the cases was considered together as majority (70%) of cases in our cohort were of advanced stage disease. Apart from these few exceptions, age, comorbidity, poor differentiation, lymph node involment (clinical/ histopathological), advanced disease, tumor size, perinueral invasion and extracapsular spread were found to be independent predictors of survival overall, and also in all the subsets.

Timelines: Delay in cancer diagnosis and treatment may be detrimental in several ways: a more advanced stage at diagnosis, poorer survival, greater disease-related and treatment-related morbidity and adverse psychological adjustment. Conversely, harm may be caused to the patients by earlier detection of cancers without improving survival (lead-time), and detection of slow-

growing tumors not needing treatment (over-diagnosis). (18) Hence in order to assess the influence of time on oral cancer survival we estimated four broad timelines in our study (table 3). Majority, of the patients were diagnosed within 7 days and the median period of diagnosis was found to 3 days. On survival analysis time required for diagnosis was not found to be associated with survival. Seoane et al in his study of oral cancer cases found that when survival was adjusted for tumor stage at diagnosis, diagnostic delay did not influence survival. And hence suggested that, survival from oral cancer is affected more by the biology of the cancer (rapid tumor growth) than by diagnostic delay.(19)

In the present study, the median time from diagnosis to initiation of treatment was found to be 30 days and it was not found to be associated with overall survival ($p > 0.05$). Jimmy J et al. in his study of locoregionally advanced head and neck cancer also reported a similar median time of 34 days and found that a longer diagnosis to treatment interval (DTI) was not significantly associated with locoregional control ($P=0.11$), distant metastases-free survival ($P=0.32$), or overall survival ($P=0.07$). (20) Furthermore, in our study overall the median time required for treatment completion was 30 days and Overall Treatment Time (OTT) i.e. time taken from registration of the patient in this centre to treatment completion was 106 days. Both were not found to be associated with overall survival ($p > 0.05$). It is generally accepted that the overall treatment time for oral cancer patients should not exceed 100 days measured from the day of surgery to the end of adjuvant therapy. (21,22) Tribuis S et al. (2016) analyzed survival in patients of head and neck cancer according to treatment duration >100 days vs. ≤100 days and observed that disease free survival and recurrence free survival was not significantly different in these 2 groups, however overall survival was lower in patients with treatment time of more than

100 days. (23) In our study we tried to see the influence of treatment time on survival by taking multiple cut-offs (≤ 60 days, 61 – 90 days, 91 - 120 days and ≥ 121days) as well as the traditional 100 days cut-off. In both the analysis we found that the patients treated for longer duration did have a lower survival (36.6% for patient treated for ≥ 121 days ; 45% for patient treated for > 100 days), however this difference in survival as compared patients with lower treatment time failed to achieve statistical significance (p> 0.05) . One reason for this could be that majority (>80%) of our patients had completed treatment within 100 days. Nonetheless, as far as possible treatment delays should be avoided, especially delay in initiating radio (chemo) therapy after surgery should be minimized as much as possible under local circumstances and considering patient characteristics.

Table 3: Descriptive analysis of Timelines

Sl. No.	Timelines	Median (days)	Minimum (days)	Maximum (days)
1.	**Time taken for Diagnosis**	03	01	56
2.	**Time taken to start Cancer Directed treatment**	30	01	188
3.	**Time taken for treatment completion**	30	01	198
4.	**Overall treatment time**	106	5	317

Loss adjusted survival rate (LAR): In our study overall 5yr survival for all cases by actuarial method was found to be 52% and Loss adjusted survival rate was found to be 51.25%. Similarly, in subset analysis for early and advanced diseases the 5yr survival by actuarial and LAR method was found to be 77% & 76.15%, and 40% & 39.40% respectively. Thus, adjustment for loss of follow-up gave an estimated 0.8% units less 5 years survival than the observed (actuarial) survival. The small difference between the absolute (actuarial) survival and the loss-adjusted survival observed in this study is much less than in other studies. (24,25) This

can be because our study had only 19% loss to follow up as compared to much higher loss to follow-up reported by other quoted studies i.e Ganesh et al. (24) loss to follow-up of 35-43%; Sriamporn et al. (25) loss to follow-up- loss to follow-up of 26.7%. The low loss to follow-up observed in our study was because our study cohort comprised of only those cases who were residents of Mumbai. This observation of small difference between the absolute (actuarial) survival and the loss-adjusted survival is not confined to cancer of the oral cavity; differences for other sites like female breast (data from six registries from developing countries) and larynx (data from Chennai and Mumbai cancer registries) have also been reported of similar (small) size. (26)

Summary and Conclusion

Summary:

- The overall 5 year survival of oral cavity cancer (all cases) was found to be 52%. The 5 year overall survival for Early stage disease (TNM I &II), Advanced stage disease (TNM III & IV), Tongue and Cheek mucosa cancer was found to be 77%, 44%, 50% and 52% respectively.
- In Oral cavity cancer (all cases) the independent predictors of prognosis were Age, Comorbidity, Poor differentiation, Tumor Size, Lymph node involvement, Advanced Stage, Perineural invasion, Extracapsualar Spread, pretreatment Monocyte count and Neutrophil-Lymphocyte ratio.
- In Early stage cancer (TNM I & II) the independent predictors of prognosis were Age, Poor differentiation, Tumor size and Perineural invasion.

- In Advanced stage cancer (TNM III & IV) the independent predictors of prognosis were Age, Comorbidity, Poor differentiation, Tumor Size, Lymph node involvement, Perineural invasion, Extracapsualar Spread, pretreatment Monocyte count and Neutrophil-Lymphocyte ratio.
- In Tongue cancer the independent predictors of prognosis were Comorbidity, Poor differentiation, Advanced stage, Tumor Size, Lymph node involvement, Perineural invasion and Extracapsualar Spread.
- In Cheek mucosa and other sites of oral cavity cancer (excluding tongue) the independent predictors of prognosis were Comorbidity, Poor differentiation, Advanced stage, Tumor Size, Lymph node involvement, Perineural invasion and Extracapsualar Spread.
- The median time period from registration to pathological confirmation of diagnosis was 3 days, from diagnosis to commencement of treatment was 30 days, from treatment commencement to treatment completion was 30 days and median overall treatment time was found to be 106 days. The time periods were not found to be associated with survival.
- Overall 5 year survival rate and loss-adjusted survival rate were found to be 52% and 51.25% respectively.

Conclusion:

The current study is one of the few Indian studies to comprehensively analyze and present a holistic picture of oral cancer survival in patients treated at a premier cancer hospital of India. Our study shows that oral cancer mortality may be reduced if lesions are detected, diagnosed, and treated at an earlier stage. The 5-year survival rates were better in patients with

the early stages of OSCC than in those with the advanced stages. Therefore, we are tempted to conclude that the periodic screening of high risk populations for OSCC and early treatment may appreciably reduce oral cancer mortality in India. Contrary to what is generally accepted socoio-demographic factors such as education and marital status were not found to affect oral cancer survival in our study. Similarly, various time periods involved in evolution of cancer treatment in the hospital namely, time for diagnosis, treatment initiation, treatment completion and overall treatment time were not found to influence overall survival. Furthermore, cancer as a disease bears such an intense burden that role other chronic co-morbities is often undermined, but our study shows that presence of co-morbidity has a significant influence on outcome of oral cancer patients. In addition, ours is the only study in India to report prognostic role of heamatological parameters such as neutrophil-lymphocyte ratio (NLR) and monocyte counts in oral cancer patients. Given the low cost, easy accessibility, and reproducibility of a full blood count, both NLR and monocyte counts seem promising candidates for use in clinical practice. Finally, our study demonstrates that, in addition to TNM classification other clinical and pathological factors also have a significant role in predicting survival. Therefore, although the TNM classification harbors very important clinical information the role of other factors viz tumor differentiation, extracapsular spread and perineural invasion cannot be ignored and hence, there is a need to develop a more powerful and precise modular prognostic system that will not only be reliable and reproducible but also flexible and easy to use.

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LIST OF ABBREVIATIONS

CDT	Cancer Directed Treatment
CT	Chemotherapy
CRT	Chemoradiotherapy
DALY	Disability-adjusted life year
ECS	Extra-capsular spread
EBRT	External Beam Radiotherapy
OC	Oral Cancer
OSCC	Oral Squamous cell carcinoma
PNI	Perineural Invasion
Sx	Surgery
RT	Radiotherapy

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CHAPTER 1

INTRODUCTION

"Physicians of the Utmost Fame
Were called at once; but when they came
They answered, as they took their Fees,
"There is no Cure for this Disease."

- Hilaire Belloc

"In solving a problem of this sort,
the grand thing is to be able to reason backwards.
That is a very useful accomplishment,
and a very easy one, but people do not practice it much."

- Sir Arthur Conan Doyle

1.1 **Brief History of Cancer:** Cancer is often described as the plague of our generation, but this disease has afflicted mankind since time immemorial. So it's no surprise that from the dawn of history people have written about cancer. The earliest recording of a cancer case dates back to around 1500-3000 BC. It's scripted on the Edwin Smith Papyrus, which is part of an ancient Egyptian textbook on surgery and medicine and describes eight breast tumors that were actually removed by cauterization, or burning the area with an ancient tool. The Egyptian writers state in the papyrus, simply: "There is no treatment". (1) However, it wasn't until the 400s BC when a term was created for the disease. Hippocrates, a Greek physician, was the first to coin the term "*carcinos".* In Greek, these words refer to a crab, most likely applied to the disease because the finger-like spreading projections from a cancer called to mind the shape of a crab. The

Roman physician, Celsus (28-50 BC), later translated the Greek term into cancer, the Latin word for crab. Galen (130-200 AD), another Greek physician, used the word oncos (Greek for swelling) to describe tumors and it is from here that we derive the modern word oncology. (2,3)

1.2 Thereafter, the war against cancer began with ancient arsenal comprising removal of affected organ and use of a variety of substances, such as honey, bees wax, oils and fats, and in combination with lead, gypsum, copper ore, rock alum etc to modern complex treatment protocols.(3) Thus, Cancer has a long and a complex history, from first record of a tumor in ancient Egypt to the modern use of targeted cancer treatments, we've learned a great deal about cancer how it spreads, how it resists, and how it's defeated but we still have a lot to learn before it can be conquered and eradicated from human race.

1.3 In today's world, millions of people are living with cancer or have had cancer. Cancer is the leading cause of death in both economically developed and developing countries alike. The burden of cancer is increasing in economically developing countries as a result of population aging and growth as well as, increased adoption of cancer-associated lifestyle choices including smoking, physical inactivity, and ''westernized'' diets. (4) Based on the GLOBOCAN 2012 estimates, about 14.1 million cancer cases and 8.2 million cancer deaths are estimated to have occurred in 2012; of these, 57% of the cases and 65% of the deaths occurred in the economically developing world. (5) Furthermore, it is estimated that between 1990 and 2013, absolute disability-adjusted life year (DALYs) due to all cancers for both sexes increased by 29% globally, by 10% in developed countries, and by 40% in developing countries. In 2013, the cancers with the highest incidence on a global scale for men were prostate cancer (1.4 million),

tracheal, bronchus, and lung (TBL) cancer (1.3 million), and colon and rectum cancer (873 000). For women, the cancers with the highest incidence were breast cancer (1.8 million), colon and rectum cancer (700 000), and TBL cancer (535 000). (6)

1.4 In India, approximately 1 million new cases were detected, and 680,000 deaths occurred due to cancer in 2012. The top three leading sites of cancer for both the sexes combined are breast, cervix and oral cavity. These three cancer sites together amount to 34% incidence and 27.8% cancer related mortality in India. (5,7) As compared to global statistics where oral cavity cancer is the eleventh leading cancer, in Indian subcontinent oral cancer is a major public health problem and is the 2nd leading cause of cancer.(6) The relatively high prevalence of oral cancer in India is mainly because of extremely popular use of the smokeless tobacco product called gutkha and betel quid chewing (with or without tobacco), which renders its population and especially its youth to a greater risk of developing oral submucous fibrosis, a premalignant disease resulting in increased incidence of oral cancer in younger patients.(8) Inspite of such disturbingly high figures, there are no organized early detection programs for oral cancers in India. As a result, these early detectable and treatable cancers usually present at late stage resulting in increased treatment morbidity and reduced survival rates.

1.5 Long-term survival reflects cure and is a positive measure that can be used by planners and health professionals to discuss the outcome of cancer diagnosis and treatment. It is also the result of most interest to patients, their families and the general public. Cancer survival can be estimated from hospitals and clinical trial settings which reflects the experience of groups of patients in specific settings, or from estimates of population-based survival based on all cancer

patients diagnosed by all means in a given geographical region or country which incorporates the influence of different socio-economic factors, natural histories, health-seeking behaviours, awareness, early detection practices and treatment availability and accessibility. Such survival estimates provide key information about efficiency of cancer health services and are an indicator of progress in cancer control in a given region. Studies have found striking differences in cancer survival between countries and within countries, these are largely related to differences in general awareness, early detection practices, availability of trained human resources, diagnosis and treatment, and development and accessibility to cancer health services. (9) Countries with well developed health services with advanced diagnostic and treatment centres have much better cancer survival rates as compared to India, where cancer health services are moderately developed with diagnostic and treatment facilities mainly centered in and around urban cities. (10)

1.6 The 5-year survival rate for oral cancer in India is approximately 37% (26–45), which much less as compared to other Asian countries such as China, South Korea, and Singapore. (10) Furthermore, there is dearth of studies pertaining specifically to Indian population. Most of the researchers have studied oral cancer survival in a fragmented approach, focusing on one or more specific variables which were of interest to their study. Therefore, this study was planned to comprehensively study and to evaluate the impact of demographic factors, patient characteristics and tumor related factors on overall survival in patients with oral cavity cancer.

CHAPTER 2

REVIEW OF LITERATURE

2.1 Descriptive Epidemiology

Oral cancers (OC) are malignant lesions occurring in the oral cavity. The majority (84-97%) of OCs are SCCs which arise from pre-existing "potentially malignant" lesions or more often from normal appearing epithelium. (11,12) Oral cancer is one of the most fatal public health problems faced by many countries across the globe and more so by India, because of cultural, ethnic, geographic factors and the popularity of addictive habits, the frequency of oral cancer is high.

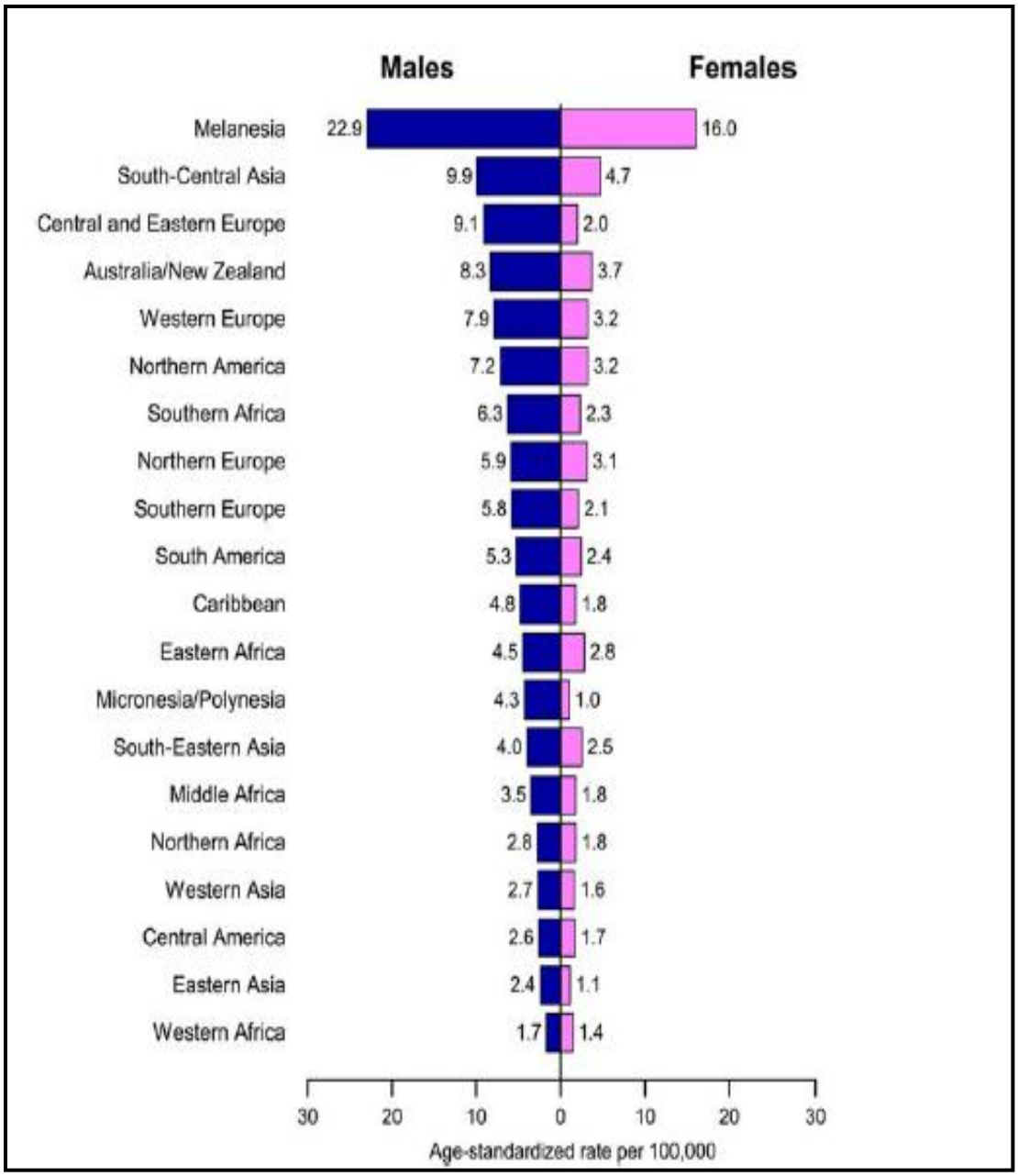
2.1.1 Burden of disease

An estimated 300,400 new cases of OC (including lip cancer) occurred in 2012 worldwide. 36% (108,651) cases were reported from South Central Asia which is known to have high incidence of OCs. India alone accounted for a quarter (77000 cases) of total number of cases across the globe. (4,5) Oral cancer is of significant public health importance to India. Because, firstly, it is diagnosed at later stages which result in low treatment outcomes and considerable costs to the patients whom typically cannot afford this type of treatment. (13) Secondly, majority of our population resides in rural areas which have inadequate access to trained providers and limited health services. As a result, delay has also been largely associated with advanced stages of oral cancer. (14) Thirdly, oral cancer affects those from the lower socioeconomic groups, that is, people from the lower socioeconomic strata of society due to a higher exposure to risk factors such as the use of tobacco. (15)

2.1.2 Incidence of the Oral Cancer

The world age adjusted incidence rates of OC is 5.5 per 100,000 for men, 2.5 per 100,000 for women and 4 per 100,000 for both sexes combined. (5) There is a significant difference in the incidence of oral cancer in different regions of the world, with the age-adjusted rates varying from over 7 per 100,000 population in India and Sri Lanka, to 5 per 100,000 in the U.S.A, and less than 2 per 100,000 in the Middle East. Overall, the highest rates of oral cancer are found in Melanesia, South-Central Asia, and Central and Eastern Europe, whereas the lowest are in Western Africa and Eastern Asia [Figure 1]. (4) In India, oral cancer is a significant public health problem and accounts for 7.6% of all cancers and has an age adjusted incidence rate 7.2 per 100,000 population. In Indian males OC age adjusted incidence rates are much higher (10.1 per 100,000) as compared to females (4.3 per 100,000) (5). Within India, there is wide variation of OC incidence rates ranging from 17.1 per 100,000 males reported by Ahemadabad urban population based cancer registry (PBCR) to as low as 1.3 per 100,000 males reported by Mizoram PBCR. (16) OC's still continues to increase in our country, major PBCR's such as Delhi, Mumbai, Bhopal and Bangalore have shown an statistically significant increase in age adjusted rates. Delhi (for 2003-2009), Mumbai (for 1999-2010) and Bangalore (for 1993-2009) has reported an significant positive annual percentage (APC) change of 7.6%, 3.3% and 2.4 % respectively. The variation in incidence and pattern of the disease can be attributed to the regional differences in the prevalence of disease-specific risk factors. (17)

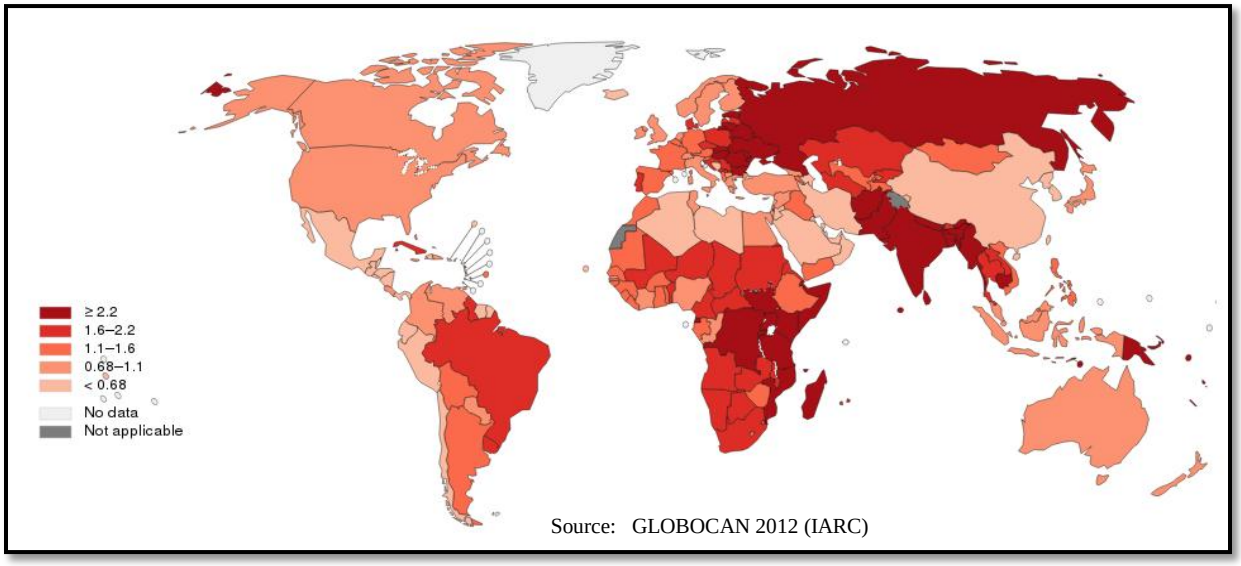
Figure 2.1: Oral Cancer Incidence Rates by Gender and World Area (global cancer statistics, 2012)



2.1.3 Mortality

The World Health Organization (WHO) has estimated that oral cancer resulted in a total of 145,353 years of life lost globally during 2012. This translated to an estimated 97,940 deaths in male and 47,413 deaths in females worldwide during 2012. Thus, 2.1% of all cancer related deaths in males were attributed to OC's (5). There is a wide variation in mortality rates due OC's across various regions of the globe with excess of 10 deaths per 100,000 in Melanasia and 4.7 deaths per 100,000 in South Central Asia to less than 1 death per 100,000 in Central and Northern America as well as Western and Eastern Asia [figure 2]. In India, an estimated 52,067 deaths occurred due to OC's in 2012, with 6.7 deaths per 100,000 males and almost half i.e 3 deaths per 100,000 in females (5). Smoking is estimated to account for about 71% of deaths from oral cavity cancer (including pharynx) in high-income countries and 37% of deaths in low-income and middle-income countries, whereas alcohol is estimated to account for about 33% and14% of deaths, respectively. (18)

Figure 2.2: Age Standardized (world) Mortality Rate (per 100,000) of Oral Cancer (both sexes). (5)



2.2 Cancer Survival

Cancer survival is the main indicator of outcome of cancer health services or treatment, and survival has long been recognized as an important component in monitoring cancer control activities.(19) Cancer registries have long served as potential sources of data for estimating survival. Hospital-based cancer registries usually report survival of a selected series of treated patients that are registered in a hospital or group of hospitals without specific coverage of geographical area or background population. On the other hand, population-based cancer registries, which include all incident cases treated or not from a specific geographical area, usually report average survival in specific regions. Cancer survival reported from both settings may have different perspectives, but estimation of survival rates is routinely done using standard life table approaches such as the actuarial (20) or Kaplan-Meier (21) methods. The life table, one of the basic tools in the description of mortality experience of a population, was first developed as early as 1693 by E. Halley in England. It forms the basis for calculation of the life table estimate of the survivor function, which is still widely used today in the analysis of data from epidemiological studies.

2.2.1 Oral Cancer Survival

The level of development of health services and their efficiency to provide early diagnosis, treatment, and clinical follow-up care have a profound effect on cancer survival. The 5-year age standardized relative survival rate for oral cavity cancer in India has been reported to be approximately 37% (26–45), which much less as compared to other Asian countries such as China (67%), Pakistan (39%), Thailand (32%) and Singapore (44%).(10) In India itself there is wide variation in tongue and oral cavity cancer survival with highest 5 year relative survival

reported in Karungappally and lowest in Barshi, Maharashtra [Table 1]. (9) The observed differences in survival between countries and different regions seems to be largely a result of differences in screening programmes, early detection services, and cancer treatment facilities in these regions which have probably contributed to variation in survival observed. (10)

Table No. 2.1: 3 and 5 year absolute and relative survival of different sites in India (9)

Sl. No.	Place (Registry)	Tongue					Oral Cavity				
		No.	% Absolute survival		% Relative survival		No.	% Absolute survival		% Relative survival	
			3 Yrs	5 Yrs	3 Yrs	5 Yrs		3 Yrs	5 Yrs	3 Yrs	5 Yrs
1.	**Barshi** (1993–2000)	47	8.5	8.5	9.5	9.9	55	30.6	21.7	32.4	23.6
2.	**Bhopal** (1991–95)	127	20.5	9.4	22.6	10.8	172	45.9	29.1	50.4	33.6
3.	**Chennai** (1993–99)	988	25.7	19.4	28.4	23.0	1662	35.3	30.5	38.8	35.7
4.	**Karungappally** (1991–97)	86	35.3	25.9	39.4	31.9	123	41.1	33.1	46.5	41.2
5.	**Mumbai** (1992–94)	2106	31.2	25.3	34.2	29.3	2769	39.4	32.3	42.8	37.0

2.2.2 Factors affecting Oral Cancer Survival

2.2.2.1 Age

The effect of age on prognosis of oral cancer patients has been controversial. Some authors have reported that as the age of the patient increases, 5-year survival rate decreases, thus indicating worse prognosis in older patients. (22,23) Conversely, many studies have found no significant relationship between age and oral cancer survival. (24–27) The lack of consensus for the age ranges that define the periods of life may attribute to the discrepancies in the influence of age on survival**.** (28)

2.2.2.2 Gender

Most of the researchers have found no prognostic differences between males and females. (24,29) However, some researchers have reported higher survival rates for females as compared to males.(30,31) The reasons for these higher survival rates in women could be associated with a biological superiority of women in response to illness and treatment, or a higher awareness in women concerning their bodies, and consequently, a higher percentage of early-state diagnosis females.(32,33)

2.2.2.3 Level of education

It has been previously shown and generally accepted that cancer incidence is strongly influenced by a person's social position or education, as the risk factors of cancer may not be evenly distributed**.** The less educated may well be less aware of early symptoms and may experience a delay in diagnosis. Thus, educational status has been reported to be associated with survival of oral cancer patients, with illiterate or patients with lower educational level having poorer survival. A higher education may help in navigating within the health system thus enabling better and more timely care. For example, a higher education of the patient can improve the patient–doctor interaction and the ability to follow care regimens.(34–37) However, few studies have failed to find any association between education status and OC prognosis. (31)

2.2.2.4 Marital Status

Forty-seven percent of Indians are married. (38) However this percentage varies from country to country depending upon the cultural and social architecture of a particular nation. Studies assessing the impact of marital status on survival among patients with cancer have

yielded conflicting results ranging from, with protective,(39–43) mixed,(44,45) and nonsignificant. (46–48) One of the larger studies conducted on 1,260,898 patients of various cancer sites including head and neck cancers found that married patients are less likely to die as a result of their cancer after adjusting for demographics, stage, and treatment (adjusted hazard ratio, 0.80; 95% CI, 0.79 to 0.81; P< 0 .001) than unmarried patients and these associations remained significant when each individual cancer was analyzed.(49) Psychologically, the diagnosis of cancer may result in more distress than other diagnoses.(50) Patients who are married display less distress, depression, and anxiety than their unmarried counterparts after a diagnosis of cancer, as a partner can share the emotional burden and provide appropriate social support.(51) Depression may, in part, be a mediator of the association between marital status and adherence to medical recommendations. DiMatteo et al. demonstrated a strong relationship between depression and nonadherence, and married patients display lower risk of major depression. (52) Given that patients who lack emotional support mechanisms do poorly after diagnosis with numerous health-related conditions, the importance of adequate support cannot be understated. If the benefits of marriage on survival are mediated through improved support, then the most effective way to combat the increased risks associated with unmarried status in patients with cancer would be to aggressively promote support mechanisms.(53)

2.2.2.5 Lifestyle Habits (Tobacco chewing, smoking and Alcohol)

Tobacco and alcohol consumption are the established risk factors for oral cancer which may act either separately or synergistically. (54) However, its influence on patient survival is still unclear. Smokers and alcohol drinkers seem to be at higher risk for the development of second primary oral cancer than nonsmokers and nondrinkers, thus facing more onerous outcomes. (55–

58) This is also the case for those who maintain tobacco and alcohol consumption following diagnosis of the primary tumor. (55,57–59) Thus, though some authors have reported higher mortality in smokers and alcohol drinkers (23,56,60), there are studies which deny any association between survival and smoked tobacco or alcohol consumption (24,61). Another causative factor for oral cancer associated with lifestyle habit, particularly in the South Asia, Southeast Asia and Pacific Islands countries, is betel quid chewing (62). Betel quid, also referred to as pan consist of pieces of areca nut, processed or unprocessed tobacco, aqueous calcium hydroxide (slaked lime), and some spices wrapped in the leaf of piper betel vine leaf. This is very common and is accepted socially and culturally in many parts of India. Additionally, gutka, zarda, kharra, mawa, and khainni are all dry mixtures of lime, areca nut flakes, and powdered tobacco custom mixed by vendors. In recent years, commercially available sachets of premixed areca nut, lime, condiments with or without powdered tobacco have become very popular, particularly among younger Indians. (63) Indian studies have reported a significant association between oral cancer incidence and tobacco chewing. (64,65) However, effect of tobacco chewing on OC survival is uncertain as some studies have found poorer prognosis in tobacco chewers (66) and some have reported no association. (61,67)

2.2.2.6 Comorbidity

Comorbidity is defined as the "coexistence of disorders in addition to a primary disease of interest". (68) Comorbidities are generally more common among the elderly than younger adults, and many of these are Chronic diseases which are not life threatening in the short term. Consequently, many people live with, rather than die from, chronic health conditions. Cancer itself is a chronic disease with long-term consequences for health and quality of life and is more

prevalent among older people. The importance of comorbidities is that they influence overall survival and frequently influence treatment options for individual patients. (56) Comorbid conditions have a significant impact on the survival of patients with head and neck cancer. Studies have reported poor prognosis in OC patients with comorbidities and this effect was found to remain significant after even after adjusting for the confounding effects of stage and other tumor related factors. (69)

2.2.2.7 Blood group

The associations between ABO blood group and survival have been evaluated in several malignancies. (70) Few studies in Indian population, have suggested that patients with blood group A may have predisposition for oral cancer, but there is a dearth of evidence regarding role of blood group in oral cancer survival. (71,72)

2.2.2.8 Tumor-related factors

2.2.2.8.1 Anatomic site

The site of primary tumour has an important influence on patient survival for reasons including ease of early diagnosis and accessibility for surgical removal with sufficient margin. (73) In addition, the vascular and lymphatic networks which vary between different sites may influence the metastatic capacity and hence the prognosis (28). Different opinions exist in the literature with regard to influence of oral cancer sites on patient survival. These disparities are perhaps due to misclassification of the original tumour site owing to the complex anatomical structures in the oral cavity. Besides, tumours that arise from adjacent sites may both spread and become overlap easily. It is thus quite common for a certain level of uncertainties in determining

the intraoral sub-sites of tumour origin to occur, particularly in advanced stages (35). However, most studies agreed that lip cancer was associated with the best survival rates while tongue had the worst. (35,74,75)

2.2.2.8.2 Disease staging (TNM Staging)

The French surgeon, Denoix (76) developed the TNM system at the Institut Gustave-Roussy in Paris between 1943 and 1952, and in 1953 it was proposed to the Union Internationale Centre le Cancer (UICC) as a prognostic system that would be applicable for staging solid tumors. (77) In the United States, the American Joint Committee on Cancer (AJCC) was established in 1959 with the mission of formulating and publishing systems of classification of cancer that would be useful not only for selection of treatment and determining prognosis, but also for continuing evaluation of cancer control measures. The AJCC and UICC versions of the TNM system were unified in 1987 and these organizations have since maintained a liaison to ensure compatibility of revised staging classifications through continuous collaboration.(77) The AJCC/UICC TNM staging system is now in its seventh version and the next edition is due for publication in 2016. The TNM consists of (1) the size of the primary tumor (Tis, T1, T2, T3, T4), (2) description of regional (N0, N1, N2a, N2b, N2c, N3), and (3) distant metastasis (M0, M1). Each combination of these three variables can be seen as a bin into which patients with these characteristics are placed. This is called the TNM-bin model and consists of 60 bins (5X6X2). (78) Over the years, the TNM system has fulfilled its original mandate remarkably and has become the most widely accepted prognostic system in routine clinical practice worldwide because of its timetested consistency and user-friendliness. It is the mainstay of cancer outcome prediction in patients with head and neck squamous cell carcinoma (HNSCC). (79)

2.2.2.8.3 Tumour size

Surface greatest dimension—‘‘tumour diameter’’— is used to indicate tumour size in the TNM staging classification system (80). In pathological assessment of resection specimens (81), the maximum diameter are measured to the nearest millimetre using an optical micrometer to supplement the macroscopic inspection of the resection specimen. The size of the primary tumour affects both the choice and outcome of treatment. Tumour size is an important factor in determining the surgeon’s ability to obtain tumour-free margins, and the dose necessary to effect a cure in patients treated by radiotherapy. (82) Large size at presentation is associated with an increased risk of local recurrence; (83,84) increased cervical lymph node metastasis; (85) and poor survival. (86,87)

2.2.2.8.4 Node metastases

Cervical node metastases have variable incidence and are widely accepted as one of the major prognostic factors in patients with OSCC. (88–90) Cervical lymph node metastases may be subdivided into two categories: overt nodal disease (clinical metastases) and nonovert nodal disease (occult or subclinical metastases). There are two classes of occult metastases. (91) The first consists of occult metastases identified by ‘‘established’’ or traditional methods. These are metastatic deposits small enough to evade detection on clinical or radiographic examination using the most sensitive and technologically advanced procedures, (91,92) but that are detected by light microscopy. The incidence of these established occult metastases varies with the location, size and thickness (93) of the primary tumor. A second class of occult metastases may be designated ‘‘subpathological’’ or ‘‘submicroscopic’’, because they are too small to be

detected by light microscopy on hematoxylin and eosin-stained slides, but may be detected in the pathologically dissected lymph nodes by means of Immunohistochemistry and/or molecular analysis. (94,95) These newer techniques are capable of converting the status of nodes from negative (as assessed by conventional microscopy and sampling) to positive. (96) Even though these techniques are not used in regular clinical practice, there appears to be tremendous interest in these approaches to enhance detection, as the presence of cervical lymph node metastasis is the single most adverse independent prognostic factor in OSCC. The presence of cervical node metastasis is associated with a decrease in global survival to roughly half as well as with higher recurrence rates. (93,94,97)

2.2.2.8.5 Extracapsular spread (ECS)

Extracapsular spread is defined as extranodal extension of metastatic deposits outside the lymph node capsule. A descriptive evaluation system of ECS extension subdivides it into macro- and microscopic. Macroscopic ECS is evident to the naked eye, and microscopic ECS is only demonstrable during histologic analysis. The extent of ECS is recorded by noting the tissues/structures that are involved by tumour (for example, the internal jugular vein, sternocleidomastoid muscle, perinodal adipose tissue, immediate pericapsular fibrous tissue). (97) ECS shows a significant correlation with unfavourable histological features at the primary tumour site such as a non-cohesive pattern of invasion, vascular and perineural invasion, and close/involved resection margins. ECS is a simple, readily detectable indicator of tumour aggression.(85) Thus, ECS is a noticeably important prognostic factor, associated with higher locoregional recurrence rates, distant metastases, and lower survival rates. (88,89,97)

2.2.2.8.6 Perineural invasion (PNI)

Perineural invasion is defined as a tropism of tumour cells for nerve bundles in the surrounding tissues. It is a form of tumor spread exhibited by neurotropic malignancies that correlates with aggressive behavior.(98) PNI is considered a tumour spread similar to but distinct from vascular or lymphatic invasion, that hinders the ability to establish local control of a malignancy because neoplastic cells can travel along nerve tracts far from the primary lesion and are often missed during surgery.(98,99) Studies show that infiltration of the perineural space of nerves at the advancing front of the tumour is related to the site, the diameter and thickness of the tumour, pattern of invasion at the advancing tumour front, presence of nodal metastasis; close/involved resection margins and survival.(84,100) PNI is considered as a significant prognostic indicator due to its association with regional recurrence and poor overall survival. (99,101)

2.2.2.8.7 Bone involvement

Oral carcinoma may progress to directly invade the bone, a feature associated with a worse prognosis. Bone invasion is one criterion of the American Joint Committee on Cancer classification for the most advanced primary stage (T4) and overall stage (IV) for these tumors. (80) Bone invasion by oral squamous cell carcinoma may progress by either an infiltrative or an erosive histological pattern. The infiltrative pattern is marked by nests and cords of tumor cells along an irregular tumor front, and the erosive pattern exhibits a broad, pushing tumor front. The erosive pattern of bone invasion has been hypothesized to extend in a more predictable fashion than the infiltrative pattern. (102) The infiltrative pattern of bone invasion by oral squamous cell carcinoma is correlated with a significantly worse prognosis when compared with the erosive

pattern of invasion. The infiltrative pattern clearly exhibits a more aggressive behavior with an increased likelihood of positive margins, recurrence, death with disease, and shorter disease-free survival. Studies of mandibular resections from previously untreated patients, (103–105) have found that an infiltrative, but not an erosive, pattern of invasion was predictive for local recurrence and survival even after taking into account the prevailing soft tissue prognosticators. Thus, though postoperative determination of an erosive or infiltrative pattern of bone invasion is an easy assessment to make based on simple histological characteristics and does not incur any additional costs, it is not typically reported by pathologists in their analysis of bone specimens. (102) Therefore, this non-characterization of bone invasion have resulted in uncertainties on the prognostic significance of bone involvement. (99)

2.2.2.8.8 Skin involvement

Direct skin involvement has been found to be a prognostic sign of poor outcome on oral squamous cell carcinoma. However, Cole and McGuirt (106) in their found study found lymphatic spread to skin was an even more ominous sign with a median survival of only three months as compared to seven months in patients with direct spread. Furthermore, involvement of facial skin was found to be better prognostically for duration of survival than was involvement of neck skin.(106)

2.2.2.8.9 Histological grade (differentiation)

The potential prognostic significance of cellular morphology has long recognized in squamous cell carcinoma. Hence, it has been customary to grade OSCC according to the method originally described by Broders, (107) and adopted by the WHO which takes into account a

subjective assessment of the degree of keratinisation, cellular and nuclear pleomorphism, and mitotic activity. The WHO grading system recommends three categories: grade 1 (well differentiated); grade 2 (moderately differentiated) and grade 3 (poorly differentiated). In a tumour showing different grades, the higher grade determines the final categorization. Most authors have established significant correlations between lower histologic differentiation and poorer prognosis (24,26,108–110), however, some researchers did not find such association (29,60,111).The subjective nature of the assessment; small biopsies from tumours showing histological heterogeneity and inadequate sampling; reliance on structural characteristics of the tumour cells rather than functional ones; have all been cited as possible explanations for not finding association between tumor differentiation and survival. (99)

2.2.2.9 Treatment

Treatment of OSCC traditionally includes single modality surgery, radiotherapy [external beam radiotherapy (EBRT) and/or brachytherapy], or various combinations of these modalities with or without systemic therapy (chemotherapy and/or target agents). The selection of treatment is based on considerations of disease control, anticipated functional and cosmetic outcomes, and availability of resources and expertise. However, of the three modalities, the mainstay of treatment for OSCC is surgery, and EBRT with or without chemotherapy is generally employed in selected situation as illustrated in table-2. (112,113) The past few years have witnessed considerable improvements in preoperative imaging assessment, technical advances in tumor resection, new reconstruction methods, effective radiotherapy, stringent case selection, and the fruitful cooperation of multidisciplinary clinical teams. These developments have contributed to safely treating tumors involving the oral cavity while providing a good

quality of life for patients. (114) However, inspite of these advances in cancer treatment, advanced stage OCSCC remains a challenging disease to treat. Management of advanced stage oral cavity squamous cell carcinoma (OCSCC) has classically involved surgical resection with postoperative adjuvant radiotherapy (S-RT) (115). Despite this aggressive dual modality therapy, local or regional disease recurrence and low survival remain a concern (116) Patients with adverse features of ECS, LVI, and PNI are at particular risk of disease progression and higher death rates. (117) The treatment options expanded in 2004 when level I evidence was established with the findings of the Radiation Therapy Oncology Group (RTOG) 9501 and European Organization for Research and Treatment of Cancer 22931 trials. (118,119) These two largescale, independent, but similar, trials conducted in the U.S. and Europe demonstrated that compared to postoperative radiotherapy (RT) alone, adjuvant concurrent chemo-radiotherapy (CRT) for advanced stage OCSCC was more efficacious in local and regional control as well as disease-free survival. (120–122) Based in part on these landmark trials, many centers today have adopted triple modality therapy consisting of surgery and adjuvant concurrent chemotherapy and RT (S-CRT) for advanced stage OCSCC. The basis of adding concurrent chemotherapy to adjuvant RT is that advanced tumors respond better to concurrent CRT rather than to RT alone. (123–126)

Table No. 2.2: Summary of Role of Radiotherapy and Chemoradiotherapy in Oral Cavity Cancer

	External Beam Radiotherapy (EBRT)	Chemotherapy	Interstitial Brachytherapy
Primary setting	• Early disease when patient intolerant of surgery • Early disease when anticipated cosmetic consequence of surgery is a concern, especially for lip cancer involving commissure • Unresectable disease, usually combined with chemotherapy • Advanced disease for patients intolerant of surgery due to poor performance status or comobidities	• Advanced disease or unresectable disease, in combination with radiotherapy	• Early and superficial welldefined tumor located more than 5 mm from the mandible
Adjuvant setting	• Unfavorable pathological features • Combined with chemotherapy for positive resection margins and extracapsular nodal extension	• Combined with radiotherapy for positive resection margins or extracapsular nodal extension	• Brachytherapy alone for positive resection margins • In combination with external beam radiotherapy to augment radiotherapy dose to the high risk area
Salvage setting	• Adjuvant treatment after salvage surgery • Primary treatment modality, usually combined with chemotherapy if further surgery is not feasible	• Combined with radiotherapy	• Especially useful for reirradiation: o for persistent or recurrent disease after previous radiation, o 2nd primary cancer occurrence within previous radiation field

2.2.2.9 Baseline Laboratory parameters

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. The complete blood cell count components (i.e., white blood cell count, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, and hemoglobin level) in the recent past have been found to be of prognostic value in regard to clinical outcomes in patients with malignant disorders. (127)

2.2.2.9.1 Hemoglobin

Anemia commonly occurs in patients with head and neck cancer and may be due to a number of causes, including comorbid illness, intraoperative blood loss, toxicity from chemotherapy and/or radiation, and malignancy-associated anemia of chronic disease. Anemia is commonly thought to enhance radioresistance via enhancing tumor hypoxia. Numerous retrospective studies have suggested a strong association between anemia and inferior local-regional control and survival among patients treated for HNSCC. (128–132) The optimal timepoint to assess anemia for the purposes of prognostication is unclear and varies widely throughout the literature. (133–135) Options include pretreatment hemoglobin, midradiation hemoglobin, postoperative hemoglobin, and drop in hemoglobin concentration during radiation. Due to colinearity in these measures, they all likely confer some degree of prognostic significance. The optimal hemoglobin cutpoint for defining anemia is also unclear, ranging from 10 to 14 g/dL, depending on the study. Two studies have shown a strong dose-response

relationship when hemoglobin is divided into quartiles, (133,134) suggesting that a single cutpoint for defining anemia may be inadequate.

2.2.2.9.2 White Blood Cell count (WBC)

The absolute white blood cell (WBC) count obtained from the CBC count has been historically used as a marker of infection and inflammation. It is a widely available tool for clinicians to identify the presence of infection and monitor the patient's response to treatment, such as antibiotics. Nonetheless, the role of the WBC count has gone beyond the assessment of infectious processes and it has become an important prognostic measurement of outcomes in cancer treatment. The inflammatory process that takes place during cancer development and progression are, in part, reflected in abnormalities of the WBC count. (127) In addition to hematologic malignancies, the WBC count has been reported to be of prognostic value in solid tumors. Pre-treatment leukocytosis, defined as a WBC count >10,000/μl, has been shown to be an independent prognostic factor of survival in cervical cancer (136) and non-small cell lung cancer patients. (137) A large study of 143,748 post-menopausal women conducted to determine the association of WBC count with the incidence of cancer and cancer mortality, concluded that women with higher WBC counts have an increased risk of developing invasive breast, colorectal, endometrial, and lung cancer, as well as a higher risk of overall mortality in breast and lung cancer. (138) However, a study of 278 patients with oral cancer failed to demonstrate any association between elevated WBC count and recurrence or further metastases. (139)

2.2.2.9.3 Absolute Neutrophil count (ANC)

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. (140,141) Neutrophils are central to this inflammatory response. The prognostic significance of the absolute neutrophil count (ANC) has been extensively studied, with evidence to suggest that blood neutrophils provide significant information when monitoring cancer progression, anticipating possible complications and assessing patient's tolerance to therapy. (142–144)

2.2.2.9.4 Absolute Lymphocyte Count (ALC)

The absolute lymphocyte count (ALC) has been studied in hematologic and solid malignancies as a marker of host antitumor immunity. Its prognostic significance has been evaluated during different clinical stages of cancer, including at diagnosis, at different phases of chemotherapy or radiation treatment, and after autologous stem-cell transplantation (ASCT). ALC is proven to be an independent prognostic factor for survival, and it is included in several validated prognostic scores, such as the IPS in advanced Hodgkin's Lyphoma.(145) A low ALC has been identified as an adverse prognostic factor associated to inferior OS in both hematological and solid malignancies.(145–148)

2.2.2.9.5 Absolute Monocyte Count

It has been postulated that monocytes promote tumor progression and support host antitumor immunity. Moreover, an increased monocyte count in the peripheral blood is considered a predictive factor of poor prognosis in cancer patients. There is substantial evidence

in advanced cancer that the host systemic immune response is an important independent predictor of outcome, and that pretreatment measurements of the systemic inflammatory immune response can be used to independently predict cancer survival. (149) Many studies have demonstrated that a high pretreatment monocyte count is an independent indicator of prognosis for patients with metastatic gastric cancer, (150) skin, (151) colon, (152) and oral cavity. (153)

2.2.2.9.6 Neutrophil-to-lymphocyte ratio (NLR)

The tumor microenvironment and, in particular, the inflammatory response play an important role in cancer development and progression and may be associated with systemic inflammation. (154,155) An elevated ratio of peripheral neutrophils-to-lymphocytes (NLR) has been recognized as a poor prognostic indicator in various cancers including oral cancer. (156) The mechanisms underlying the association of high NLR and poor outcome of cancer patients are poorly understood. One potential mechanism underlying the prognostic impact of NLR may be an association of high NLR with inflammation. Neutrophilia as an inflammatory response inhibits the immune system by suppressing the cytolytic activity of immune cells such as lymphocytes, activated T cells, and natural killer cells.(157,158) The importance of lymphocytes has been highlighted in several studies in which increasing infiltration of tumors with lymphocytes has been associated with better response to cytotoxic treatment and prognosis in cancer patients.(159) Thus, it can be assumed that in cancer patients NLR optimally represents the two opposing but interconnected pathways of the immune system .(160)

2.2.3 Timelines

2.2.3.1 Symptomatic diagnosis of cancer is important and has been the subject of considerable intervention in recent years to achieve timelier and earlier-stage diagnosis. A

Longer time to diagnosis may be detrimental in several ways: a more advanced stage at diagnosis, poorer survival, greater disease-related and treatment-related morbidity and adverse psychological adjustment. (161) Thus it is easy to presume that delay in diagnosis results in a larger cancer and a reduction in survival. However, it is unclear whether more timely cancer diagnosis brings favorable outcomes, with much of the evidence, in head and neck cancer, being equivocal. (162)

2.2.3.2 Physicians and patients are also often concerned regarding any prolonged treatment delay from the time of diagnosis of a squamous cell carcinoma of the head and neck. This concern stems from the belief that delays allow the growth of the local tumor and increase the likelihood of distant metastases. Clearly, delays that exceed a certain threshold will eventually result in progression. Patients with locoregionally advanced head and neck cancer (LAHNC) often present with many baseline difficulties that require social, dental, and nutritional interventions. Also, the treatment planning process for these complex tumors may take longer than that for other tumors. This process has become increasingly complex with the advent of treatment planning procedures that may include the fusion of magnetic resonance or positron emission images with computed tomographic (CT) images. (163) Current evidences fail to conclusively prove association between time to treatment initiation and survival, as some studies have shown positive association (164,165) and some have found to no association. (163)

2.2.3.3 The treatment time factor is a key element in oncology and generally, overall treatment time should be as short as reasonably possible especially in patients with locally advanced head and neck cancer. (166) Therefore, the importance of delays during a course of treatment has been emphasized in recent decades, and different recommendations on the delay-compensation options have been published. (167–169) However, treatment delays in completing

radiotherapy have been much more extensively studies as compared to other modalities (surgery/ chemotherapy or combination) in head and neck cancer. In, radiotherapy treated patients, fast tumor cell repopulation has been suggested as the main reason why prolonging overall treatment time (OTT) negatively affects local control (LC) and overall survival (OS) in many human tumors. (170) However, there is still a considerable lack of high-level evidence supporting this observation. (171)

2.2.4 Loss-adjusted survival of cancer patients

Cancer survival data is a key indicator for monitoring progress against cancer. There are several publications on oral cancer survival from all over the world, but in spite of it being a major public health problem studies from Indian subcontinent are sparse which is essentially due lack of adequate follow-up. The same is true for many developing countries, where health information systems are not well developed. Sufficient follow-up is the key for estimating survival because if the proportion of cases lost to follow-up is substantial and if the loss to follow-up is correlated with the probability of death (prognosis) of the patient after he or she was lost the survival estimates likely to be biased (172). Socio-demographic and clinical characteristics of patients may help to predict loss to follow-up as the losses are also likely to be related to the patient's prognosis: low social status is related to lack of continuous patient surveillance; extent of disease is related to the motivation of follow-up, etc. Thus, Information on the association between prognostic factors and loss to follow-up can be used to reduce the bias in estimates of survival (173). Ganesh et al. in 1995 (174) proposed a method to reduce this bias by computation of loss-adjusted survival. This method takes into consideration differential losses, by assuming that patients lost to follow-up within strata defined by certain 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 patients lost to follow-up and with complete follow-up to be more similar within a prognostic group, than when all patients are considered together. The difference between the crude actuarial survival and the loss adjusted value thus indicates the magnitude of the effect of differential loss to follow-up (173).

CHAPTER 3

AIMS AND OBJECTIVES

3.1 Aim

To determine and study factors affecting survival in oral cavity cancer patients.

3.2 Primary Objectives

3.2.1 To compute overall survival of oral cavity cancer patients.

3.2.2 To identify the difference in survival with regards to subsite, clinical extent and stage of the disease at diagnosis, Lymph node involvement including histopathological characteristics, treatment modalities and selected baseline laboratory parameters.

3.3.3 To evaluate the effect of demographic factors, Lifestyle factors (smoking, tobacco chewing, alcohol etc), major co-morbidities on overall survival of oral cavity cancer patients.

3.3. Secondary Objective

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

3.3.2 To study patterns and factors which contribute to loss to follow-up and to compute loss adjusted follow-up for the associated factors.

CHAPTER 4

MATERIAL AND METHODS

4.1 Study Design:

The study was a retrospective analysis of hospital records of oral cavity cancer patients from the Tata memorial hospital (TMH) cancer registry. All Oral cancer patients who are residents of Mumbai and registered in TMH from 01 January 2006 to 31 December 2008 were included in the study.

4.2 Inclusion Criteria:

- All newly diagnosed oral cavity cancer patients registered in TMH between 01st January 2006 to 31st December 2008.
- Oral cavity cancer patients who are residents of Mumbai (who have been residing in Mumbai for more than 1 year)
- All cases who have completed atleast 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 Attributes of the study cohort:

4.4.1 Oral Cavity Cancer cases: Patients with cancer of following subsites (table- 2) were included as Oral cavity cancer in the study.

Table 4.1: Subsites of oral cavity included in the study with ICD Codes

Sl. No.	Subsite (ICD code as per ICD-10)	Specific site (nomenclature as per AJCC manual 7th edition) with ICD-10 codes	Specific site (nomenclature as per Medical records of TMH) with ICD-10 codes
1.	**Lip (C00) Excludes skin of lip**	Mucosa of Upper lip (C00.3)	Upper lip (C00.3)
		Mucosa of Lower lip (C00.4)	Lower lip (C00.4)
2.	**Tongue (C02) Excludes base of tongue**	Dorsal surface of tongue (C02.0)	Dorsal surface of tongue (C02.0)
		Tongue border (C02.1)	Tongue border (C02.1)
		Ventral surface of tongue (C02.2)	Ventral surface of tongue (C02.2)
		Anterior 2/3rd of tongue (C02.3)	Anterior 2/3rd of tongue (C02.3)
		Tongue, NOS (C02.9)	Tongue, NOS (C02.9)
3.	**Gum (C03)**	Upper Gum (C03.0)	Upper Alveolar (C03.0)
		Lower Gum (C03.1)	Lower Alveolar (C03.1)
		Gum, unspecified (C03.9)	Alveolar, unspecified (C03.9)
4.	**Floor of mouth (C04)**	Floor of mouth, Unspecified (C04.9)	Floor of mouth, Unspecified (C04.9)
5.	**Hard Palate (C05.0)**	Hard Palate (C05.0)	Hard Palate (C05.0)
6.	**Other and Unspecified parts of mouth (C06)**	Cheek Mucosa (C06.0)	Buccal Mucosa (C06.0)
		Vestibule of mouth (C06.1)	Mouth vestibule (C06.1) **(includes buccal and labial sulcus)**
		Retromolar Area (C06.2)	Retromolar Trigone (C06.2)

4.4.2 Newly Diagnosed Cases: Patients who had the first diagnosis confirmed at TMH.

4.4.3 Prior Treated Cases: Those patients who have received any form of partial or complete cancer directed treatment before registration at TMH.

4.4.4 Completed cancer directed treatment: Patients who had received atleast one modality of cancer directed treatment i.e surgery, radiotherapy, chemotherapy either alone or in combination as per treatment planned in TMH.

4.4.5 No/ Incomplete cancer directed treatment: Patient who had not received or not accepted treatment, or those patients who had taken incomplete treatment at TMH or patients in whom treatment status was unknown as per the hospital records.

4.4.6 Residents of 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 1 year.

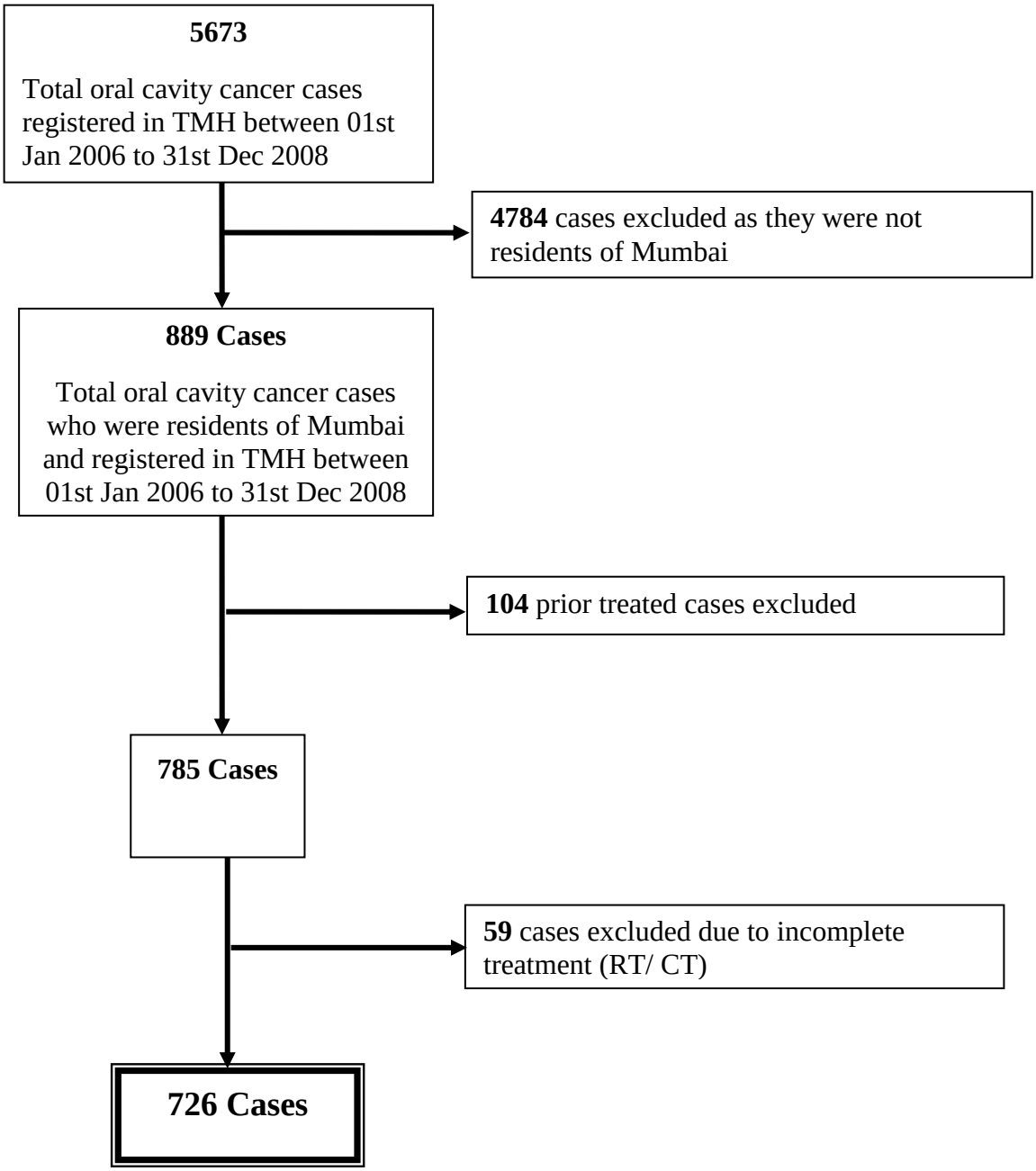
4.5 Period of enrolment:

All oral cavity cancer patients registered in TMH between 01st January 2006 to 31st December 2008

4.6 Sample Size:

Records of 726 oral cavity cancer patients were selected as per the inclusion and exclusion criteria (Fig 4.1) and retrospectively analyzed.

Fig 4.1. Flowchart for selection of cases



4.7 Data Collection:

Data of the following factors was retrieved from the patient file and hospital based electronic medical record system (EMR).

4.7.1 Demographic variables

4.7.1.1 Age: This refers to the age in completed years on the date of registration in TMH. The date was calculated from the date of birth of the patient mentioned in the hospital records till the date of registration.

4.7.1.2 Gender: Gender of the patient was recorded as male/ female.

4.7.1.3 Marital Status: Marital status at the time of registration was recorded as Unmarried/ Married/ Widow/ Widower.

4.7.1.4 Education Status: Educational Status at the time of registration was recorded illiterate/ school level (Primary, Middle or Higher secondary)/ college and above.

4.7.2 Disease (tumor) related factors

4.7.2.1 Specific subsite: Specific site of the tumor was recorded from the medical records as per the ICD-10 coding and the clinical notes.

4.7.2.2 Primary Histology: Primary histological type of the tumor was obtained from the biopsy reports (Squamous Cell Carcinoma/ Mucoepidermoid Carcinoma/ others).

4.7.2.3 TNM Staging: Details of TNM staging was obtained from the clinical notes in the medical records. All patients were staged according to the seventh edition of the American Joint committee on cancer (AJCC) staging manual on TNM classification system.

4.7.2.4 Histological characteristic of the tumor: Details of the histological characteristics of the tumor such as tumor grade, tumor size (maximal cross-sectional diameter of a resected tumor), skin involvement, bone involvment, perineural invasion, lymphovascular invasion, histological lymph node involvement and extrcapsular spread was obtained histopathological reports of the surgical specimen.

4.7.3 Treatment Given: Details of the cancer directed treatment i.e surgery, radiotherapy, chemotherapy either alone or in combination provided, was obtained from the patient's medical records and the hospital based electronic medical record system (EMR).

4.7.4 Baseline laboratory parameters: Pretreatment counts of certain heamatological factors namely heamoglobin levels, total white blood cell count, and absolute neutrophil, lymphocyte and monocyte counts were obtained from the medical

records. 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.

4.7.5 Co-morbid conditions: Presence of following co-morbid conditions was obtained from medical records.

- Hypertension
- Diabetes Mellitus
- Ischeamic heart disease
- Asthama
- Human immunodeficiency virus positivity.

4.7.6 Lifestyle habits: Presence/ absence of following Lifestyle habits was obtained from medical records. However further details such as age of starting, duration of use, per day consumption etc were not available in the patient's medical records.

- Cigarette
- Beedi
- Tobacco chewing
- Alcohol consumption
- Pan masala chewing
- Use of Mishri
- Betel nut chewing
- Gutkha chewing

4.7.7 Timelines: Following time periods for each patient was calculated for each patient.

4.7.7.1 Time between registration and diagnosis: Time between registration to diagnosis was calculated as time from date of registration to the date of pathological reporting of malignancy at TMH.

4.7.7.2 Time between diagnosis and commencement of treatment: Time between diagnosis and treatment commencement was calculated as time from date of pathological reporting of malignancy to the date surgery or date of Ist cycle of chemotherapy or date of Ist fraction of planned dose of Radiotherapy, or in case of multimodality treatment, date of initiation of whichever modality of treatment given first to the patient.

4.7.7.3 Time between treatment commencement and treatment completion:

Time between treatment commencement to treatment completion was calculated as follows depending on the type of treatment administered to the patient.

- **Patients treated with only Surgery:** From date of surgery to date of discharge.
- **Patients treated with only Radiotherapy:** From date of giving Ist fraction of planned dose to date of administering the last fraction.
- **Patients treated with more than one modality of treatment:** From date of initiation of whichever modality of treatment given first to the last date of last modality of treatment given to the patient.

- **Overall treatment time:** From the date of registration at Tata Memorial hospital to completion of Cancer Directed Treatment (CDT) at this centre

4.8 Statistical Analysis:

The only event in this study was death due to any cause. Patients' overall survival duration (OS) 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. The Overall survival was calculated by using actuarial method (20) and the difference in survival rates with regards to various factors were studied univariately by Kaplan-Meier method (21) and the log-rank test (175). The Cox-regression model (176) was used to investigate the effect of these factors simultaneously on overall survival in a multifactorial setting. All statistical analyses were performed using the Statistical Package for Social Science program (SPSS for Windows, version 20, SPSS, Chicago, IL). A probability, p value < 0.05 was considered to be statistically significant.

4.8.1 Statistical Analysis for timelines:

Time periods in days were calculated from date of registration to diagnosis, diagnosis to treatment commencement and treatment commencement to treatment completion. These periods have been described in median, minimum and maximum period. The median time was taken as cut-off for categorization of time period and for analysis of its effect on overall survival using Kaplan-Meier method and the log-rank test.

4.8.2 Computation of Loss-adjusted survival:

Loss-Adjusted Survival Rate (LAR) a method proposed by Ganesh (174) in 1995 was applied to obtain the corrected survival rates for various groups. Loss-adjusted survival is estimated under the assumption that survival of patients lost to follow-up is the same as that for patients with known follow-up time and have similar characteristics of different prognostic factors at first entry. Thus, using this method the estimated deaths in those with complete follow-up were calculated and then subsequently, these estimates were applied to those with incomplete follow-up to get expected deaths. A standard framework, such as the actuarial one, was then applied with the sum of observed and expected outcome events. The above methods along with mathematical derivations are described in detail elsewhere. (173,174)

CHAPTER 5

RESULTS

5.1 Descriptive Analysis: Medical records of 726 pathologically proven oral cancer patients were retrospectively analyzed. Distribution of these patients as per patient characteristics and tumor related factors is presented in succeeding paragraphs.

5.1.1 Age and gender distribution: The age and gender distribution of all patients is summarized in table 5.1.1. As shown, the overall median age was 51 years (range: 18-85 years), and the percentage of males and females were 72.9% and 27.1% respectively. Maximum number of case were in the age group 40 to 49 yrs at the time of diagnosis and more than 50% of cases were diagnosed between 40 to 60 years for both males as well as females. The median age of diagnosis for males (50 yrs) was slightly less than females (53 yrs) and almost 20% of males were less than 40 yrs as compared to only 13% in females.

Table 5.1.1: Distribution as per age and gender of patients

Age (years)	Males (%)	Females (%)	Total (%)
< 40	104 (19.7)	26 (13.2)	130 (17.9)
40 to 49	155 (29.3)	50 (25.4)	205 (28.2)
50 to 59	150 (28.4)	48 (24.4)	198 (27.3)
60 to 69	97 (18.3)	52 (26.4)	149 (20.5)
≥ 70	23 (4.3)	21 (10.7)	44 (6.1)
Total	529 (100%)	197 (100%)	726 (100%)
Median Age (All patients)	51 Years (Range: 18-85 years)		
Median Age (Male patients)	50 Years (Range: 18-85 years)		
Median Age (Female patients)	53 Years (Range: 18-85 years)		

5.1.2 Education Status: 76.3% of patients were found to be literate with almost 50% patients reported to have high school or above level of education (table 5.1.2). Only 23.7% patients were found to be illiterates.

Table 5.1.2: Distribution as per education status of patient

Education Status	Number (%)
Illiterate	172 (23.7)
Primary School	162 (22.3)
Middle School	28 (3.9)
High School	257 (35.4)
Graduation and above	107 (14.7)
Total	726 (100%)
Illiterate	172 (23.7)
Literate	554 (76.3)

5.1.3 Marital Status: Majority of the patients (83.7%) were married and only 5% were found to be unmarried (table 5.1.3).

Table 5.1.3: Distribution as per marital status of patient

Marital Status	Number (%)
Unmarried	37 (5.0)
Married	608 (83.7)
Widow/ widower	81 (11.1)

5.1.4 Blood group: Distribution of patients as per blood group is presented in table 5.1.4. As shown, B^{+ve} (31.%) was the most common and AB^{+ve} was the least common blood group.

Table 5.1.4: Distribution as per blood group of the patient

Blood Group	Number (%)	Blood Group (Rh group)	Number (%)
A	201 (27.7)	**A Positive**	193 (26.6)
		A Negative	8 (1.1)
B	239 (32.9)	**B Positive**	226 (31.1)
		B Negative	13 (1.8)
AB	61 (8.4)	**AB Positive**	59 (8.1)
		AB Negative	2 (.3)
O	225 (31.0)	**O Positive**	216 (29.8)
		O Negative	9 (1.2)

5.1.5 Lifestyle habits: Gender wise distribution of lifestyle habits has been depicted in table 5.1.5. Tobacco chewing (54.5%) was the most common habit in both the sexes combined. Males were found to have much higher frequency of smoking (Cigarette/ Biddi) and gutkha use, whereas females were found to use mishri and betal nut more as compared to males. 17.2% patient's reported of drinking alcohol of which 98.4% were males. 30.5% of the female patients did not have any form of lifestyle habit as compared to only 11.9% males. Overall, of the 726 oral cavity cancer patients 83.1% (both sexes combined) were found to have some form of lifestyle habit.

Table 5.1.5: Distribution of lifestyle habits as per gender

Lifestyle habits	Males (%)	Females (%)	Total (%)
Cigarette smoking	119 (22.5)	1(0.5)	120(16.5)
Biddi smoking	68 (12.9)	2 (1)	70 (9.6)
Tobacco chewing	312 (42.6)	84 (59)	396 (54.5)
Paan Masala	44 (6.1)	12 (8.3)	56 (7.7)
Gutkha	89 (16.8)	6 (3)	95 (13.1)
Mishri	16 (3)	50 (25.4)	66 (9.1)
Betul nut chewing	94 (17.8)	46 (23.4)	140 (19.3)
Alcohol consumption	122 (23.1)	3 (1.5)	125 (17.2)
Use of alcohol and tobacco together	**110 (20.8)**	**3 (1.5)**	**113 (15.6)**
Use of more than one tobacco product	**137 (25.9)**	**24 (12.2)**	**161 (22.2)**
No Habit (not even betul nut)	**63 (11.9)**	**60 (30.5)**	**123 (16.9)**

5.1.6 Comorbidity: Record of five main comobidities namely Hypertension, Diabetes mellitus, Heart Disease, Asthma and Human Immunodeficiency Virus (HIV) infection was obtained from the medical records of the patients and their distribution is given in table 5.1.6. 247 (34%) cases were found to have single or multiple comobidities and Hypertension (24.7%) was the most commonest comorbidity among all patients.

Table 5.1.6: Distribution as per co-morbidities

Co-morbidities	**Number (%)**
Hypertension	179 (24.7)
Diabetes mellitus	102 (14)
Heart Disease	29 (4)
Others (Asthma and HIV)	22 (3)
Hypertension and Diabetes	52 (7.2)
Co-morbidity present (any of the above mentioned)	**247 (34)**

5.1.7 Subsites of oral cavity: Tongue (C02) and cheek Mucosa (C06.0) were the leading sites, contributing to more than 60% of total patients. Lip, Hard palate and Floor of the mouth were found to be the least common sites and all three combined contributed to less than 10% of all patients (table 5.1.7).

5.1.8 TNM Staging: All the 726 patients were staged according to the seventh edition of the American Joint committee on cancer (AJCC) staging manual on TNM classification system. 56% (385) cases had clinical lymph node involment at the time of presentation (table 5.1.8). Majority of cases 69% were found to have advanced stage disease (stage III/ IV) at the time of diagnosis (table no 5.1.9).

Table 5.1.7: Distribution as per subsites of oral cavity

Sl. No.	Subsite (ICD code as per ICD-10)	Specific site (nomenclature as per AJCC manual 7th edition) with ICD-10 codes	Specific site No. (%)	Subsite Total (%)
1.	**Lip (C00) Excludes skin of lip**	Mucosa of Upper lip (C00.3)	2 (0.2)	**22 (3.0)**
		Mucosa of Lower lip (C00.4)	20 (2.6)	
2.	**Tongue (C02) Excludes base of tongue**	Dorsal surface of tongue (C02.0)	5 (0.7)	**229 (31.5)**
		Tongue border (C02.1)	216 (29.7)	
		Ventral surface of tongue (C02.2)	1 (0.1)	
		Anterior 2/3rd of tongue (C02.3)	7 (1)	
3.	**Gum (C03)**	Upper Gum (C03.0)	14 (2)	**112 (15.4)**
		Lower Gum (C03.1)	97 (13.3)	
		Gum, unspecified (C03.9)	1 (0.1)	
4.	**Floor of mouth (C04)**	Floor of mouth, Unspecified (C04.9)	16 (2.2)	**16 (2.2)**
5.	**Hard Palate (C05.0)**	Hard Palate (C05.0)	20 (2.8)	**20 (2.8)**
6.	**Other and Unspecified parts of mouth (C06)**	Cheek Mucosa (C06.0)	232 (32.0)	**232 (32.0)**
		Vestibule of mouth (C06.1)	74 (10.2)	**74 (10.2)**
		Retromolar Area (C06.2)	21 (2.9)	**21 (2.9)**
Total				**726 (100%)**

Table 5.1.8: Distribution as per clinical T and N classification

Classification	N0	N1	N2	N3	Total
T 1	78	17	8	0	104
T 2	145	50	28	1	227
T 3	26	18	19	0	66
T 4	92	116	122	6	329
Total	341	201	177	7	726
**** No case has distant metastasis (All cases were M0)**					

Table 5.1.9: Distribution as per TNM Stage

TNM Stage	Number (%)
Stage I	78 (10.7)
Stage II	145 (20)
Stage III	111 (15.3)
Stage IV	392 (54)
Total	726 (100%)

5.1.9 Primary Tumor Histology: Squamous Cell Carcinoma was the most common primary tumor histology and other histological variants were very few accounting for only 2.6% cases (table 5.1.10).

Table 5.1.10: Distribution as per primary tumor histology

Sl. No.	Tumor Histology	Number (%)
1.	Squamous Cell Carcinoma, Nos	558 (76.9)
2.	Squamous Cell Carcinoma, Keratinising, NOS	144 (19.8)
3.	Squamous Cell Carcinoma, Sarcomatoid	5 (0.7)
4.	Verrucous Carcinoma, Nos	14 (1.8)
5.	Basaloid squamous cell carcinoma	2 (0.3)
6.	Mucoepidermoid Carcinoma	2 (0.3)
7.	Myoepithelial carcinoma	1 (0.1)
Squamous Cell Carcinoma		**707 (97.4)**

5.1.10 Treatment: Surgery individually or in combination with Radiotherapy/ Chemotherapy was the main modalities of treatment adopted in all stages of oral cancer. In stage I the main modality of treatment was only surgery (75.6%), whereas in Stage II, III and IV the most common form treatment given to the patients was surgery in combination with radiotherapy. 24% of stage IV patients received a combination of all three modalities of treatment. 55 cases did not receive any form of surgical intervention (table5.1.11)

Table 5.1.11: Distribution as per <u>treatment and stage</u>

Stage	Type of treatment					
	Surgery only	**Radiotherapy only**	**Surgery + Radiotherapy**	**Surgery + Radiotherapy + Chemotherapy**	**Radiotherapy + Chemotherapy**	**Total**
I (%)	59 (75.6)	1 (1.3)	16 (20.5)	2 (2.6)	0 (0.0)	**78 (100)**
II (%)	65 (44.8)	1 (0.7)	63 (43.4)	16 (11.0)	0 (0.0)	**145 (100)**
III (%)	42 (37.8)	3 (2.7)	46 (41.4)	20 (18.0)	0 (0.0)	**111 (100)**
IV (%)	96 (24.5%)	20 (5.1)	152 (38.8)	94 (24.0)	30 (7.7)	**392 (100)**
Total	**262 (36.1)**	**25 (3.4)**	**277 (38.2)**	**132 (18.2)**	**30 (4.1)**	**726 (100)**

5.1.11 <u>Histopathological Features</u>: Histological characteristics of the tumor were obtained from histopathological reports of 671 cases that had undergone surgical intervention. The distribution of these histological features is as follows

5.1.11.1 Tumor Size: 75% (488) of the 671 surgically treated patients had tumor size of more than 2 cms of which 28% (137) had tumor of more than 4 cms (Table 5.1.12)

Table 5.1.12: Distribution as per tumor size (histopathological, n=671)

Size in greatest dimension	Number (%)
2 cms or less	183 (25.2)
2.1 – 4 cms	351 (48.3)
4.1 – 6 cms	122 (16.8)
6.1 – 8 cms	11 (1.5)
More than 8 cms	4 (0.6)
Total	671 (100)

5.1.11.2 Infiltration into surrounding tissue: 27.4% cases showed histological evidence of bone infiltration, whereas skin involvement was seen only in 7.7 % cases. Similarly, lymphvascular involvement was also seen in only 1.9% cases and perineural invasion was seen in 18.9% of surgically treated cases (table 5.1.13).

Table 5.1.13: Distribution as per infiltration/ invasion into surrounding tissues (histopathological, n=671)

Infiltration/ Invasion	Number (%)
Skin	52 (7.7)
Bone	184 (27.4)
Lymphovascular	13 (1.9)
Perineural	127 (18.9)

5.1.11.3 Lymph Node Involvment (histopathological): Information on histopathological node involvement was not available for 142 cases (Non surgically treated cases = 55 + Lymph nodes not dissected = 87). Out of the remaining 584 cases almost 50% were

positive for nodal metastatsis and bilateral nodal involvement was seen in only 7.3% cases (table 5.1.14). Extracapsular spread (ECS) was seen in 224 (38.3%) cases.

Table 5.1.14: Distribution as per lymph node involvement *(n=584)*

Lymph Node involvement	Number (%)
Nodes Negative for metastasis	293 (50.1)
Ipsilateral Positive	243 (41.0)
Contralateral Positive	5 (0.8)
Bilateral Positive	43 (7.3)
Extracapsular spread Positive	224 (38.3)

5.2. Survival Analysis of oral cavity cancer (All cases, n= 726)

5.2.1 Overall Survival: Patients' overall survival (OS) was calculated as the time interval between the date of diagnosis and the date of death or the date of last follow-up. The closing date for recording the last follow-up was taken as 31st December 2014. Out of the 726 patients, at the end of follow-up (31st Dec 2014), 329 (45.3%) patients had expired, and 397 (54.7%) were censored. The median follow-up period was 31 months (range, 1 to 103 months). The 5 year overall survival of the cohort calculated by using actuarial method was found to be 52% (table 5.2.1).

Table 5.2.1: Overall survival

Total Number	Survival in percentage				
	1 Yr	2 Yr	3 Yr	4 Yr	5 Yr
726	78	62	57	54	52

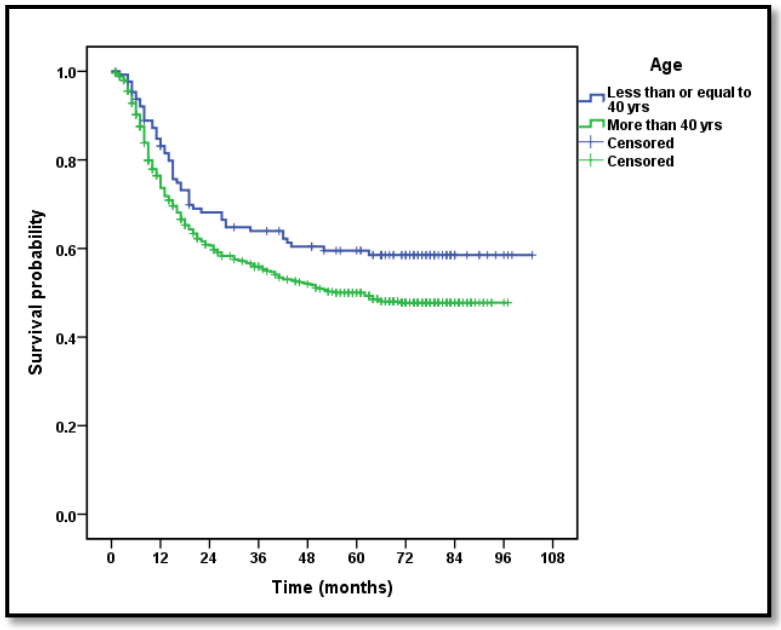
5.2.2 Survival according to Age: Patients were categorized according to several cut-offs of age at registration and its effect on survival was analyzed using Kaplan-Meier curves and the log-rank test. The difference in 5 yr overall survival rate between age group less than 40 yrs, 40-49, 50-59, 60-69 and more than 70 yrs was not found to be statistically significant (table 5.2.2). Similarly, no significant difference in 5yr survival was observed in age groups formed by taking median age i.e 51 yrs or 65 yrs as a cut-off. However, when 40 yrs was taken a cut-off, it was observed that patients with age less than 40 yrs had a 5yr survival of 58.5% and those of age 40 yrs and above had a 5 yr survival of 49.3%, this difference was found to be statistically significant (p=0.03) (Fig. 5.2.1).

Table 5.2.2: Observed survival rate (%) according to age

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
Age (years)							
< 40	130	83.1	68.2	63.9	60.4	58.5	0.22
40 to 49	205	73.4	56.7	52.7	50.9	50.3	
50 to 59	198	75.4	65.0	58.5	53.4	50.6	
60 to 79	149	73.6	61.2	57.9	52.0	47.5	
≥ 70	44	67.4	57.8	52.8	47.4	44.4	
Age (as per median age 51 yrs)							
≤ 51	360	77.2	62.0	56.9	54.3	52.6	0.45
> 51	366	73.5	62.1	57.5	52.7	49.8	
Age (as per cut-off of 65 yrs)							
<65	649	75.8	61.9	57.2	53.6	51.8	0.38
≥ 65	77	71.7	63.2	58.7	52.5	45.9	
Age (as per cut-off of 40 yrs)							
< 40	130	83.1	68.2	63.9	60.4	58.5	**0.03**
≥ 40	596	73.7	60.7	55.9	52.0	49.3	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Age < 40 Yrs	1						**0.03**
Age ≥ 40 Yrs	1.37 (1.01 – 1.85)						

**Calculated using Log Rank Test*

Figure 5.2.1: Observed survival rate (%) of oral cancer according to age



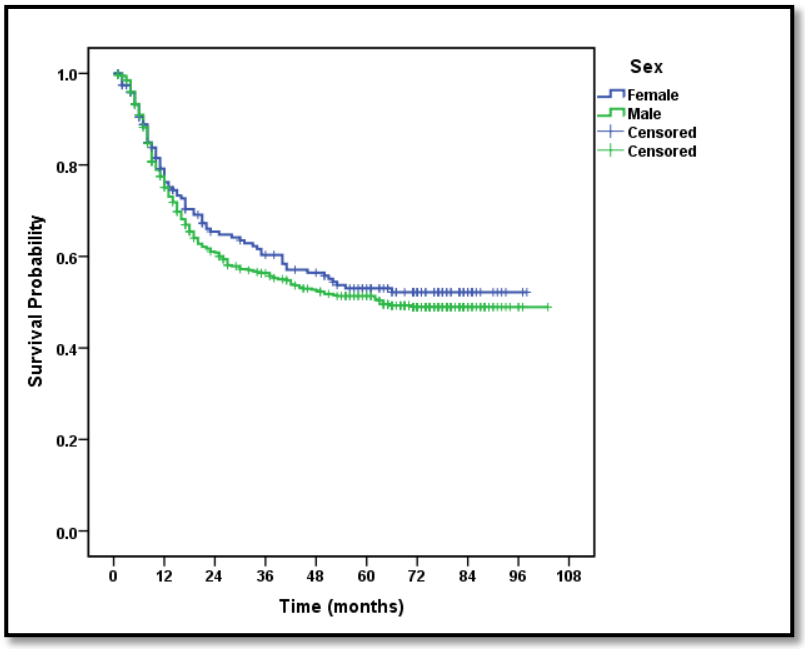
5.2.3 Survival according to Gender: A 5 yr survival rate for males and females was found to be 50.6% and 53% respectively (table 5.2.3), but this difference was not statistically significant (p=0.43) (Fig. 5.2.2).

Table 5.2.3: Observed survival rate (%) according to gender

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Gender							
Male	529	75.1	60.8	56.4	52.3	50.6	0.43
Female	197	79.2	65.4	60.3	56.4	53.0	

**Calculated using Log Rank Test*

Figure 5.2.2: Observed survival rate (%) according to gender



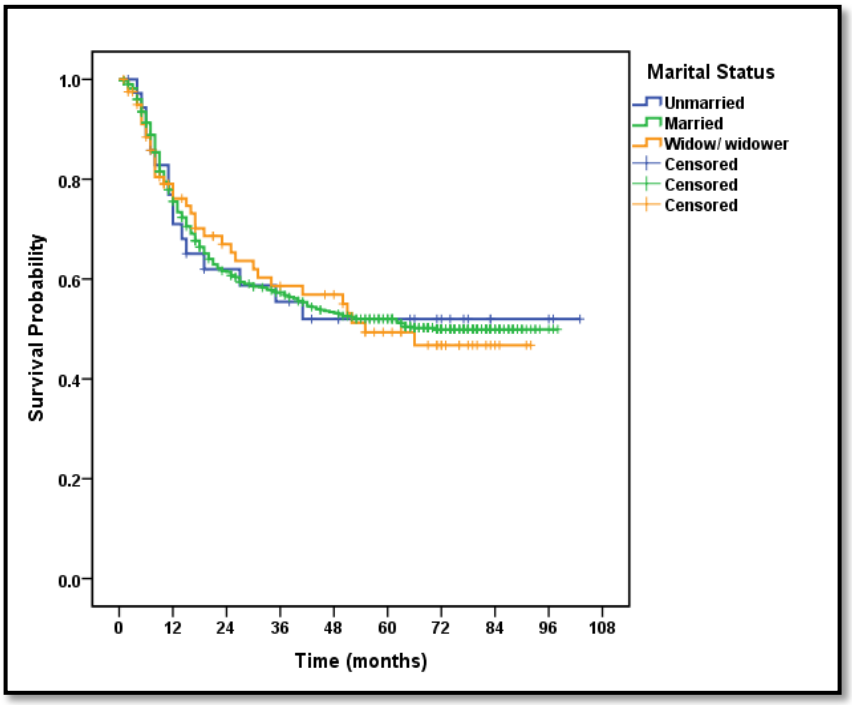
5.2.4 Survival according to Marital Status: The patients were divided into three categories as per their marital status reported at the time of registration. No significant (p=0.99) difference in survival was observed between the three groups namely unmarried, married or widow/ widower (table 5.2.4) (Fig. 5.2.3).

Table 5.2.4: Observed survival rate (%) according to marital status

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
Marital Status							
Unmarried	37	76.9	62.0	55.5	52.0	52.0	0.99
Married	608	75.6	61.4	57.3	53.2	51.3	
Widow/ widower	81	76.1	65.3	58.6	55.0	49.3	

**Calculated using Log Rank Test*

Figure 5.2.3: Observed survival rate (%) according to marital status



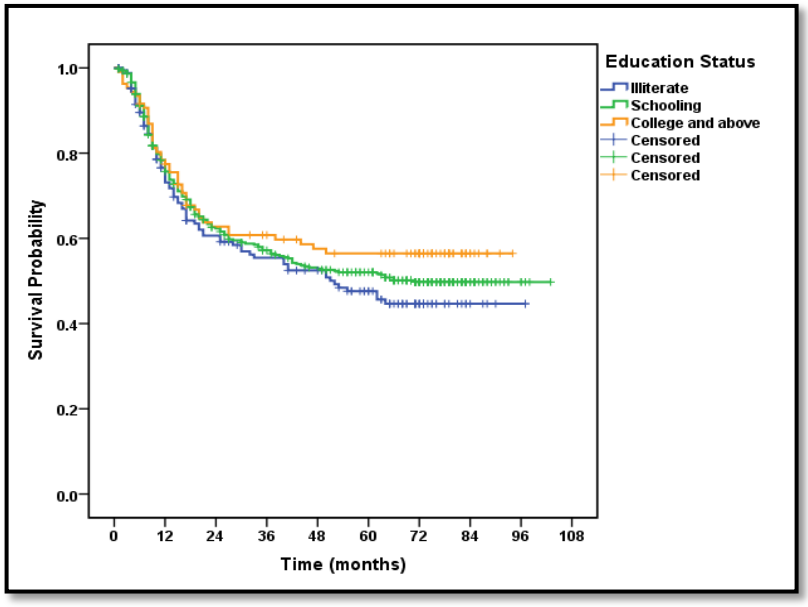
5.2.5 Survival according to Educational Status: The education level reported by the patient at the time of registration was taken into consideration for classifying the patient as per educational status. The 5yr survival rate was found to be highest for patients with educational qualification of college and above (56.5%), followed by those who had done any level of schooling (51.7%) and lowest survival rate was found to be of illiterate (45.7%) patients (table 5.2.5). However, this difference in 5yr survival between the three levels of education failed to attain statistical significance (p=0.34) (Fig. 5.2.4).

Table 5.2.5: Observed survival rate (%) according to education status

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
Education Status							
Illiterate	172	73.1	59.2	54.0	50.8	45.7	0.34
Schooling	447	75.7	62.4	56.4	52.9	51.7	
College and above	107	77.4	62.8	59.7	57.5	56.5	

**Calculated using Log Rank Test*

Figure 5.2.4: Observed survival rate (%) according to education status



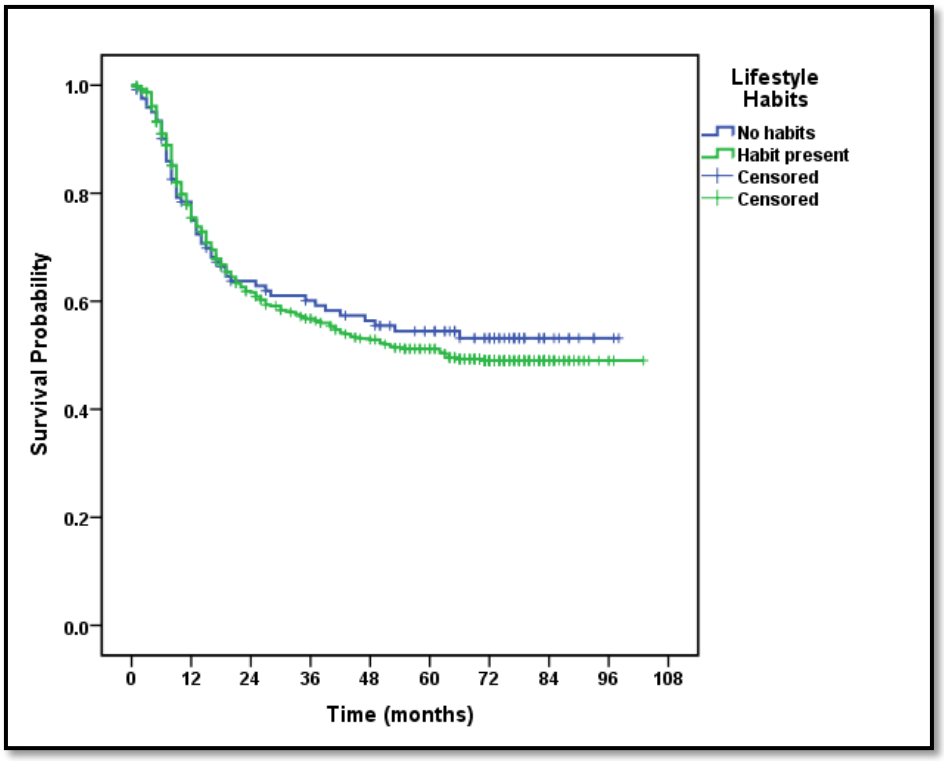
5.2.6 Survival according to Lifestyle Habits: Patients having habit of any form/ type of tobacco or alcohol were grouped in one category. There was no significant (p> 0.60) difference in survival between patients having or not having a lifestyle habit (table 5.2.6) (Fig. 5.2.5).

Table 5.2.6: Observed survival rate (%) according to presence of any habit (including smoking, any type of tobacco chewing and alcohol consumption)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Lifestyle habits							
Absent	123	75.0	62.8	60.1	56.4	54.5	0.60
Present	603	75.5	61.6	56.8	52.9	50.5	

**Calculated using Log Rank Test*

Figure 5.2.5: Observed survival rate (%) according to presence of lifestyle habit



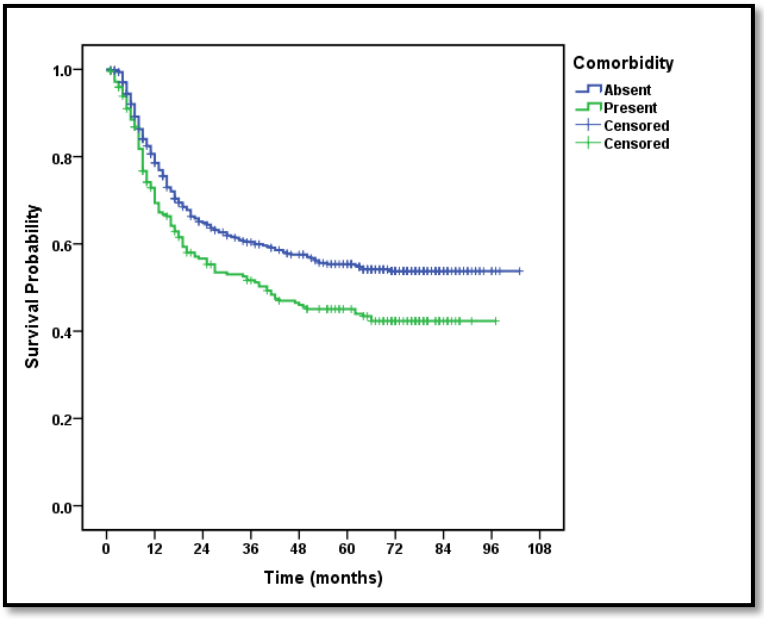
5.2.7 Survival according to Comorbidity: Oral cancer patients having a concomitant comorbidity (Hypertension, Diabetes mellitus, Heart Disease, Asthma and HIV) were found to have significantly lower survival (p<0.001) as compared to patients without any comorbidity (Fig. 5.2.6). On univariate analysis cases with comobidity were found to have unadjusted hazard of 1.38 (1.10 - 1.72) of outcome as compared to those without comorbidity (table 5.2.7).

Table 5.2.7: Observed survival rate (%) according to presence of comorbidity

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Comorbidity							
Absent	479	78.5	64.9	59.9	57.5	55.1	<0.001
Present	247	69.4	55.3	51.2	46.0	44.0	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						<0.001
Present	1.38 (1.10 - 1.72)						

**Calculated using Log Rank Test*

Figure 5.2.6: Observed survival rate (%) according to presence of comorbidity

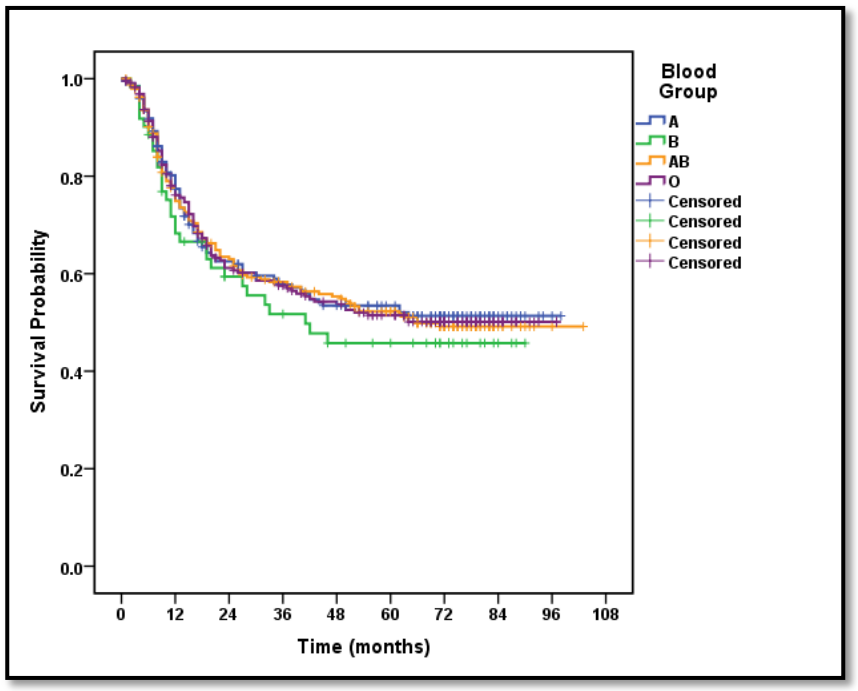


5.2.8 Survival according to Blood Group: No significant difference (p=0.85) in 5yr survival was observed in oral cancer patients when they were categorized as per their blood groups (table 5.2.8) (Fig. 5.2.7).

Table 5.2.8: Observed survival rate (%) according to blood group

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Blood Group							
A	201	77.4	62.0	57.8	53.5	52.0	0.85
B	239	77.6	63.0	57.3	55.3	51.7	
AB	61	68.3	59.4	51.7	45.8	45.8	
O	225	76.1	61.2	57.0	53.7	50.1	

Figure 5.2.7: Observed survival rate (%) according to blood group



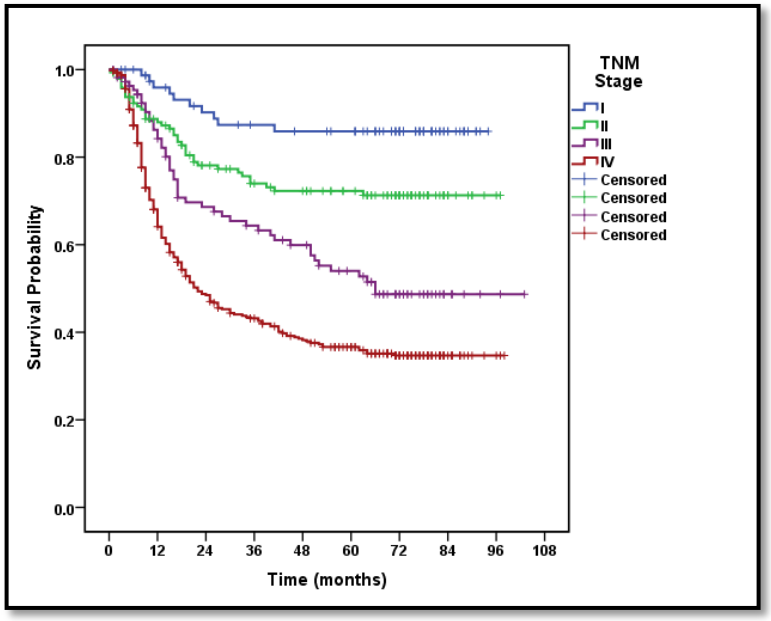
5.2.9 Survival according to TNM staging: TNM stage was found to significantly affect overall survival (p<0.001) (Fig. 5.2.8). Stage IV had the lowest 5yr survival rate of 35.9% and stage I had the highest survival rate of 84.7% (table 5.2.9). Thus, higher stages were found to have poorer prognosis as compared to lower stages.

Table 5.2.9: Observed survival rate (%) according to TNM Stage

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
TNM Stage							
I	78	94.7	89.2	86.2	84.7	84.7	<0.001
II	145	86.8	76.9	73.8	71.1	69.9	
III	111	84.2	68.6	63.3	57.6	52.8	
IV	392	64.1	48.5	42.6	38.2	35.9	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
I	1						
II	2.32 (1.15 – 4.65)						0.01
III	4.27 (2.16 – 8.45)						<0.001
IV	7.07 (3.75 – 13.33)						<0.001

**Calculated using Log Rank Test*

Figure 5.2.8: Observed survival rate (%) according to TNM Stage



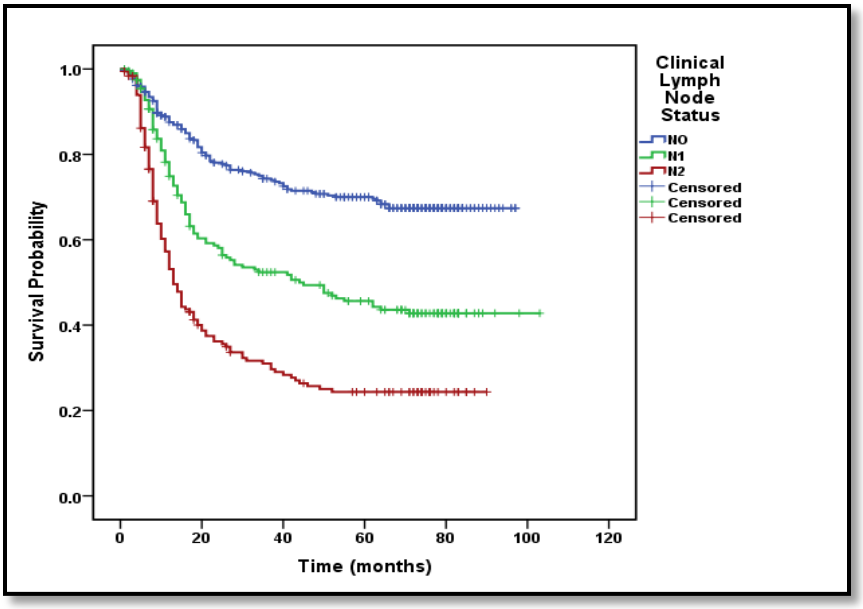
5.2.10 Survival according to Lymph Node Involvement ("N" Classification): Clinical lymph node status was found to be significantly associated with overall survival (Fig. 5.2.9). Patients with lymph node involvement had poorer survival as compared to node negative (N0) patients (table 5.2.10).

Table 5.2.10: Observed survival rate (%) according to nodal status

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
N Classification							
N0	341	87.5	77.7	74.0	70.4	69.6	<0.001
N1	201	74.9	58.1	52.4	49.4	44.3	
N2	184	53.1	35.6	31.0	25.7	24.2	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
N0	1						
N1	2.11 (1.60 – 2.78)						<0.001
N2	3.86 (2.96 – 5.04)						<0.001

**Calculated using Log Rank Test*

Figure 5.2.9: Observed Survival rate (%) according to Clinical Lymph Node status



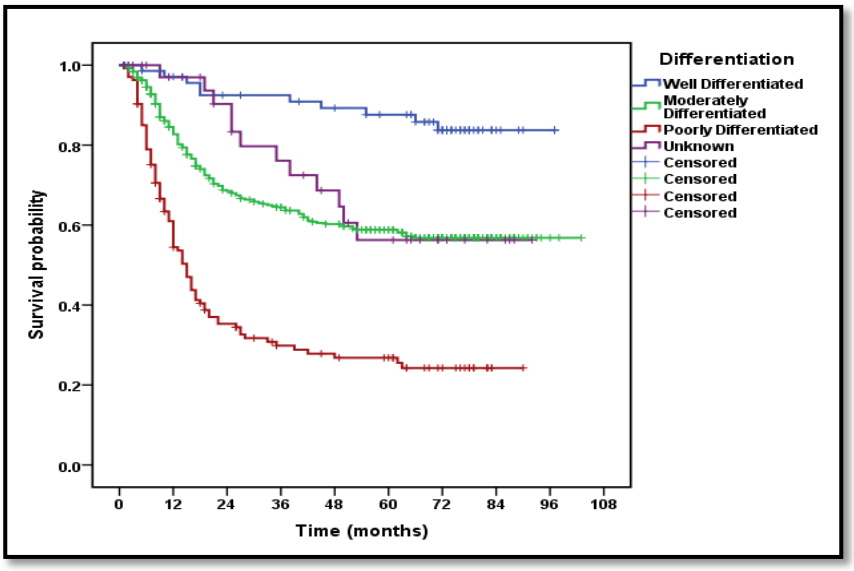
5.2.11 Survival according to differentiation (n=671): Patients having Poorly differentiated tumor were found to have the worst 5yr survival of 25.5%, whereas well and moderately differentiated tumors had better survival of 87.6% and 58.2% respectively (table 5.2.11) (Fig. 5.2.10). Tumor differentiation of 40 patients was unknown, however 5yr survival rate of these patients was not found to be significantly (p <0.001) different from well/ moderately differentiated tumors (table 5.2.11).

Table 5.2.11: Observed survival rate (%) according to tumor differentiation (n=671)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
Differentiation							
Well Differentiated	74	97.1	92.5	90.9	89.3	87.6	<0.001
Mod. Differentiated	423	82.7	68.5	63.6	60.3	58.2	
Poorly Differentiated	134	54.5	35.3	29.8	26.8	25.5	
Unknown	40	97.0	83.3	76.1	68.7	56.2	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Well Differentiated	1						
Mod.Differentiated	3.47 (1.83 – 6.58)						<0.001
Poorly Differentiated	9.48 (4.93 – 18.27)						<0.001
Unknown	2.76 (0.97 – 6.47)						0.18

**Calculated using Log Rank Test*

Figure 5.2.10: Observed survival rate (%) according to tumor differentiation



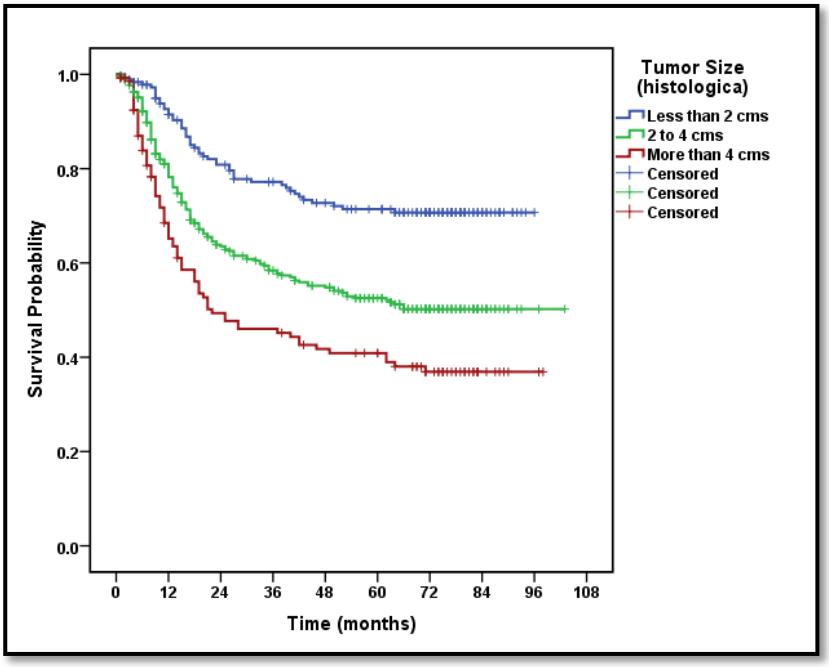
5.2.12 Survival according to Tumor size (Histopathological) (n=671): 5 yr survival rate of oral cavity cancer patients was found to be significantly associated with size of the primary tumor (Fig. 5.2.11). Patients with tumor size of more than 4 cms had poorer prognosis as compared to patients with smaller size tumors (table 5.2.12).

Table 5.2.12: Observed survival rate (%) according as per tumor size

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5Yr	
Size in greatest dimension (n=671)							
2 cms or less	183	91.5	80.8	77.2	72.7	70.7	<0.001
2.1 – 4 cms	351	78.2	63.9	58.4	54.8	52.1	
More than 4 cms	137	65.2	49.4	45.2	41.7	39.0	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
2 cms or less	1						
2.1 – 4 cms	2.01 (1.46 - 2.78)						<0.001
More than 4 cms	3.02 (2.11 – 4.33)						<0.001

**Calculated using Log Rank Test*

Figure 5.2.11: Observed Survival rate (%) according as per tumor size



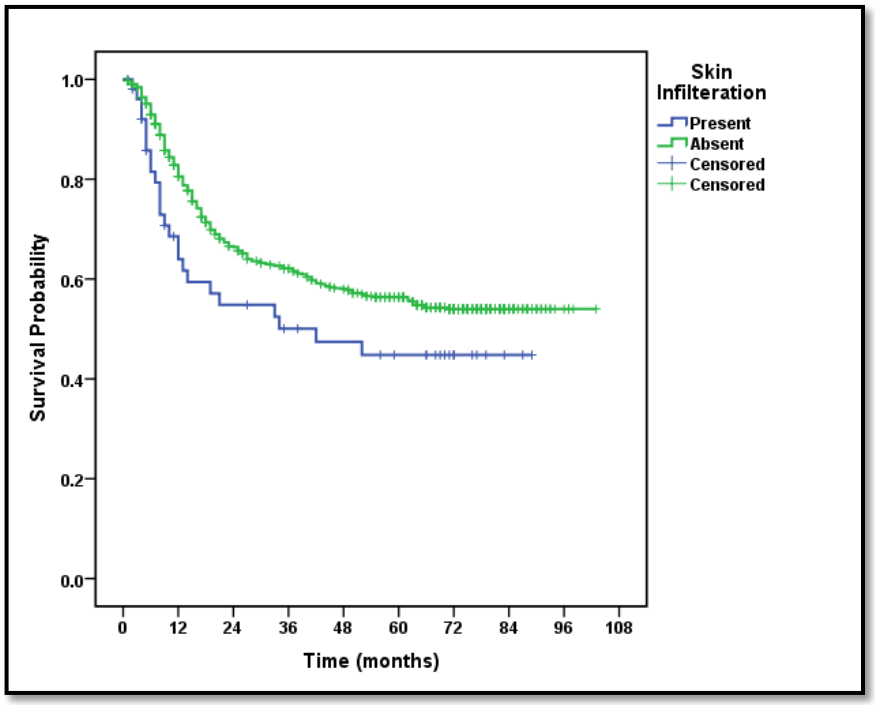
5.2.13 Survival according to skin infiltration (n=671): 5 yr survival of patients having skin infiltration was found to be 44.8% and for those not having skin infiltration was found to be 55.7% (table 5.2.13). However, this difference in survival rate failed to achieve statistical significance (p=0.06) (Fig. 5.2.12).

Table 5.2.13: Observed Survival rate (%) according to skin infiltration

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Skin Infiltration (n=671)							
Absent	619	80.5	66.4	62.1	58.0	55.7	0.06
Present	52	64.0	54.8	50.1	47.4	44.8	

**Calculated using Log Rank Test*

Figure 5.2.12: Observed Survival rate (%) according as per skin infiltration



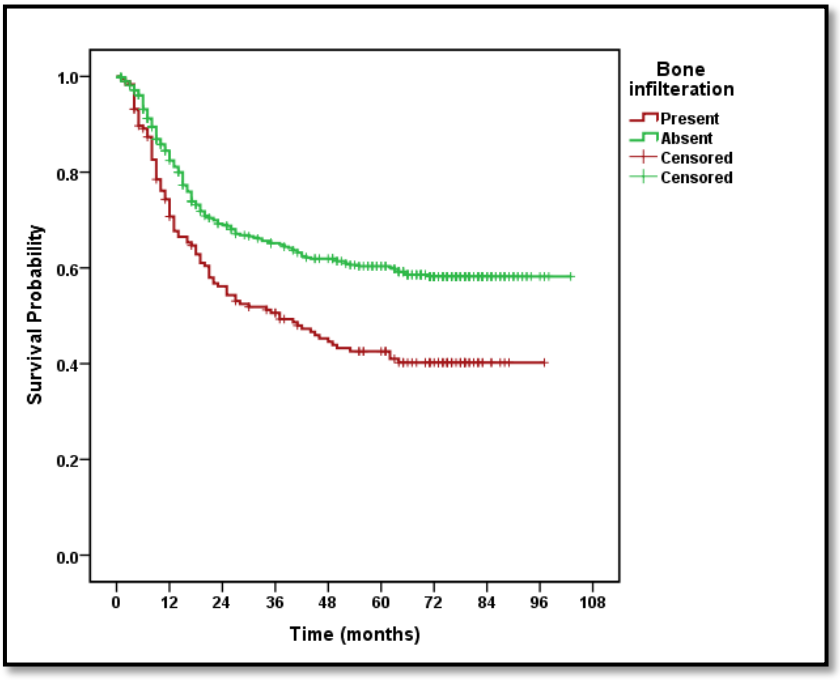
5.2.14 Survival according to bone infiltration (n=671): Patients with bone infiltration on histology were found to have significantly lower survival (p<0.001) as compared to patients without any bone involvement (Fig. 5.2.13). On univariate analysis cases with presence of bone involvement was found to have unadjusted hazard of 1.66 (1.29 - 2.12) of outcome as compared to those without evidence bone infiltration (table 5.2.14).

Table 5.2.14: Observed survival rate (%) according to bone infiltration

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Bone Infiltration (n=671)							
Absent	487	82.5	69.0	65.2	61.9	60.1	<0.001
Present	184	70.7	56.1	50.6	44.6	41.0	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						<0.001
Present	1.66 (1.29- 2.12)						

**Calculated using Log Rank Test*

Figure 5.2.13: Observed survival rate (%) according as per bone infiltration



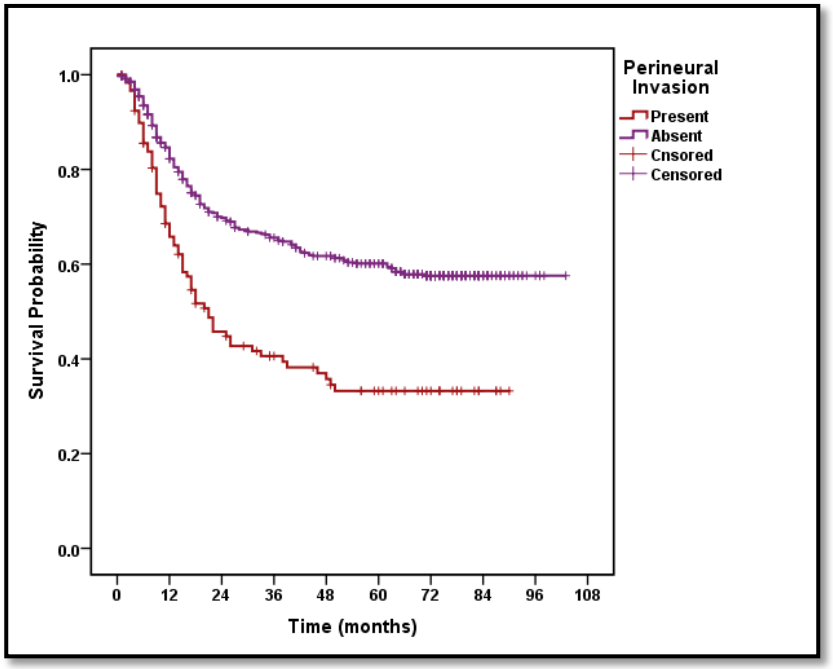
5.2.15 Survival according to Perineural invasion (PNI) (n=671): Presence of perineural invasion on histology was found to significantly affect the survival adversely. Patients with PNI had 5yr survival of only 31.2% as compared to 61.0% in those patients without PNI (table 5.2.15) (Fig. 5.2.14).

Table 5.2.15: Observed survival rate (%) according perineural invasion

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Perineural invasion (n=671)							
Absent	544	82.8	70.8	66.5	62.6	61.0	<0.001
Present	127	64.4	43.0	38.1	33.6	31.2	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						<0.001
Present	2.26 (1.74- 2.94)						

**Calculated using Log Rank Test*

Figure 5.2.14: Observed survival rate (%) according as per perineural invasion



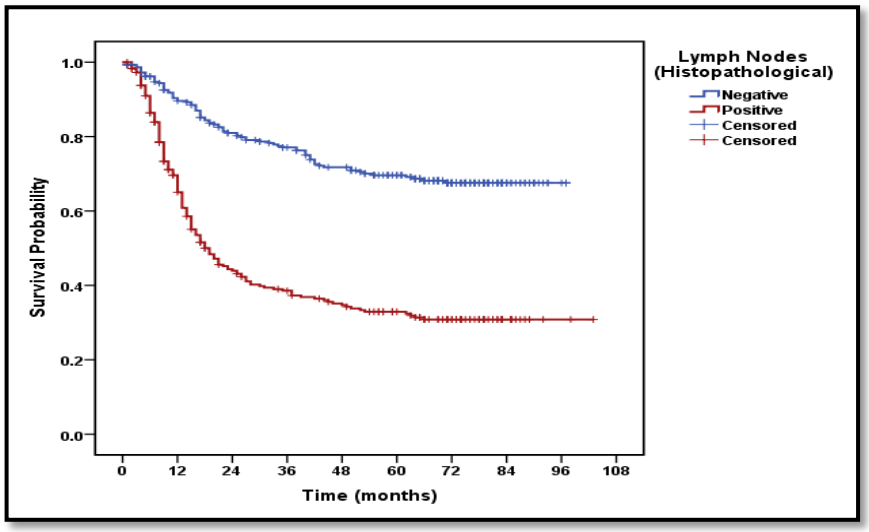
5.2.16 Survival according to histopathological Lymph Node involvement (n=584): Out of 671 patients who underwent surgical treatment, neck dissection reports were available for 584 patients, out of which 291 patients were positive for nodal metastasis. 5 yr survival for node negative and node positive patients was found to be 69.1% and 32.4% respectively (table 5.2.16) (Fig. 5.2.15).

Table 5.2.16: Observed survival rate (%) according to histopathological lymph node involvement *(n=584)*

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Lymph Node involvement (n=584)							
Nodes Negative for metastasis	293	89.6	81.0	77.1	71.8	69.1	<0.001
Nodes Positive for metastasis	291	65.1	43.9	38.6	34.7	32.4	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Nodes Negative for metastasis	1						<0.001
Nodes Positive for metastasis	3.21 (2.47 - 4.16)						

**Calculated using Log Rank Test*

Figure 5.2.15: Observed survival rate (%) as per histopathological lymph node involvement *(n=584)*



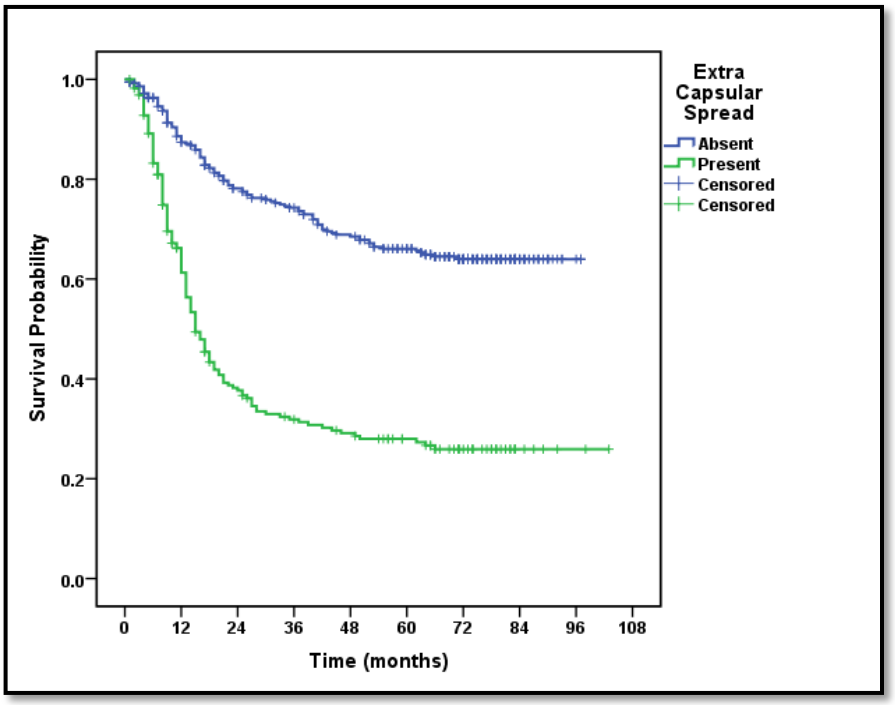
5.2.17 Survival according to Extra Capsular Spread (ECS) (n=584): Positive ECS was found in 224, these patients were found to have significantly lower 5 yr survival of 27.3% as compared to 65.7% in patients found negative for ECS (table 5.2.17) (Fig. 5.2.16).

Table 5.2.17: Observed survival rate (%) according to extra capsular spread

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Extra Capsular Spread (n=584)							
ECS negative	360	87.4	78.1	74.3	68.5	65.7	<0.001
ECS positive	224	61.3	37.7	31.9	28.6	27.3	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
ECS negative	1						<0.001
ECS positive	3.30 (2.58 - 4.22)						

**Calculated using Log Rank Test*

Figure 5.2.16: Observed survival rate (%) according as per extra capsular spread

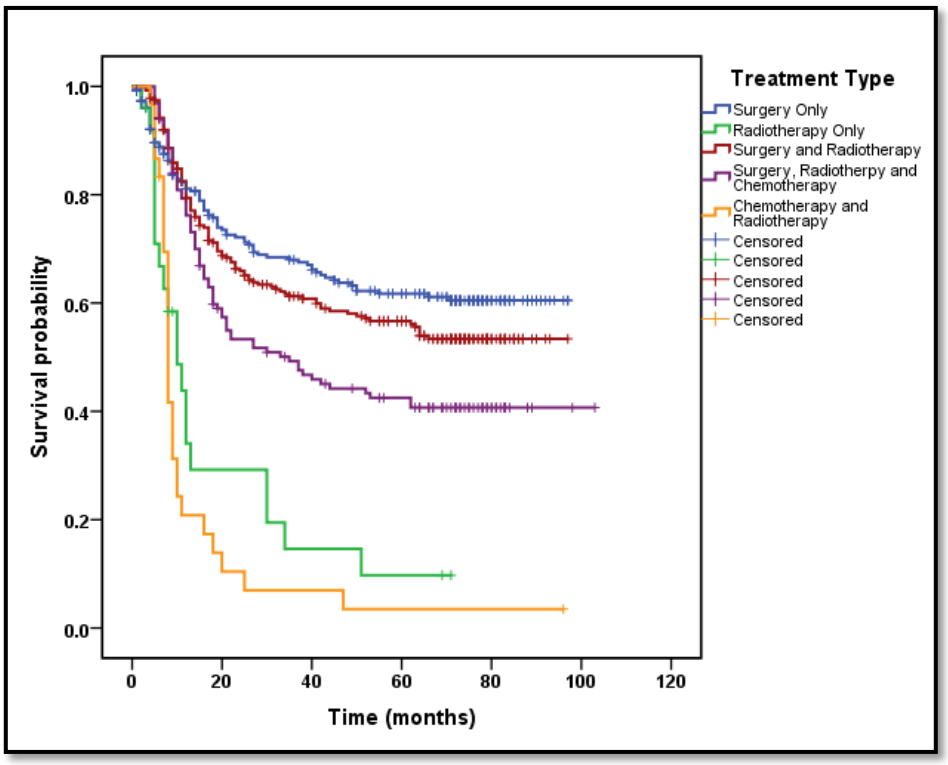


5.2.18 Survival according to Treatment: Surgery individually or in combination with Radiotherapy/ chemotherapy was the main modality of treatment. Out of 726 patients except for 55 cases, all other patients received surgery. These non-surgically treated cases had the lowest 5yr survival i.e 9.7% and 3.5%, for only radiotherapy, and chemotherapy plus radiotherapy respectively (Fig. 5.2.17). Out of the 671 surgically treated cases, only surgically treated cases had the highest 5 yr survival of 61.7% and the patients who received all the three modalities of treatment namely Surgery, Radiotherapy and Chemotherapy had the lowest survival of 40.7% (table 5.2.18).

Table 5.2.18: Observed survival rate (%) according to treatment

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
Treatment							
Surgery only	262	81.1	72.1	68.0	63.7	61.7	<0.001
Radiotherapy only	25	43.8	29.2	14.6	14.6	9.7	
Surgery + Radiotherapy	277	794	66.3	61.3	58.1	56.1	
Surgery + Radiotherapy + Chemotherapy	132	76.2	54.9	49.3	44.2	40.7	
Radiotherapy + Chemotherapy	30	20.8	10.4	6.9	3.5	3.5	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Surgery only	1						
Radiotherapy only	4.43 (2.72 – 7.22)						<0.001
Surgery + Radiotherapy	1.18 (0.89 – 1.56)						0.22
Surgery + Radiotherapy + Chemotherapy	1.67 (1.23 – 2.27)						<0.001
Radiotherapy + Chemotherapy	6.16 (3.99 – 9.50)						<0.001

Figure 5.2.17: Observed survival rate (%) according to type of treatment



5.2.19 Multifactorial analysis for determining independent prognostic factors for overall survival:

All the factors which were found to influence overall survival in univariate analysis, such as age (≥ 40yrs), presence of comorbidity, overall stage, lymph node involvement, histological tumor size, treatment modality, tumor differentiation, bone infiltration, perineural invasion and extra capsular spread were considered for further multifactorial analysis. However, as overall TNM stage includes tumor size and lymph node involvement, in order to avoid interaction between these factors two models were developed, one with overall TNM stage and other taking tumor size and lymph node involvement separately, keeping all the other variables same in both the models. The results showed that age of 40 yrs or more (HR = 1.60, 95% CI = 1.14 - 2.24; P <0.001), presence of comorbidity (HR = 1.58, 95% CI = 1.23 - 2.03; p<0.001), poor tumor

differentiation (HR = 1.92, 95% CI = 1.193 - 3.092; p <0.001), perineural invasion (HR = 1.45, 95% CI = 1.09 - 1.91; p <0.001), extra capsular spread (HR = 2.33, 95% CI = 1.79 – 3.04; p<0.001), advanced TNM stage (HR = 1.96, 95% CI = 1.37 - 2.80; p<0.001) (table 5.2.18), lymph node involvement (HR = 1.48, 95% CI = 1.11 - 1.97; p= <0.001) and tumor size of more than 4 cms (HR = 1.83, 95% CI = 1.23 – 2.74; p= 0.02) (table 5.2.19) were found to be independent predictors for poor overall survival of oral cavity cancer patients.

Table 5.2.19: Univariate and multifactorial analysis of prognostic factors for overall survival in patients with oral cavity cancer

Model-1

Parameter	No. of cases	Univariate		Multifactorial	
		HR (95% CI)	p value	HR (95% CI)	p value
Age (< 40 yrs)	130	1		1	
Age (≥ 40 yrs)	596	1.37 (1.01 – 1.85)	0.03	**1.60 (1.14 - 2.24)**	**<0.001****
Comorbidity (Absent)	479	1		1	
Comorbidity (Present)	247	1.38 (1.10 - 1.72)	<0.001	**1.58 (1.23 - 2.03)**	**<0.001****
Differentiation					
Well Differentiated	74	1		**1**	
Moderately Differentiated	423	3.47 (1.83 – 6.58)	<0.001	1.87 (0.97 – 3.59)	0.05
Poorly Differentiated	134	9.48 (4.93 – 18.27)	<0.001	**4.18 (2.11 – 8.25)**	**<0.001****
Unknown	40	2.76 (0.97 – 6.47)	0.18	1.61 (0.69 – 3.78)	0.26
Early Stage (TNM I &II)	223	1			
Advanced Stage (TNM III &IV)	503	3.48 (2.56 – 4.74)	<0.001	**1.96 (1.37 - 2.80)**	**<0.001****
Bone Infiltration (Absent)	487	1			
Bone Infiltration (Present)	184	1.66 (1.29- 2.12)	<0.001		0.45
Perineural invasion (Absent)	544	1		1	
Perineural invasion (Present)	127	2.26 (1.74- 2.94)	<0.001	**1.45 (1.09 - 1.91)**	**<0.001****
ECS (Absent)	360	1		1	
ECS (Present)	224	3.30 (2.58 - 4.22)	<0.001	**2.33 (1.79 – 3.04)**	**<0.001****
Treatment				--	0.25
Surgery only	262	1			
Radiotherapy only	25	4.43 (2.72 – 7.22)	<0.001		
Surgery + Radiotherapy	277	1.18 (0.89 – 1.56)	0.22		
Surgery + Radiotherapy + Chemotherapy	132	1.67 (1.23 – 2.27)	<0.001		
Radiotherapy + Chemotherapy	30	6.16 (3.99 – 9.50)	<0.001		

§ Abbreviations: HR, hazard ratio; CI, confidence interval; ECS, Extra capsular spread
** Significant (p value <0.05)

Table 5.2.20: Univariate and multifactorial analysis of prognostic factors for overall survival in patients with oral cavity cancer

Model-2

Parameter	No. of cases	Univariate		Multifactorial	
		HR (95% CI)	p value	HR (95% CI)	p value
Age (< 40 yrs)		1		1	
Age (≥ 40 yrs)	(130/ 596)	1.37 (1.01 – 1.85)	0.03	**1.59 (1.13 - 2.23)**	**<0.001****
Comorbidity (Absent)		1		1	
Comorbidity (Present)	(479 / 247)	1.38 (1.10 - 1.72)	<0.001	**1.55 (1.21 – 1.99)**	**<0.001****
Differentiation					
Well Differentiated	74	1		**1**	
Moderately Differentiated	423	3.47 (1.83 – 6.58)	<0.001	**1.98 (1.03 – 3.81)**	**0.04****
Poorly Differentiated	134	9.48 (4.93 – 18.27)	<0.001	**4.44 (2.48 – 8.76)**	**<0.001****
Unknown	40	2.76 (0.97 – 6.47)	0.18	1.63 (0.69 – 3.82)	0.26
Tumor Size					
< 2cms	183	1		1	
2- 4 cms	351	2.01 (1.46 - 2.78)	<0.001	1.30 (0.91 - 1.85)	0.14
> 4cms	137	3.02 (2.11 – 4.33)	<0.001	**1.83 (1.23 – 2.74)**	**<0.001****
Lymph node (Absent)	341	1		**1**	
Lymph node (Present)	385	2.81 (2.22 – 3.56)	<0.001	**1.48 (1.11 - 1.97)**	**<0.001****
Bone Infiltration (Absent)	487	1			0.62
Bone Infiltration (Present)	184	1.66 (1.29- 2.12)	<0.001		
Perineural invasion (Absent)	544	1			
Perineural invasion (Present)	127	2.26 (1.74- 2.94)	<0.001	**1.38 (1.04 - 1.82)**	**0.02****
ECS (Absent)	360	1			
ECS (Present)	224	3.30 (2.58 - 4.22)	<0.001	**2.24 (1.69 – 2.95)**	**<0.001****
Treatment				--	0.16
Surgery only	262	1			
Radiotherapy only	25	4.43 (2.72 – 7.22)	<0.001		
Surgery + Radiotherapy	277	1.18 (0.89 – 1.56)	0.22		
Surgery + Radiotherapy + Chemotherapy	132	1.67 (1.23 – 2.27)	<0.001		
Radiotherapy + Chemotherapy	30	6.16 (3.99 – 9.50)	<0.001		

§ Abbreviations: HR, hazard ratio; CI, confidence interval; ECS, Extra capsular spread, ** Significant (p value <0.05)

Early Disease (TNM Stage I and II)

5.3 Survival Analysis of Early Stage Oral Cavity Cancer (n= 223)

5.3.1 Overall Survival: At the end of follow-up (31st Dec 2014) out of the 223 patients, , 48 (21.5%) patients had expired, and 175 (78.5%) were censored. The median follow-up period was 66 months (range, 1 to 97 months). The 5-year overall survival of the cohort calculated by using actuarial method was found to be 77% (table 5.3.1).

Table 5.3.1: Overall survival of early stage oral cancer

Total Number	Survival in percentage				
	1 Yr	2 Yr	3 Yr	4 Yr	5 Yr
223	91	82	79	77	77

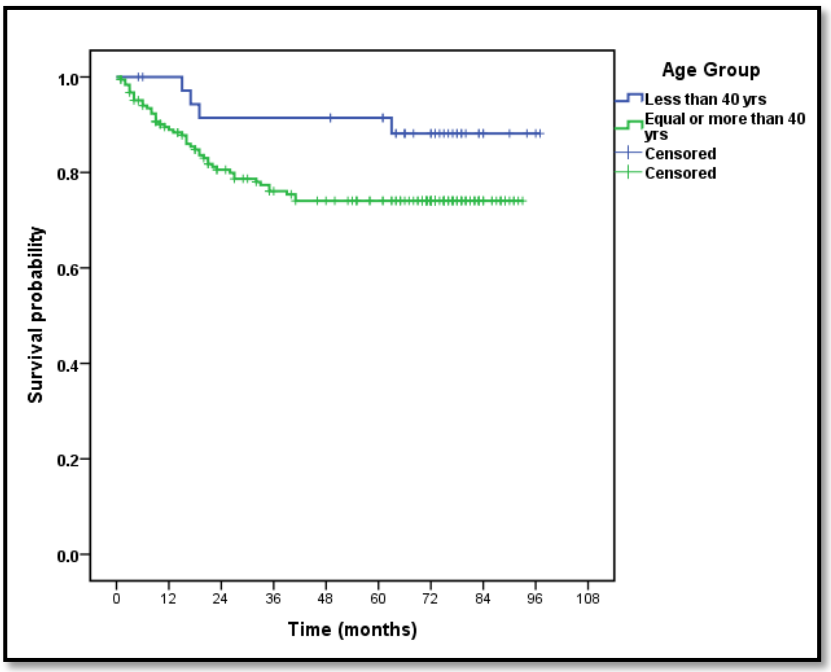
5.3.2 Survival according to Age: Patients were categorized according to cut-offs based on age at registration and its effect on survival was analyzed using Kaplan-Meier curves and the log-rank test. The difference in 5 yrs overall survival rate between age group less than 40 yrs, 40-49, 50-59, 60-69 and more than 70 yrs was not found to be statistically significant (table 5.3.2). Taking, 40 yrs as a cut-off, it was observed that patients with age less than 40 yrs had a 5yr survival of 88.2% and those of age 40yrs and above had a 5yr survival of 74.1%, however this difference was not found to be statistically significant (p=0.06) (Fig. 5.3.1).

Table 5.3.2: Observed survival rate (%) of early stage cancer according to age

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Age (years)							
< 40	37	100	91.4	88.2	88.2	88.2	0.27
40 to 49	62	90.3	77.9	76.0	74.1	74.1	
50 to 59	61	86.4	81.0	73.2	69.1	69.1	
60 to 69	46	95.3	85.6	80.2	80.2	80.2	
≥ 70	17	74.6	74.6	74.6	74.6	74.6	
Age (as per cut-off of 40 yrs)							
< 40	37	100	91.4	88.2	88.2	88.2	0.06
≥ 40	186	88.9	80.6	76.1	74.1	74.1	

**Calculated using Log Rank Test*

Figure 5.3.1: Observed survival rate (%) of early stage oral cancer according to age



5.3.3 Survival according to Gender, Marital and Educational Status: A 5 yr survival rate for males and females was found to be 74.7% and 82.3% respectively (table 5.3.3), but this difference was not statistically significant (p=0.25). Patients were categorized as per their marital and educational status at the time of registration. No significant difference was seen in 5 yr survival of patients based on marital and educational status (table 5.3.3).

Table 5.3.3: Observed survival rate (%) of early stage cancer according to gender, marital status and education

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Gender							
Male	170	89.7	80.1	76.8	75.5	74.7	0.25
Female	53	91.9	89.7	84.8	82.3	82.3	
Marital Status							
Unmarried/ Widow/ Widower/ Divorced	31	100	96.0	91.4	86.6	86.6	0.12
Married	192	89.2	80.3	76.7	75.5	74.9	
Education Status							
Illiterate	39	94.3	91.1	84.4	81.1	81.1	0.54
Schooling	129	90.3	80.1	76.4	74.6	73.5	
College and above	55	87.1	81.5	79.6	79.6	79.6	

**Calculated using Log Rank Test*

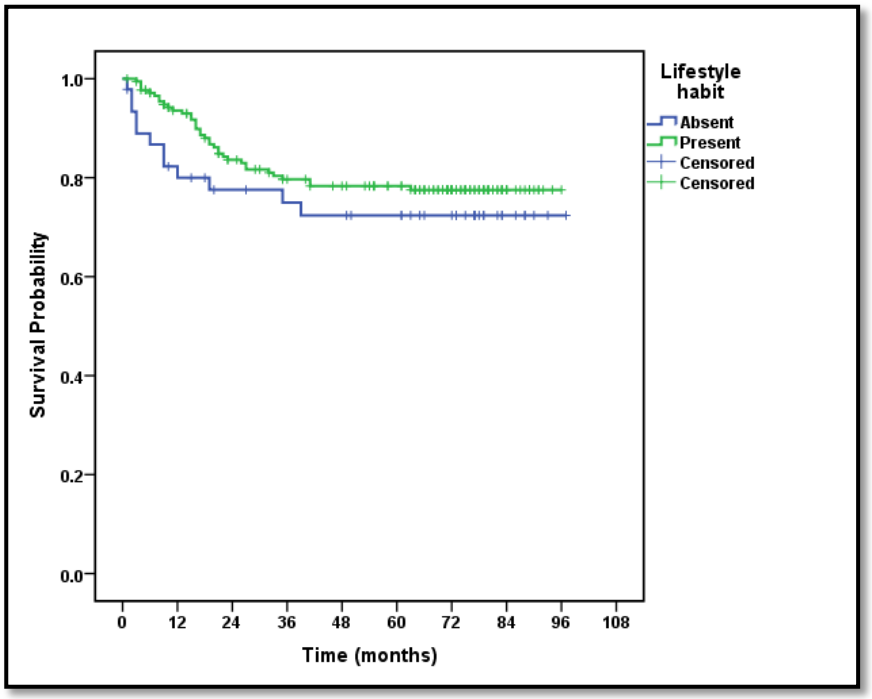
5.3.4 Survival according to Lifestyle Habits: Patients having habit of any form/ type of tobacco or alcohol were grouped in one category and their effect on survival was analyzed. There was no significant (p= 0.30) difference in survival between patients having or not having a lifestyle habit (table 5.3.4) (Fig. 5.3.2).

Table 5.3.4: Observed survival rate (%) according to presence of any habit (including smoking, any type of tobacco chewing and alcohol consumption)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Lifestyle habits							
Absent	46	80.0	77.6	75.0	72.4	72.4	0.30
Present	177	93.6	83.6	79.7	78.3	77.5	

**Calculated using Log Rank Test*

Figure 5.3.2: Observed survival rate (%) according to presence of lifestyle habit



5.3.5 Survival according to Comorbidity: Early stage oral cancer patients having a concomitant comorbidity (Hypertension, Diabetes mellitus, Heart Disease, Asthma and HIV) were found to have 5yr survival of 69.9% as compared to 80.3% in patients without any

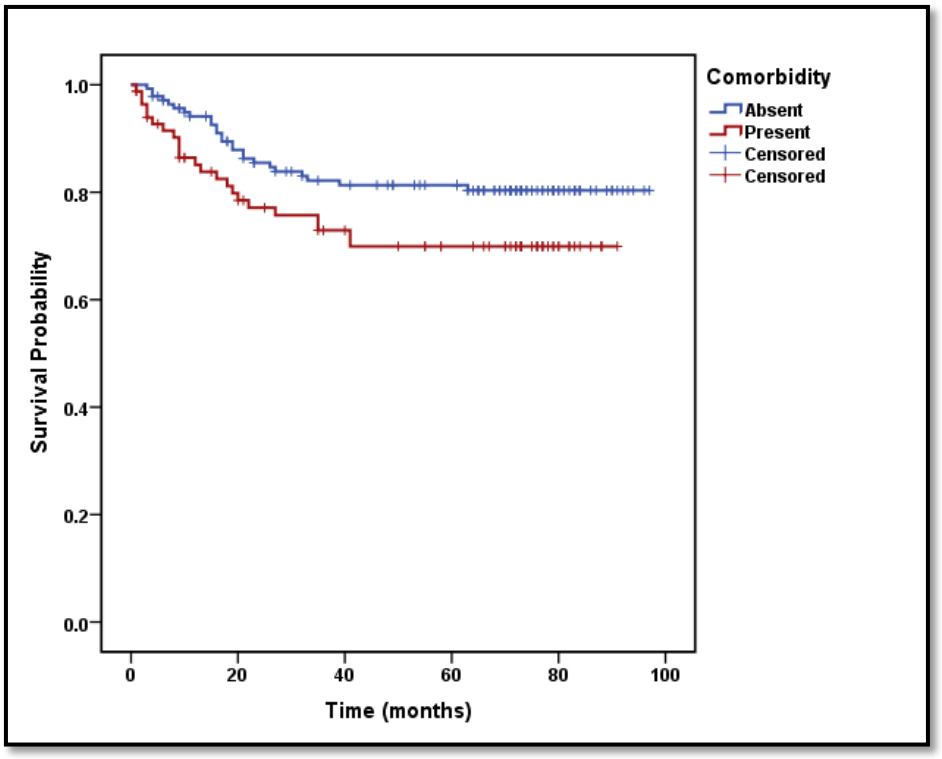
comobidity (Fig. 5.3.3), but this difference did not achieve statistical significance (p= 0.06) (table 5.3.5).

Table 5.3.5: Observed survival rate (%) according to presence of comorbidity

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Comorbidity							
Absent	139	94.1	85.4	82.1	81.3	80.3	0.06
Present	84	85.1	77.1	72.9	69.9	69.9	

**Calculated using Log Rank Test*

Figure 5.3.3: Observed survival rate (%) of early stage cancer according to presence of comorbidity



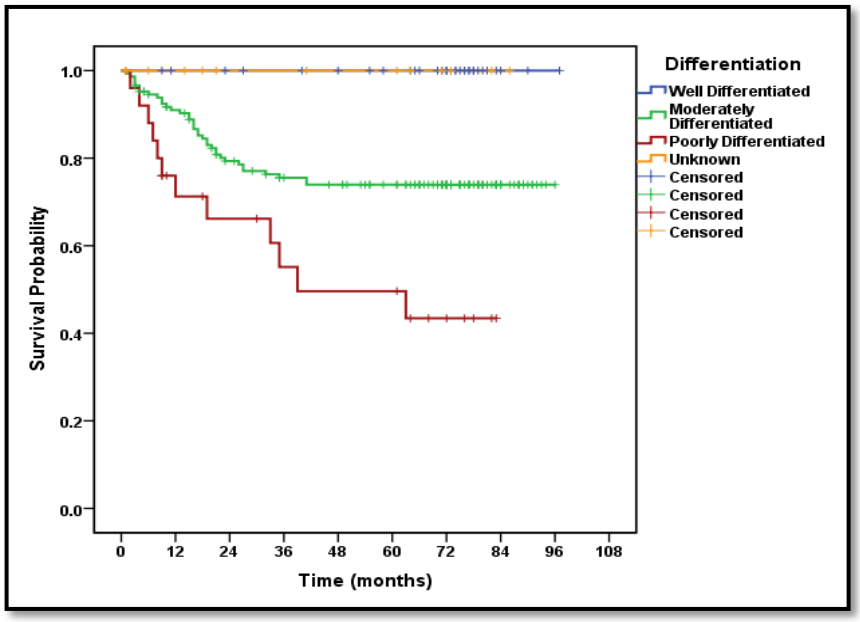
5.3.6 Survival according to differentiation (n=221): Out of the 223 patients 02 patients did not receive surgical treatment hence their tumor differentiation could not be ascertained as the histopathological report for them was not available. Patients having Poorly differentiated tumor were found to have the worst 5yr survival of 42.2%, whereas patients with well differentiated tumors or for those whose tumor differentiation was not reported/ available had near 100% 5yr survival i.e there was no reported deaths in this group of patients (Fig. 5.3.4). Therefore, in order to compute hazard ratio in univariate analysis, patients with Well/ Moderately / Unknown differentiation were clubbed together and was used as a reference category. The patients with poorly differentiated tumor were found to have significantly higher hazard of an event i.e death as compared to the reference category (table 5.3.6).

Table 5.3.6: Observed Survival rate (%) according to tumor differentiation (n=221)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Differentiation							
Well Differentiated	36	No Death in 5 yr follow-up					<0.001
Moderately Differentiated	147	91.4	81.6	78.2	76.8	76.8	
Poorly Differentiated	25	70.0	64.6	53.8	48.4	42.4	
Unknown	13	No Death in 5 yr follow-up					
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Well/ Moderately Differentiated/ Unknown	1						
Poorly Differentiated	3.39 (1.76 – 6.53)						0.02

**Calculated using Log Rank Test*

Figure 5.3.4: Observed survival rate (%) of early stage cancer according to tumor differentiation



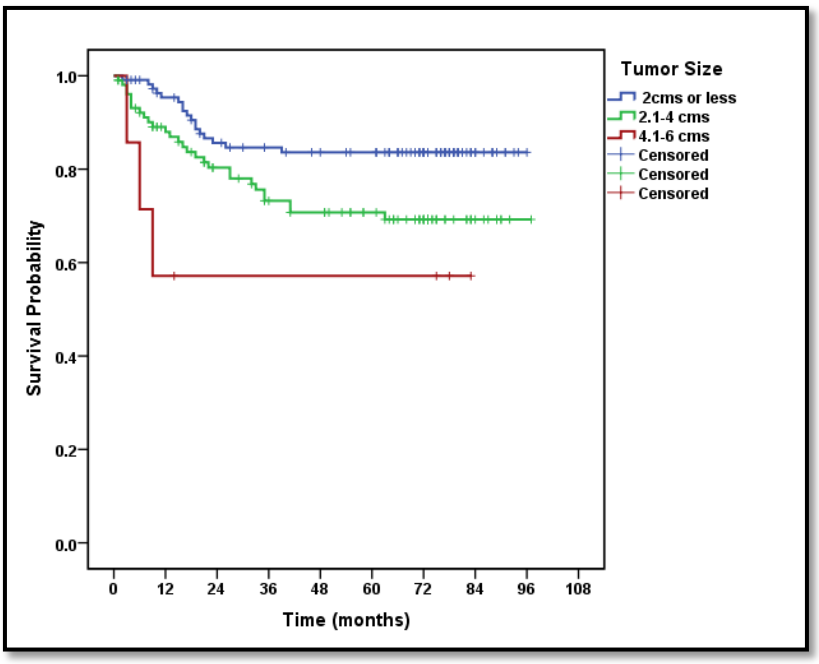
5.3.7 Survival according to Tumor size (Histopathological) (n=221): 5 yr survival rate of oral cavity cancer patients was found to be significantly associated with size of the primary tumor (Fig. 5.3.5). Patients with tumor size of more than 4 cms had poorer prognosis as compared to patients with smaller size tumors (table 5.3.7).

Table 5.3.7: Observed Survival rate (%) according as per tumor size

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Size in greatest dimension (n=221)							
2 cms or less	111	95.3	85.6	84.6	83.6	83.6	0.01
2.1 – 4 cms	103	87.9	80.3	73.2	70.7	69.2	
More than 4 cms	7	57.1	57.1	57.1	57.1	57.1	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
2 cms or less	1						
2.1 – 4 cms	1.99 (1.09 – 3.65)						0.02
More than 4 cms	4.24 (1.24 – 14.53)						0.02

**Calculated using Log Rank Test*

Figure 5.3.5: Observed Survival rate (%) according as per tumor size (Histological)



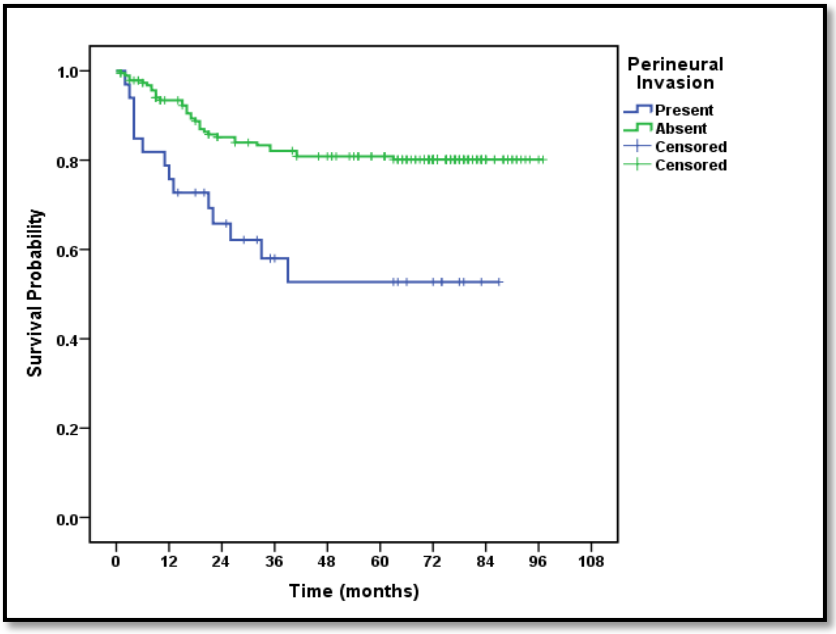
5.3.8 Survival according to Perineural invasion (PNI) (n=221): Presence of perineural invasion on histology was found to significantly affect the survival adversely. Patients with PNI had 5 yr survival of only 52.7% as compared to 80.1% in those patients without PNI (table 5.3.8) (Fig. 5.3.6).

Table 5.3.8: Observed survival rate (%) according perineural invasion

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Perineural extension (n=221)							
Absent	188	93.4	85.1	82.0	80.8	80.1	<0.001
Present	33	75.7	65.8	58.0	52.7	52.7	
Univariate analysis (Cox- Proportional Hazard Model)							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						<0.001
Present	2.88 (1.54 - 5.39)						

**Calculated using Log Rank Test*

Figure 5.3.6: Observed Survival rate (%) according as per Perineural invasion



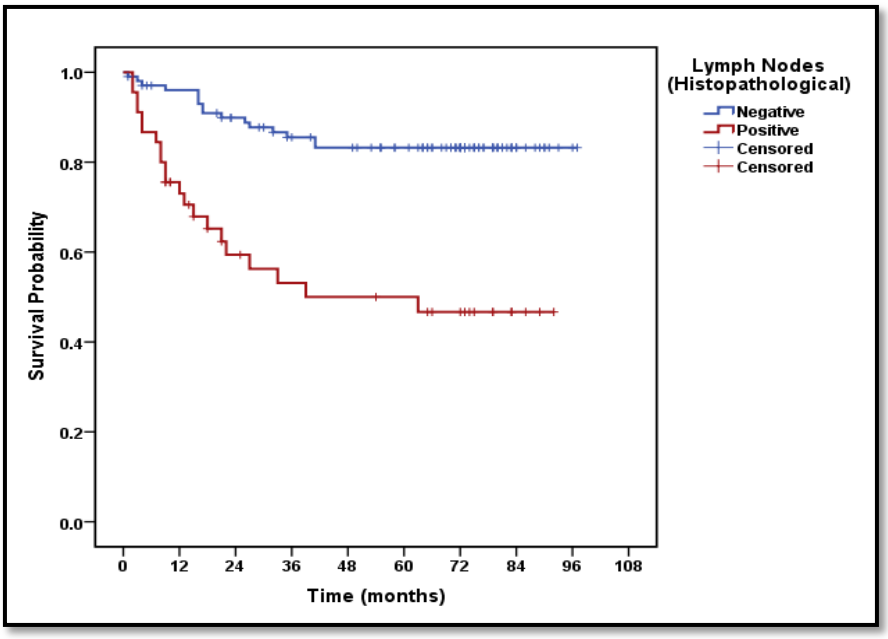
5.3.9 Survival according to Histopathological Lymph Node involvement (n=221): 221 patients who underwent surgical treatment, neck dissection reports were available for 147 patients, out which 45 patients had positive for nodal metastasis. 5yr survival for node negative and node positive patients was found to be 83.2% and 46.6% respectively (table 5.3.9).

Table 5.3.9: Observed survival rate (%) according to lymph node involvement (histo)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Lymph Node involvement (n=147)							
Nodes Negative for metastasis	102	96.0	89.8	85.5	83.2	83.2	<0.001
Nodes Positive for metastasis	45	73.0	59.3	53.1	50.0	46.6	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Nodes Negative for metastasis	1						<0.001
Nodes Positive for metastasis	4.28 (2.22 – 8.25)						

**Calculated using Log Rank Test*

Figure 5.3.7: Observed survival rate (%) as per lymph node involvement (histo)



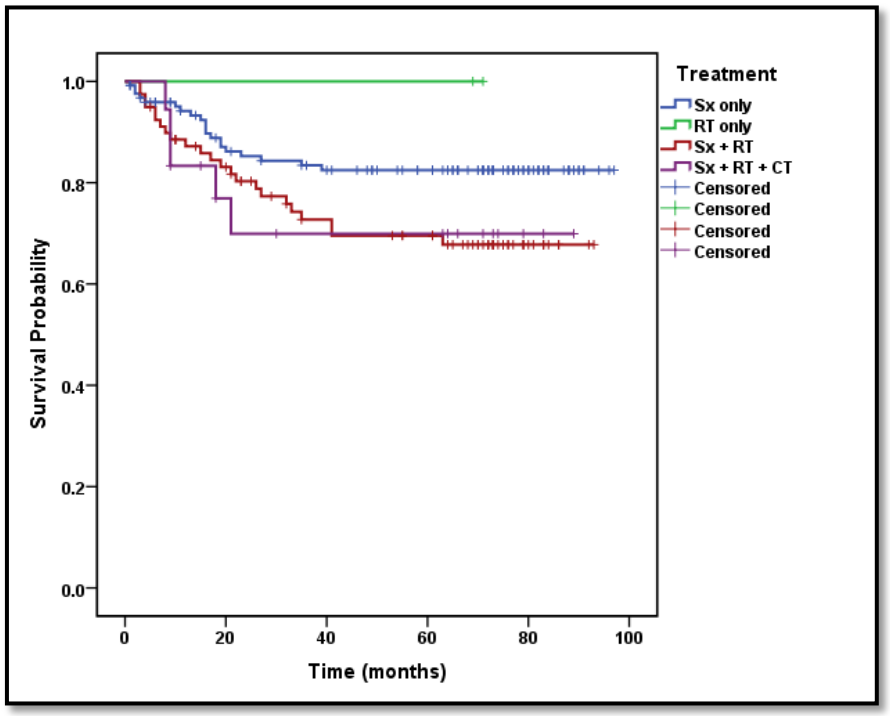
5.3.10 Survival according to Treatment: Surgery individually or in combination with Radiotherapy/ chemotherapy was the main modalities of treatment. Out of 221 patients except for 2 cases all other patients received surgery. Out of the 221 surgically treated cases only surgically treated cases had 5 yr survival of 82.5% (table 5.3.10), however no significant (p> 0.13) difference was observed between surgery alone or surgery given in combination with other treatment such as Radiotherapy and Chemotherapy (Fig. 5.3.8).

Table 5.3.10: Observed survival rate (%) according to treatment

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Treatment							
Surgery only	124	94.2	85.2	83.4	82.5	82.5	0.13
Radiotherapy only	2	100	100	100	100	100	
Surgery + Radiotherapy	79	87.2	87.2	72.7	69.6	67.8	
Surgery + Radiotherapy + Chemotherapy	18	83.3	69.9	69.9	69.9	69.9	

**Calculated using Log Rank Test*

Figure 5.3.8: Observed survival rate (%) according to type of treatment



5.3.11 Multifactorial analysis for determining independent prognostic factors for overall survival:

All the factors which were found to influence overall survival in univariate analysis, such histological tumor size, tumor differentiation, histological lymph node involvement and perineural invasion were considered for further multifactorial analysis. In addition, age (≥40 yrs) and treatment was also considered so as to adjust for their effect in multifactorial model. Thus, using, multifactorial cox propotional step down reduction method we found, age (≥40 yrs) (HR = 2.85, 95% CI = 1.01 – 8.03; p=0.04), poor tumor differentiation (HR = 3.33, 95% CI = 1.67 – 6.60; p<0.001), tumor size (> 2 cms) (HR = 1.86, 95% CI = 11.01 – 3.42; p=0.04) and presence of perineural invasion (HR = 2.06, 95% CI = 1.07 – 3.96; p=0.04) as independent predictors for poor overall survival in early stage oral cancer patients (table 5.3.11).

Table 5.3.11: Univariate and multifactorial analysis of prognostic factors for overall survival in patients with early stage oral cavity cancer

	No. of cases	Univariate		Multifactorial	
Parameter		**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Age (< 40)	37			1	
Age (≥ 40)	184	--	0.06	**2.85 (1.01 – 8.03)**	**0.04****
Well/ Moderately Differentiated/ Unknown	196	1		**1**	
Poorly Differentiated	25	3.39 (1.76 – 6.53)	0.02	**3.33 (1.67 – 6.60)**	**<0.001****
Tumor Size (≤2 cms)	111	1		1	
Tumor Size (>2 cms)	110	2.05 (1.13 – 3.71)	0.01	**1.86 (1.01 – 3.42)**	**0.04****
Perineural invasion Absent	188	1		1	
Perineural invasion Present	33	2.88 (1.54 - 5.39)	<0.001	**2.06 (1.07 – 3.96)**	**0.03****
Treatment	--	--	0.13	--	0.80

§ Abbreviations: HR, hazard ratio; CI, confidence interval
** Significant (p value <0.05)

Advanced Disease (TNM Stage III and IV)

5.4 Survival Analysis of Advanced Stage Oral Cavity Cancer (n= 503)

5.4.1 Overall Survival of advanced stage cancer: At the end of follow-up (31st Dec 2014) out of the 503 patients, 281 (55.9%) patients had expired, and 222 (44.1%) were censored. The median follow-up period was 19 months (range, 1 to 103 months). The 5-year overall survival of the cohort calculated by using actuarial method was found to be 40% (table 5.4.1).

Table 5.4.1: Overall Survival of advanced stage cancer

Total Number	Survival in percentage				
	1 Yr	2 Yr	3 Yr	4 Yr	5 Yr
503	72	53	47	43	40

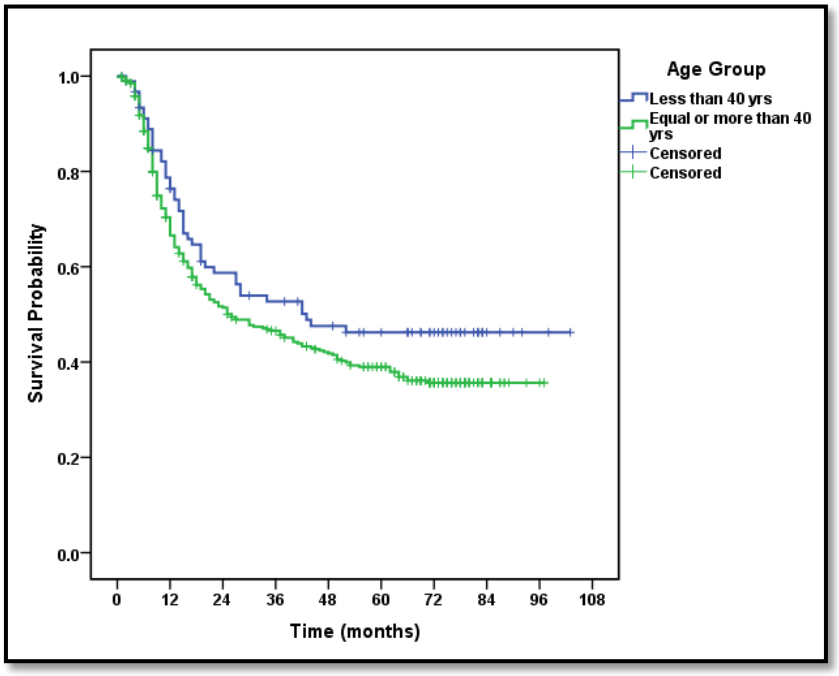
5.4.2 Survival according to Age: Patients were categorized according to cut-offs based on age at registration and its effect on survival was analyzed using Kaplan-Meier curves and the log-rank test. The difference in 5 yrs overall survival rate between age group less than 40 yrs, 40-49, 50-59, 60-69 and more than 70 yrs was not found to be statistically significant (table 5.4.2). Taking, 40 yrs as a cut-off, it was observed that patients with age less than 40 yrs had a 5yr survival of 46.2% and those of age 40yrs and above had a 5yr survival of 37.9%, however this difference was not found to be statistically significant ($p>0.09$) (Fig. 5.4.1).

Table 5.4.2: Observed survival rate (%) of advanced stage cancer and according to age

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Age (years)							
< 40	93	76.4	58.7	52.7	47.6	46.2	0.17
40 to 49	143	65.6	47.0	42.1	40.4	39.5	
50 to 59	137	70.3	57.6	50.8	46.2	42.2	
60 to 69	103	63.9	50.3	46.8	39.5	33.1	
≥ 70	27	63.0	48.1	40.1	36.1	28.1	
Age (as per cut-off of 40 yrs)							
< 40	93	76.4	58.7	52.7	47.6	46.2	0.09
≥ 40	410	66.6	51.4	46.6	41.8	37.9	

**Calculated using Log Rank Test*

Figure 5.4.1: Observed Survival rate (%) of advanced stage oral cancer according to Age



5.4.3 Survival according to Gender, Marital and Educational Status: A 5 yr survival rate for males and females was found to be 41.4% and 46.6% respectively (table 5.4.3), but this difference was not statistically significant (p=0.38). Patients were categorized as per their marital and educational status at the time of registration. No significant difference was seen in 5 yr survival based on marital and educational status (table 5.4.3).

Table 5.4.3: Observed survival rate (%) of advanced stage cancer according to gender, marital and educational status

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
Gender							
Male	170	359	68.0	51.5	46.4	41.4	0.38
Female	53	144	69.2	56.0	51.0	46.6	
Marital Status							
Unmarried	30	71.0	56.1	56.1	56.1	56.1	0.43
Married	416	69.1	52.5	48.1	42.6	39.8	
Widow/ widower	57	65.9	53.7	42.9	40.8	32.2	
Education Status							
Illiterate	133	65.7	51.5	46.8	43.9	37.9	0.37
Schooling	318	69.7	55.0	49.3	44.0	42.4	
College and above	52	67.3	42.8	38.5	34.0	31.7	

**Calculated using Log Rank Test*

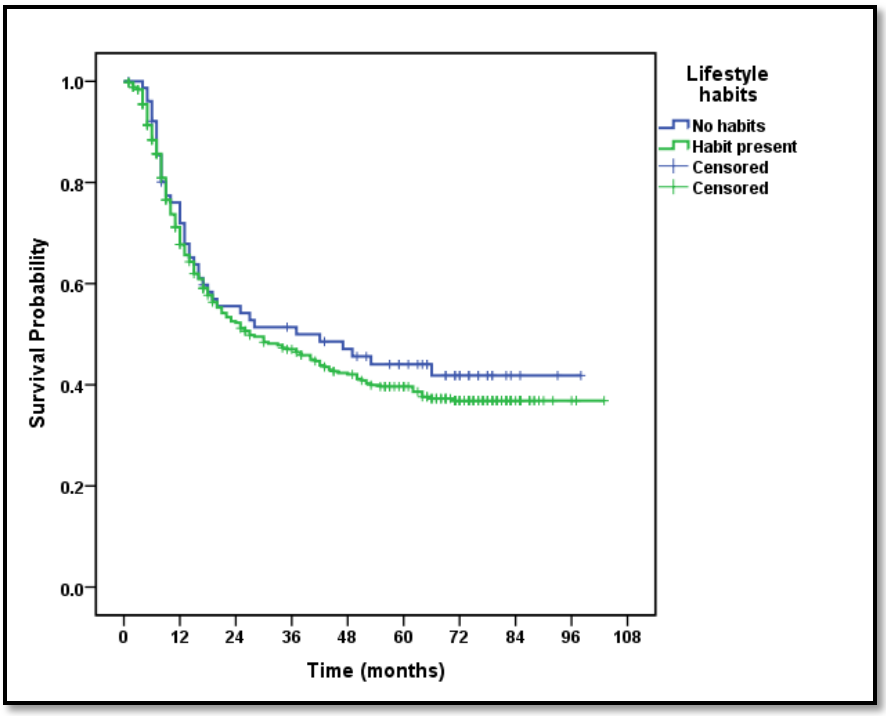
5.4.4 Survival according to Lifestyle Habits: Patients having habit of any form/ type of tobacco or alcohol were grouped in one category and their effect on survival was analyzed. There was no significant (p=0.46) difference in survival between patients having or not having a lifestyle habit (table 5.4.4) (Fig. 5.4.2).

Table 5.4.4: Observed survival rate (%) of advanced stage cancer according to presence of any habit (including smoking, any type of tobacco chewing and alcohol consumption)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Lifestyle habits							
Absent	77	71.9	54.2	50.0	47.1	44.0	0.46
Present	426	67.7	52.3	47.0	42.1	38.6	

**Calculated using Log Rank Test*

Figure 5.4.2: Observed survival rate (%) of advanced stage cancer according to presence of lifestyle habit



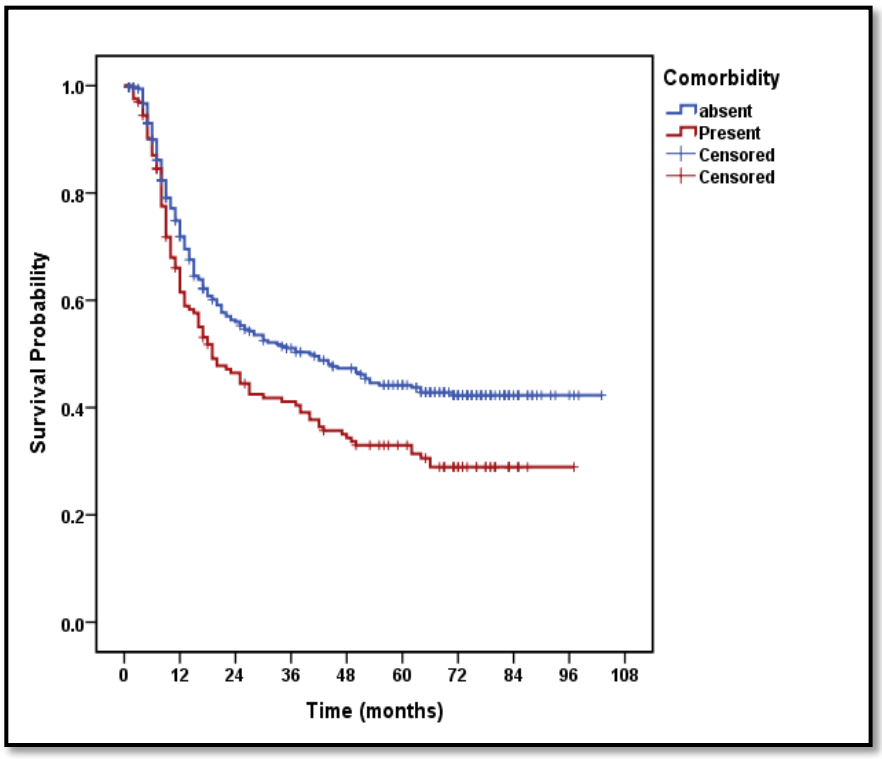
5.4.5 Survival according to Comorbidity: Advanced stage oral cancer patients having a concomitant comorbidity (Hypertension, Diabetes mellitus, Heart Disease, Asthma and HIV) were found to have significantly lower survival as compared to patients without any comorbidity (Fig. 5.4.3). On univariate analysis cases with comobidity were found to have unadjusted hazard of 1.39 (1.09 – 1.77) of outcome as compared to those without comorbidity (table 5.4.5).

Table 5.4.5: Observed survival rate (%) of advanced stage cancer according to presence of comorbidity

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Comorbidity							
Absent	340	71.9	56.0	50.3	47.7	43.7	<0.001
Present	163	61.5	46.5	40.4	34.3	31.4	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						<0.001
Present	1.39 (1.09 – 1.77)						

**Calculated using Log Rank Test*

Figure 5.4.3: Observed survival rate (%) of advanced stage cancer according to presence of comorbidity



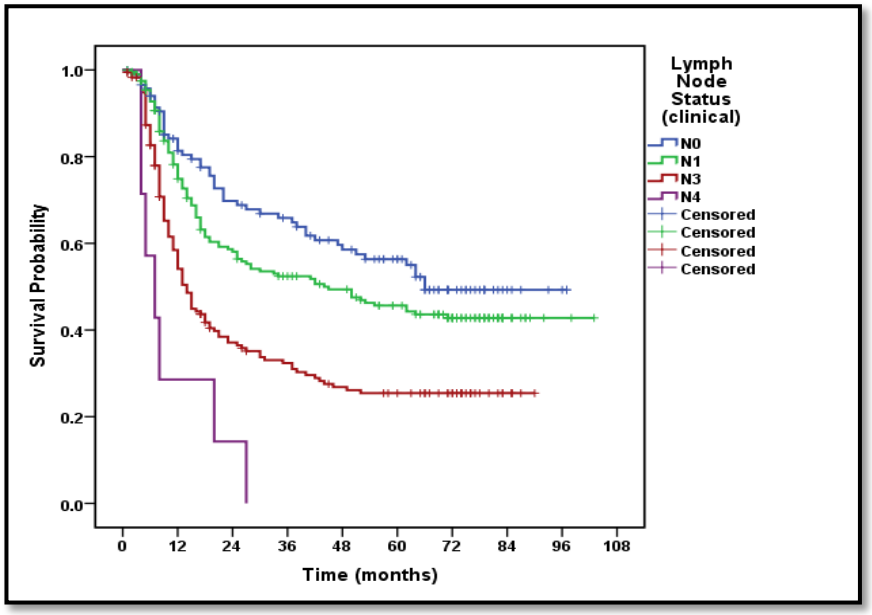
5.4.6 Survival according to Lymph Node Involvement ("N" Classification): Clinical lymph node status was found to be significantly associated with overall survival (Fig. 5.4.4). Patients with lymph node involvement had poorer survival as compared to node negative (N0) patients (table 5.4.6).

Table 5.4.6: Observed survival rate (%) of advanced stage cancer according to clinical nodal status

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
N Classification							
N0	118	81.3	69.8	65.8	58.5	55.0	<0.001
N1	201	74.9	58.1	52.4	49.4	44.3	
N2	177	54.1	37.1	32.4	26.8	25.4	
N3	7	28.6	14.3	00.0	00.0	00.0	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
N0	1						
N1	1.29 (0.92 – 1.81)						0.12
N2	2.31 (1.66 – 3.21)						<0.001
N3	6.17 (2.79 – 13.67)						<0.001

**Calculated using Log Rank Test*

Figure 5.4.4: Observed survival rate (%) of advanced stage cancer according to clinical nodal status



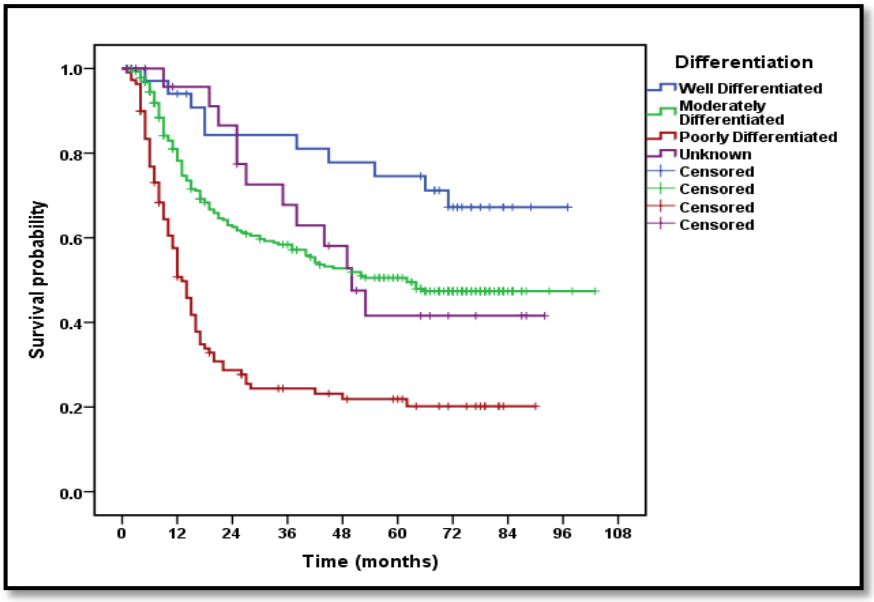
5.4.7 Survival according to differentiation (n= 450): Out of the 503 patients 53 patients did not receive surgical treatment hence their tumor differentiation could not be ascertained as the histopathological report for them was not available. Patients having Poorly differentiated tumor were found to have the worst 5yr survival of 20.2%, whereas well and moderately differentiated tumors had better survival of 74.6% and 49.5% respectively (table 5.4.7) (Fig. 5.4.5). Tumor differentiation of 27 patients was unknown, however 5yr survival rate of these patients was not found to be significantly (p=0.14) different from well/ moderately differentiated tumors (table 5.4.7).

Table 5.4.7: Observed survival rate (%) of advanced stage cancer according to tumor differentiation (n=450)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Differentiation							
Well Differentiated	38	94.0	84.3	81.1	77.8	74.6	<0.001
Moderately Differentiated	276	78.2	62.5	58.4	52.8	49.5	
Poorly Differentiated	109	50.7	28.7	24.4	21.9	20.2	
Unknown	27	95.7	77.4	67.8	58.1	41.6	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Well Differentiated	1						
Moderately Differentiated	2.07 (1.09 – 3.95)						0.02
Poorly Differentiated	5.18 (2.67 – 10.02)						<0.001
Unknown	1.88 (0.81 – 4.36)						0.14

**Calculated using Log Rank Test*

Figure 5.4.5: Observed survival rate (%) of advanced stage cancer according to tumor differentiation



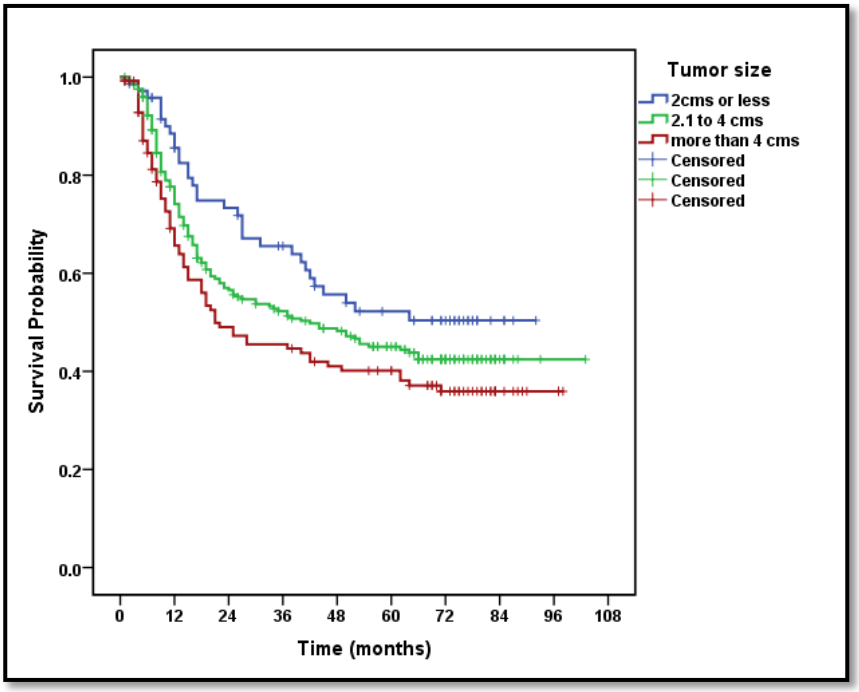
5.4.8 Survival according to Tumor size (Histopathological) (n=450): 5 yr survival rate of oral cavity cancer patients was found to be significantly associated with size of the primary tumor (Fig. 5.4.6). Patients with tumor size of more than 4 cms had poorer prognosis as compared to patients with equal to or less than 2 cms size tumors (table 5.4.8).

Table 5.4.8: Observed survival rate (%) of advanced stage cancer according as per tumor size

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Size in greatest dimension (n=217)							
2 cms or less	72	88.5	73.3	65.5	57.4	50.4	0.04
2.1 – 4 cms	248	77.6	56.6	52.3	48.2	45.0	
4.1 – 6 cms	130	65.6	49.0	44.6	40.1	38.1	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
2 cms or less	1						
2.1 – 4 cms	1.35 (0.91 – 1.99)						0.12
More than 4 cms	1.675 (1.10 – 2.53)						0.01

**Calculated using Log Rank Test*

Figure 5.4.6: Observed survival rate (%) of advanced stage cancer according to tumor size



5.4.9 Survival according to skin infiltration (n=450): 5 yr survival of patients having skin infiltration and of those not having skin infiltration was found to be almost similar i.e 44.8% and 44.9% respectively (p= 0.74) (table 5.4.9).

Table 5.4.9: Observed Survival rate (%) of advanced stage cancer according to skin infiltration

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Skin Infiltration (n=450)							
Absent	398	74.8	57.5	52.8	47.4	44.9	0.74
Present	52	64.0	54.8	50.1	47.4	44.8	

**Calculated using Log Rank Test*

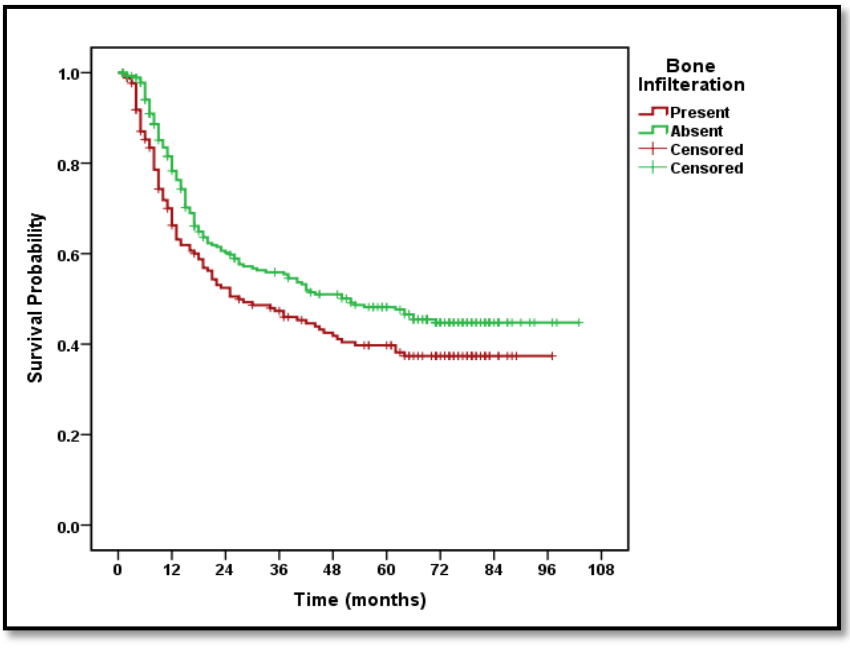
5.4.10 Survival according to bone infiltration (n=450): Patients with bone infiltration on histology were found to have significantly lower survival (p=0.03) as compared to patients without any bone involvement (Fig. 5.4.7). On univariate analysis cases showing presence of bone involvement were found to have unadjusted hazard of 1.66 (1.29 - 2.12) of outcome as compared to those without evidence bone infiltration (table 5.4.10).

Table 5.4.10: Observed survival rate (%) of advanced stage cancer according to bone infiltration

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Bone Infiltration (n=450)							
Absent	277	78.3	60.2	55.4	51.0	48.2	0.03
Present	173	66.3	52.4	47.3	41.8	38.2	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						0.03
Present	1.31 (1.01 - 1.70)						

**Calculated using Log Rank Test*

Figure 5.4.7: Observed survival rate (%) of advanced stage cancer according to bone infiltration



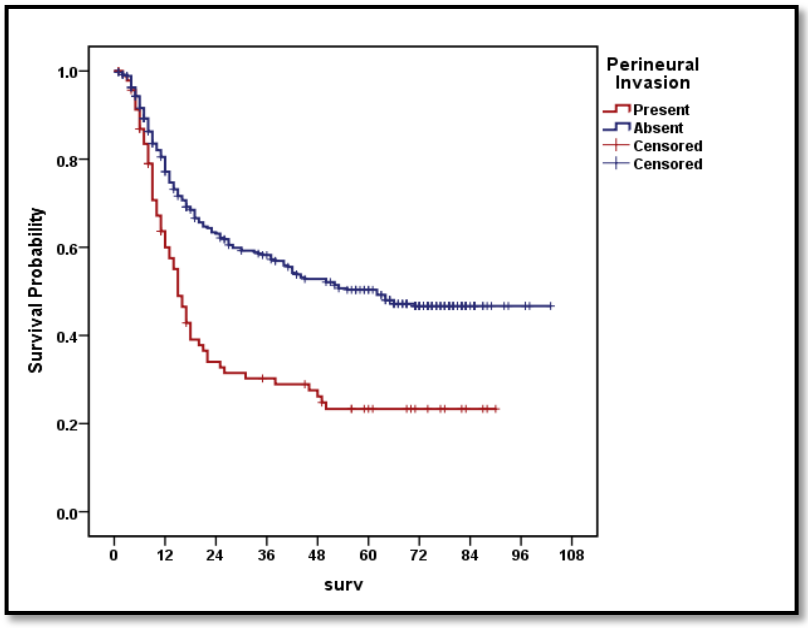
5.4.11 Survival according to Perineural Invasion (PNI) (n=671): Presence of perineural invasion on histology was found to adversely affect survival. Patients with PNI had 5 yr survival of only 23.3% as compared to 49.2% in those patients without PNI (table 5.4.11) (Fig. 5.4.8).

Table 5.4.11: observed survival rate (%) of advanced stage cancer according perineural infilteration

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Perineural extension (n=450)							
Absent	351	77.2	63.1	58.2	52.8	49.2	<0.001
Present	99	60.0	34.0	30.2	26.2	23.3	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						<0.001
Present	2.19 (1.64 - 2.90)						

**Calculated using Log Rank Test*

Figure 5.4.8: observed survival rate (%) of advanced stage cancer according to perineural invasion



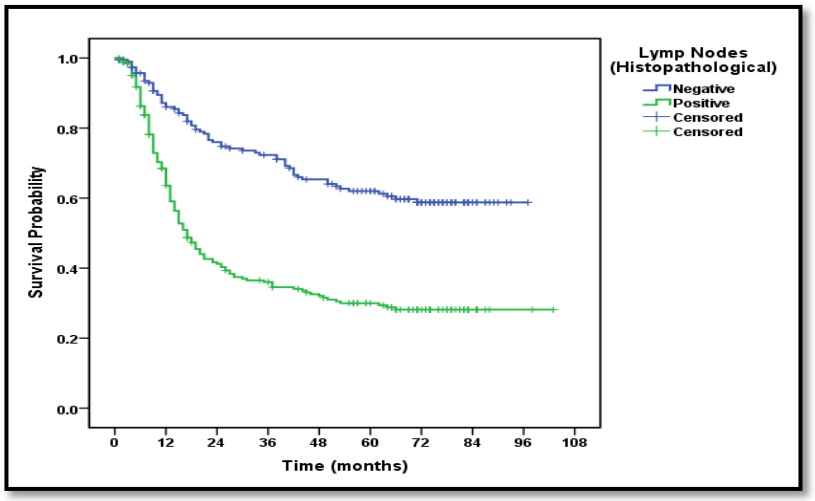
5.4.12 Survival according to histopathological Lymph Node involvement (n=437): 450 patients who underwent surgical treatment, neck dissection reports were available for only 437 patients, out which 246 patients were positive for nodal metastasis. 5 yr survival for node negative and node positive patients was found to be 62.0% and 29.4% respectively (table 5.4.12) (Fig. 5.4.9).

Table 5.4.12: observed survival rate (%) of advanced stage cancer according to histopathological lymph node involvement *(n=437)*

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Lymph Node involvement (n=437)							
Nodes Negative for metastasis	191	86.0	76.0	71.1	65.3	62.0	<0.001
Nodes Positive for metastasis	246	63.6	41.2	36.0	32.0	29.4	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Nodes Negative for metastasis	1						<0.001
Nodes Positive for metastasis	2.67 (2.05 – 3.56)						

**Calculated using Log Rank Test*

Figure 5.4.9: observed survival rate (%) of advanced stage cancer according to histopathological lymph node involvement *(n=437)*



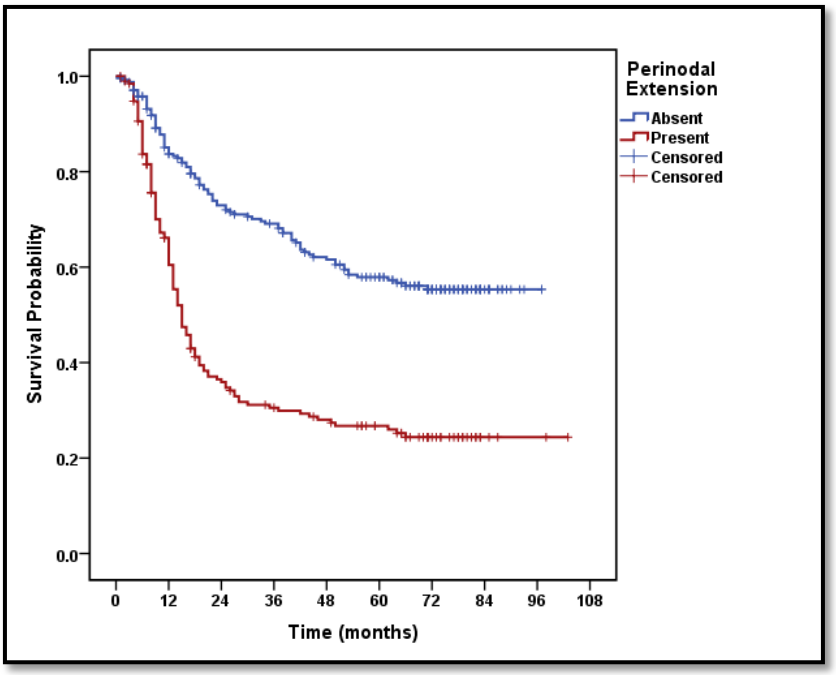
5.4.13 Survival according to Extra Capsular Spread (ECS) (n=437): Positive ECS was found in 194, these patients were found to have significantly lower 5 yr survival of 26.0% as compared to 57.9% in patients negative for ECS (table 5.4.13) (Fig. 5.4.10).

Table 5.4.13: Observed survival rate (%) of advanced stage cancer according ECS

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Extra Capsular Spread (n=437)							
ECS negative	243	83.7	73.0	68.1	61.6	57.9	<0.001
ECS positive	194	60.5	35.9	30.5	28.0	26.0	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
ECS negative	1						<0.001
ECS positive	2.64 (2.02 – 3.45)						

**Calculated using Log Rank Test*

Figure 5.4.10: Observed survival rate (%) of advanced stage cancer according to ECS



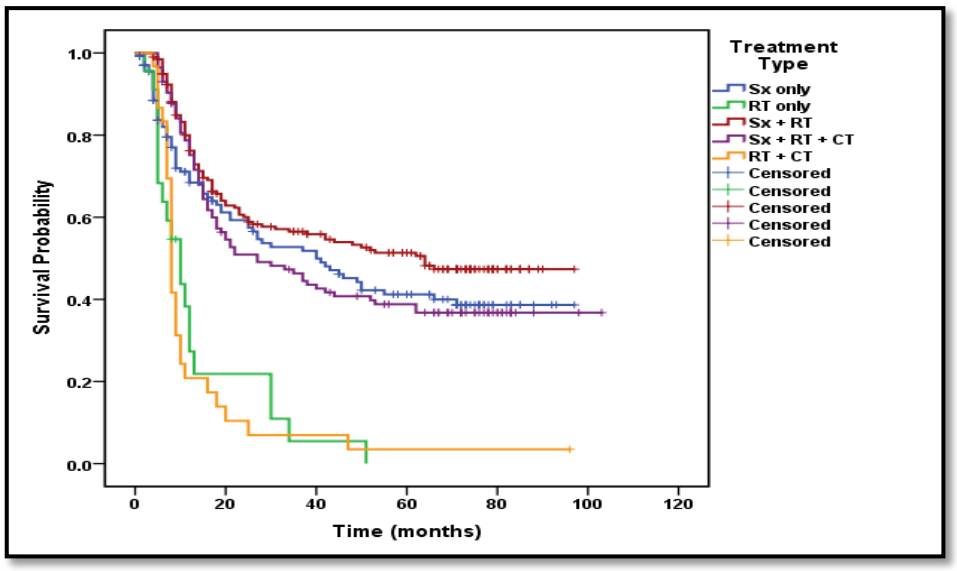
5.4.14 Survival according to Treatment: Surgery individually or in combination with Radiotherapy/ Chemotherapy was the main modality of treatment. Majority of the patients 62% received either RT or CT in addition to surgery (table 5.4.14). Out of the 450 surgically treated cases, surgery plus radiotherapy treated cases had the highest 5 yr survival of 50.6% and the patients who received all the three modalities of treatment namely Surgery, Radiotherapy and Chemotherapy had the lowest survival of 36.8% (Fig. 5.4.11)

Table 5.4.14: Observed survival rate (%) of advanced stage according to treatment

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Treatment							
Surgery only	138	68.4	59.3	51.8	45.2	41.2	<0.001
Radiotherapy only	23	27.3	21.9	05.5	05.5	00.0	
Surgery + Radiotherapy	198	76.2	60.0	56.5	53.3	50.6	
Surgery + Radiotherapy + Chemotherapy	114	75.1	50.9	46.3	40.8	36.8	
Radiotherapy + Chemotherapy	30	20.8	10.4	06.9	03.5	03.5	
Univariate analysis (Cox- Proportional Hazard Model)							
	Hazard Ratio (95% CI)						**p Value**
Surgery only	1						
Radiotherapy only	3.26 (1.97 – 5.38)						<0.001
Surgery + Radiotherapy	0.75 (0.55 – 1.03)						0.77
Surgery + Radiotherapy + Chemotherapy	.998 (0.77– 1.39)						0.99
Radiotherapy + Chemotherapy	3.49 (2.23 – 5.46)						<0.001

**Calculated using Log Rank Test*

Figure 5.4.11: Observed survival rate (%) of advanced stage cancer according to treatment



5.4.15 Multifactorial analysis for determining independent prognostic factors for overall survival:

All the factors which were found to influence overall survival in univariate analysis, such as presence of comorbidity, histological lymph node involvement, histological tumor size, tumor differentiation, extra capsular spread, bone infiltration, perineural invasion and treatment modality were considered for further multifactorial analysis. In addition, age (>40 yrs) was also considered so as to adjust for its effect in multifactorial model. Thus, using, multifactorial cox proportional step down reduction method we found that age ≥ 40 yrs (HR = 1.51, 95% CI = 1.06 - 2.15; P= 0.02), presence of comorbidity (HR = 1.44, 95% CI = 1.09 – 1.89; p<0.001), poor tumor differentiation disease (HR = 3.12, 95% CI = 1.56 - 6.26; p<0.001), tumor size more than 4 cms (HR = 1.43, 95% CI = 1.06 - 2.21; p= 0.04), perineural invasion (HR = 1.53, 95% CI = 1.13 - 2.06; p<0.001), extra capsular spread (HR = 1.53, 95% CI = 1.01 – 2.33; p= 0.04), histological lymph node involvement (HR = 1.64, 95% CI = 1.04 - 2.57; p= 0.03) (table 5.4.14) were found to be independent predictors for poor overall survival of advanced stage oral cavity cancer patients.

Table 5.4.15: Univariate and multifactorial analysis of prognostic factors for overall survival in patients with advanced stage oral cavity cancer

	No. of cases	Univariate		Multifactorial	
Parameter		**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Age (< 40 yrs)	93	1		1	
Age (≥ 40 yrs)	410	1.30 (0.94 – 1.78)	0.10	**1.51 (1.06 - 2.15)**	**0.02****
Comorbidity (Absent)	340	1		**1**	
Comorbidity (Present)	163	1.39 (1.09 – 1.77)	<0.001	**1.44 (1.09 – 1.89)**	**<0.001****
Differentiation					
Well Differentiated	38	1		1	
Moderately Differentiated	276	2.07 (1.09 – 3.95)	0.02	1.41 (0.72 – 2.76)	0.30
Poorly Differentiated	109	5.18 (2.67 – 10.02)	<0.001	**3.12 (1.56 – 6.26)**	**<0.001****
Unknown	27	1.88 (0.81 – 4.36)	0.14	1.24 (0.52 – 2.92)	0.62
Tumor Size					0.06
< 2cms	72	1		1	
2- 4 cms	248	1.35 (0.91 – 1.99)	0.12	1.03 (0.68 – 1.55)	0.88
> 4cms	130	1.67 (1.10 – 2.53)	0.01	**1.43 (1.06 – 2.21)**	**0.04****
Histological Lymph node (Absent)	190	1		**1**	
Histological Lymph node (Present)	247	2.67 (2.05 – 3.56)	<0.001	**1.64 (1.04 - 2.57)**	**0.03****
Bone Infiltration (Absent)	277	1		--	0.97
Bone Infiltration (Present)	173	1.31 (1.01 - 1.70)	0.03		
Perineural invasion (Absent)	351	1		**1**	
Perineural invasion (Present)	99	2.19 (1.64 - 2.90)	<0.001	**1.53 (1.13 - 2.06)**	**<0.001****
ECS (Absent)	243	1		**1**	
ECS (Present)	194	2.64 (2.02 - 3.45)	<0.001	**1.53 (1.01 – 2.33)**	**0.04****
Treatment				--	0.09
Surgery only	138	1			
Radiotherapy only	23	3.26 (1.97 – 5.38)	<0.001		
Surgery + Radiotherapy	198	0.75 (0.55 – 1.03)	0.77		
Surgery + Radiotherapy + Chemotherapy	114	0.99 (0.77 – 1.39)	0.99		
Radiotherapy + Chemotherapy	30	3.49 (2.23 – 5.46)	<0.001		

§ Abbreviations: HR, hazard ratio; CI, confidence interval, ** Significant (p value <0.05)

Tongue Cancer

5.5 Survival Analysis of Tongue Cancer (n= 245)

5.5.1 Overall Survival of Tongue Cancer: At the end of follow-up (31st Dec 2014) out of the 245 patients, 115 (46.9 %) patients had expired, and 130 (53.1%) were censored. The median follow-up period was 26 months (range, 1 to 98 months). The 5-year overall survival of the cohort calculated by using actuarial method was found to be 40% (table 5.5.1).

Table 5.5.1: Overall survival of tongue cancer

Total Number	Survival in percentage				
	1 Yr	2 Yr	3 Yr	4 Yr	5 Yr
245	76	58	52	51	50

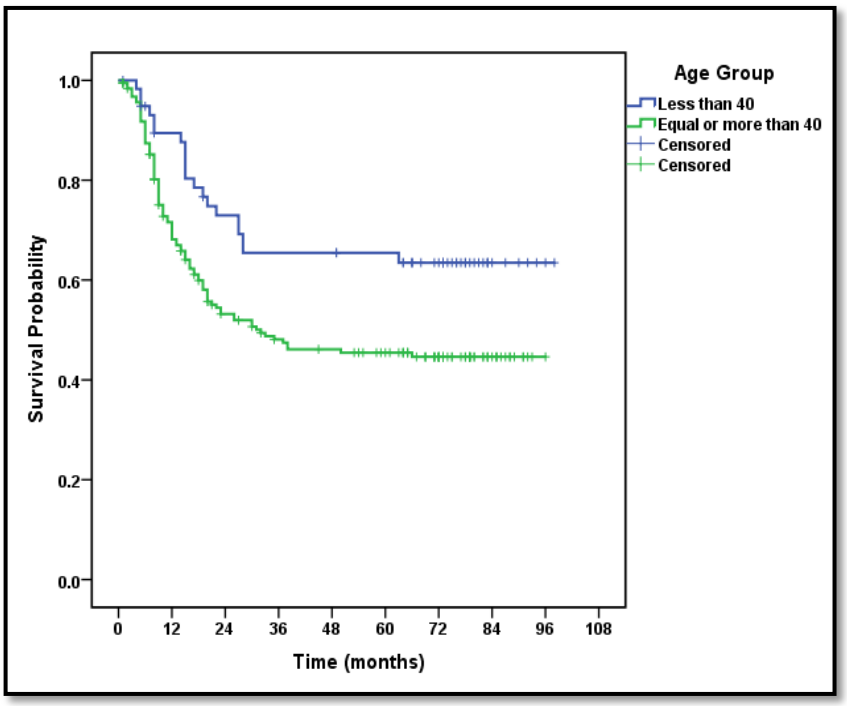
5.5.2 Survival according to Age: Patients were categorized according to cut-offs based on age at registration and its effect on survival was analyzed using Kaplan-Meier curves and the log-rank test. The difference in 5 yrs overall survival rate between age group less than 40 yrs, 40-49, 50-59, 60-69 and more than 70 yrs was not found to be statistically significant (table 5.5.2). Taking, 40 yrs as a cut-off, it was observed that patients with age less than 40 yrs had a 5yr survival of 63.5% and those of age 40yrs and above had a 5yr survival of 45.5%, this difference was found to be statistically significant (p=0.01) (Fig. 5.5.1).

Table 5.5.2: Observed survival rate (%) of tongue cancer according to age

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Age (years), Median – 48 years (18-80 yrs)							
< 40	59	89.5	72.9	65.5	65.5	63.5	0.01
40 to 49	68	70.8	57.1	55.3	55.3	53.3	
50 to 59	62	66.4	51.9	43.9	41.9	41.9	
60 to 79	46	70.7	52.5	47.4	41.9	41.9	
≥ 70	10	50.0	40.0	30.0	30.0	20.0	
Age (as per cut-off of 40 yrs)							
< 40	59	89.5	72.9	65.5	65.5	63.5	0.01
≥ 40	186	68.1	53.2	47.4	46.1	45.5	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Age < 40 Yrs	1						0.01
Age ≥ 40 Yrs	1.83 (1.13 – 2.97)						

**Calculated using Log Rank Test*

Figure 5.5.1: Observed survival rate (%) of tongue cancer according to age



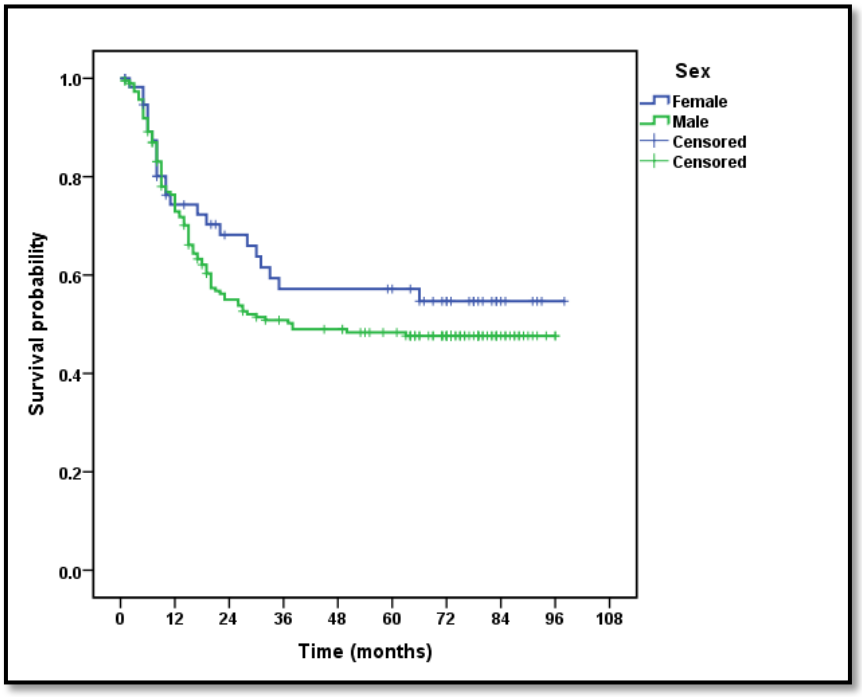
5.5.3 Survival according to Gender: A 5 yr survival rate for males and females was found to be 47.6% and 54.7% respectively (table 5.5.3), but this difference was not statistically significant (p=0.32) (Fig. 5.5.2).

Table 5.5.3: Observed survival rate (%) of tongue cancer according to gender

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Gender							
Male	187	72.9	55.0	50.2	48.3	47.6	0.32
Female	58	74.3	68.2	54.7	54.7	54.7	

**Calculated using Log Rank Test*

Figure 5.5.2: Observed survival rate (%) of tongue cancer according to gender



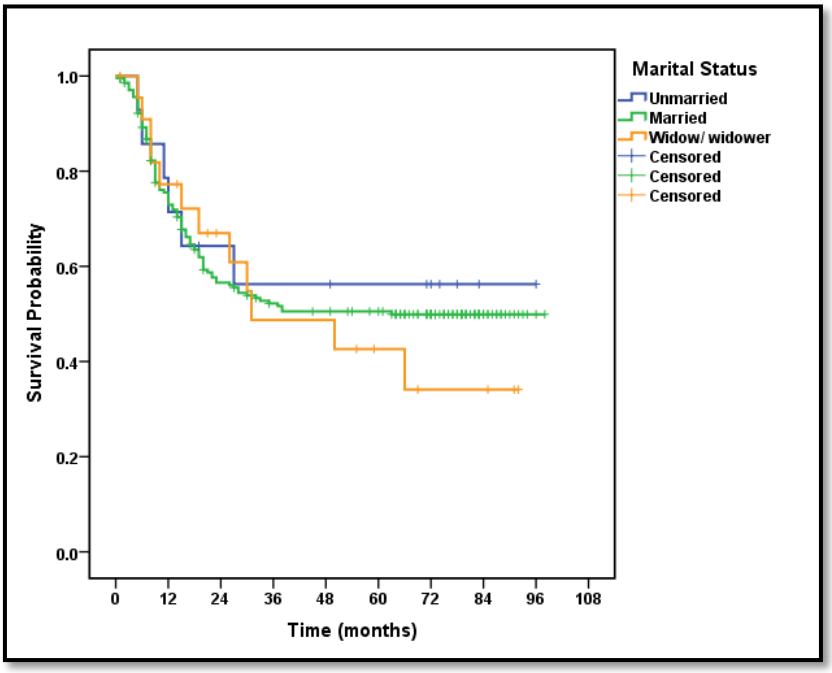
5.5.4 Survival according to Marital Status: The patients were divided into three categories as per their marital status reported at the time of registration. No significant (p=0.84) difference in survival was observed between the three groups namely unmarried, married or widow/ widower (table 5.5.4) (Fig. 5.5.3).

Table 5.5.4: Observed survival rate (%) of tongue cancer according to marital status

Factor	Total Number	Survival in percentage					p Value *
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Marital Status							
Unmarried	14	71.4	64.3	56.3	56.3	56.3	0.84
Married	208	72.9	56.6	52.2	50.5	50.5	
Widow/ widower	23	77.3	60.9	48.7	48.7	42.6	

**Calculated using Log Rank Test*

Figure 5.5.3: Observed survival rate (%) of tongue cancer according to marital status



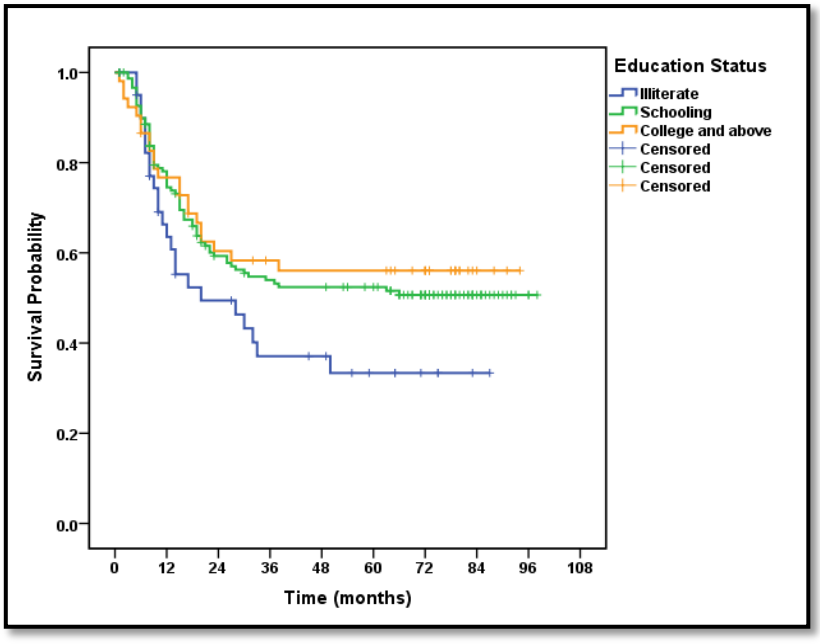
5.5.5 Survival according to Educational Status: The education level reported by the patient at the time of registration was taken into consideration for classifying the patient as per educational status. The 5yr survival rate was found to be highest for patients with educational qualification of college and above (56.1%), followed by those who had done any level of schooling (51.6%) and lowest survival rate was found to be of illiterate (33.4%) patients (table 5.5.5). However, this difference in 5yr survival between the three levels of education failed to attain statistical significance (p=0.11) (Fig. 5.5.4).

Table No. 5.5.5: Observed survival rate (%) of tongue cancer according to education

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Education Status							
Illiterate	42	63.5	49.4	37.1	37.1	33.4	0.11
Schooling	151	74.5	59.3	54.0	52.4	51.6	
College and above	52	76.7	60.4	58.3	56.1	56.1	

**Calculated using Log Rank Test*

Figure 5.5.4: Observed survival rate (%) of tongue cancer according to education status



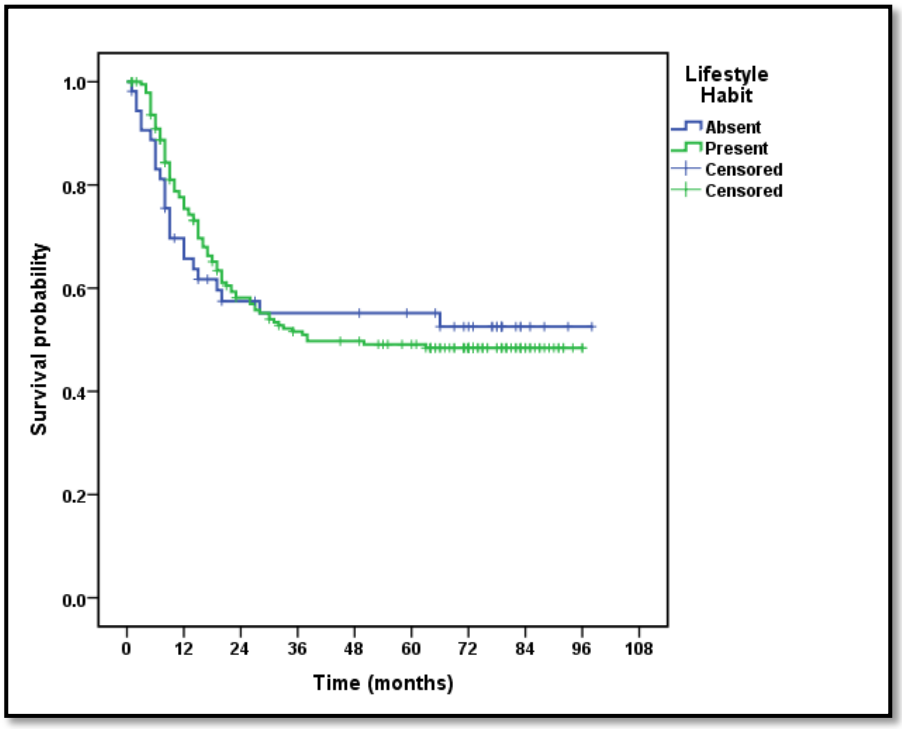
5.5.6 Survival according to Lifestyle Habits: Patients having habit of any form/ type of tobacco or alcohol were grouped in one category. There was no significant (p=0.96) difference in survival between patients having or not having a lifestyle habit (table 5.5.6) (Fig. 5.5.5).

Table 5.5.6: Observed survival rate (%) of tongue cancer according to presence of any habit (including smoking, any type of tobacco chewing and alcohol consumption)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Habit							
Absent	54	65.7	57.5	55.2	55.2	55.2	0.96
Present	191	75.4	58.1	51.6	49.7	48.4	

**Calculated using Log Rank Test*

Figure 5.5.5: Observed survival rate (%) according to presence of lifestyle habit



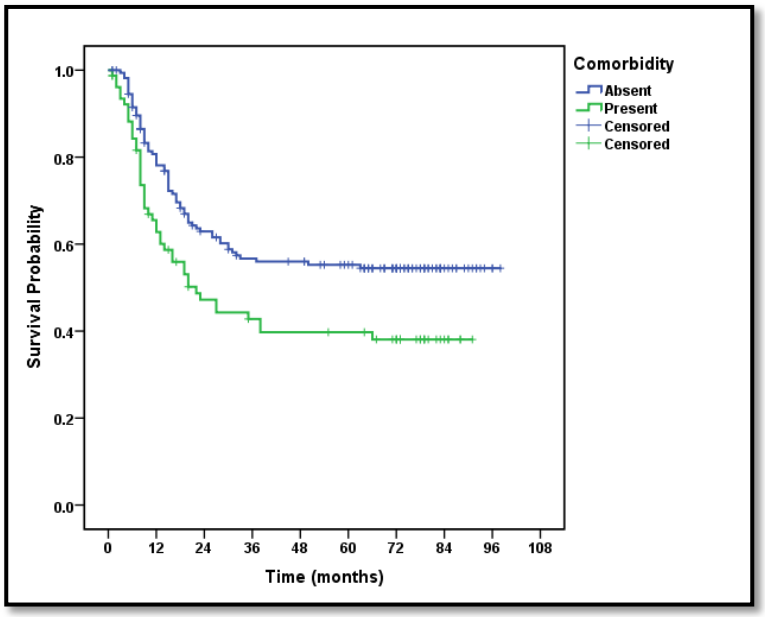
5.5.7 Survival according to Comorbidity: Tongue cancer patients having a concomitant comorbidity (Hypertension, Diabetes mellitus, Heart Disease, Asthma and HIV) were found to have significantly lower survival (p=0.01) as compared to patients without any comorbidity (Fig. 5.5.6). On univariate analysis cases with comobidity were found to have unadjusted hazard of 1.62 (1.12 – 2.37) of outcome as compared to those with comorbidity (table 5.5.7).

Table 5.5.7: Observed Survival rate (%) according to presence of comorbidity

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Comorbidity							
Absent	155	78.1	62.9	56. 7	56.0	55.2	<0.001
Present	74	62.8	47.2	42.8	39.7	38.1	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						0.01
Present	1.62 (1.12 – 2.37)						

**Calculated using Log Rank Test*

Figure 5.5.6: Observed survival rate (%) according to presence of comorbidity



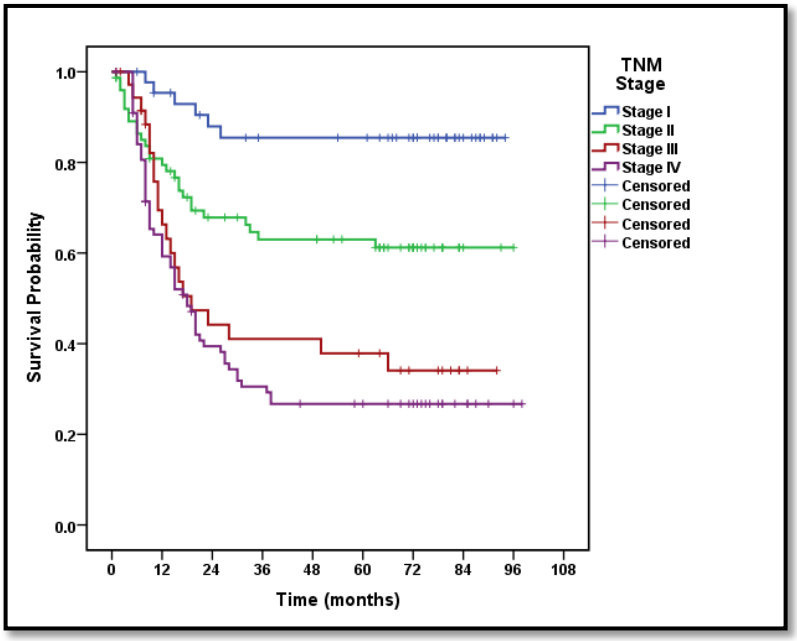
5.5.8 Survival according to TNM staging: TNM stage was found to significantly affect overall survival (p<0.001) (Fig. 5.5.7). Stage IV had the lowest 5yr survival rate of 26.7% and stage I had the highest survival rate of 85.4% (table 5.5.8). Thus, higher stages were found to have poorer prognosis as compared to lower stages.

Table 5.5.8: Observed survival rate (%) of tongue cancer according to TNM Stage

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
TNM Stage							
I	44	95.3	90.5	85.4	85.4	85.4	<0.001
II	75	79.5	67.8	63.0	63.0	61.2	
III	37	66.3	44.2	41.0	37.9	37.9	
IV	89	59.3	39.4	30.5	29.3	26.7	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
I	1						
II	3.29 (1.35 – 7.97)						<0.001
III	6.38 (2.57 – 15.84)						<0.001
IV	8.09 (3.49 – 18.77)						<0.001

**Calculated using Log Rank Test*

Figure 5.5.7: Observed survival rate (%) according to TNM Stage



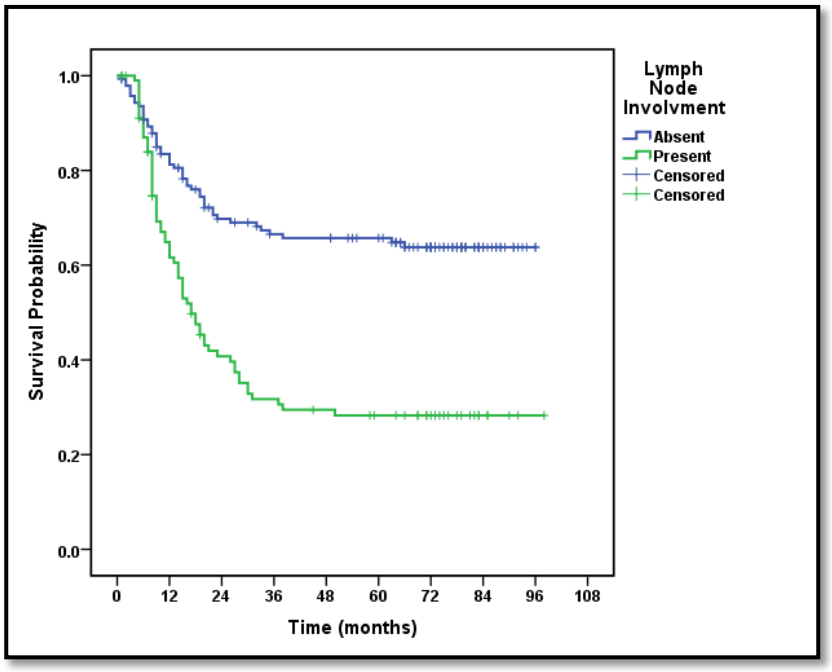
5.5.9 Survival according to Lymph Node Involvement: Clinical lymph node status was found to be significantly associated with overall survival (Fig. 5.5.8). Patients with lymph node involvement had poorer survival as compared to node negative (N0) patients (table 5.5.9).

Table 5.5.9: Observed survival rate (%) according to clinical nodal status

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Lymph Node Involvement (clinical)							
Absent	142	81.3	69.8	66.5	65.7	64.8	<0.001
Present	103	61.6	40.8	30.6	29.5	28.3	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						
Present	2.63 (1.81 – 3.82)						<0.001

**Calculated using Log Rank Test*

Figure 5.5.8: Observed survival rate (%) according to clinical lymph node status



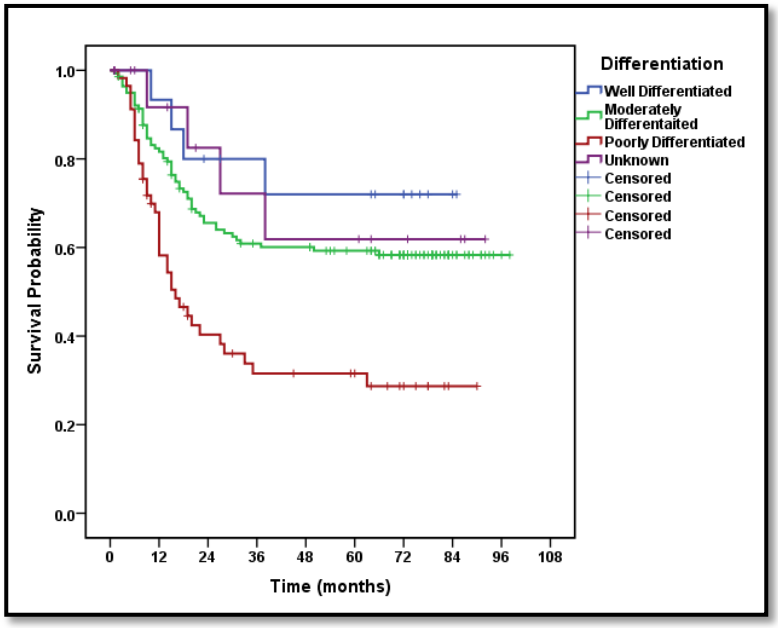
5.2.10 Survival according to differentiation (n=229): Out of the 245 patients 16 patients did not receive surgical treatment hence their tumor differentiation could not be ascertained as their histopathological report was not available. Patients having poorly differentiated tumor were found to have the worst 5yr survival of 28.7% , whereas well and moderately differentiated tumors had better survival of 72.0% and 59.3% respectively (table 5.5.10) (Fig. 5.5.9). In addition, tumor differentiation of 18 patients was not mentioned in the histopathological reports hence a separate category of "unknown differentiation" was created and taken into consideration for survival analysis. However, 5 yr survival rate of these patients was not found to be significantly (p=0.71) different from well/ moderately differentiated tumors (table 5.2.10).

Table 5.5.10: Observed Survival rate (%) of tongue cancer according to tumor differentiation (n=229)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Differentiation *(n=229)*							
Well Differentiated	15	93.3	80.0	72.0	72.0	72.0	<0.001
Moderately Differentiated	139	81.6	65.6	60.9	60.1	59.3	
Poorly Differentiated	57	58.2	40.3	33.8	31.6	28.7	
Unknown	18	91.7	82.5	72.2	61.9	61.9	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Well Differentiated	1						
Moderately Differentiated	1.73 (0.62 – 4.78)						0.28
Poorly Differentiated	3.94 (1.40 – 11.07)						<0.001
Unknown	1.29 (0.32 – 5.16)						0.71

**Calculated using Log Rank Test*

Figure 5.5.9: Observed Survival rate (%) to tumor differentiation (n=229)



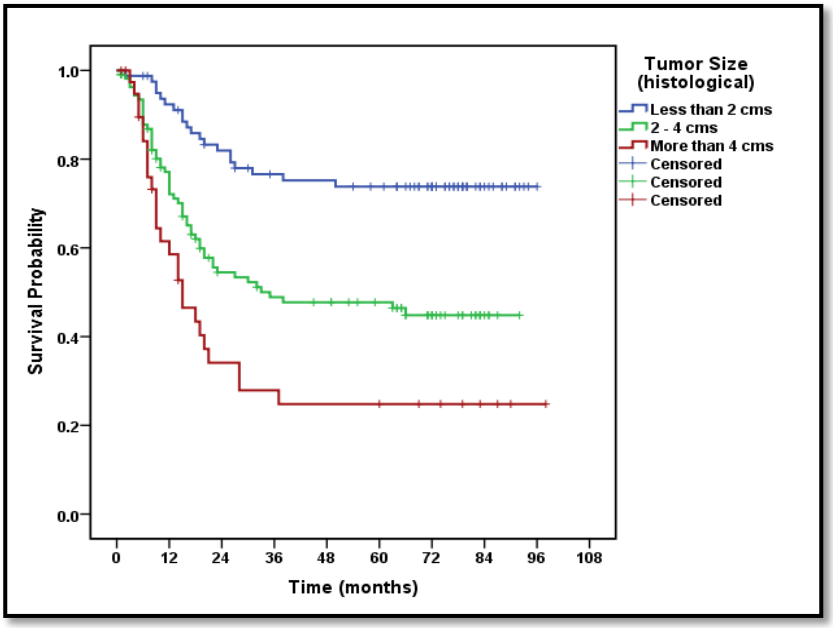
5.5.11 Survival according to Tumor Size (Histopathological) (n=229): 5 yr survival rate of tongue cancer patients was found to be significantly associated with size of the primary tumor (Fig. 5.5.10). Patients with tumor size of more than 4 cms had the worst survival of 24.8% followed by 46.4% 5yr survival of patients with tumor more than 2 cms but less than 4cms. (table 5.5.11).

Table 5.5.11: Observed survival rate (%) according as per tumor size

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Size in greatest dimension (n=229)							
2 cms or less	80	92.3	81.9	76.6	75.2	73.8	<0.001
2.1 – 4 cms	109	72.1	54.5	48.9	47.7	46.4	
More than 4 cms	40	58.6	34.1	27.9	24.8	24.8	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
2 cms or less	1						
2.1 – 4 cms	2.69 (1.61 – 4.50)						<0.001
More than 4cms	4.76 (2.64 – 8.56)						<0.001

**Calculated using Log Rank Test*

Figure 5.5.10: Observed survival rate (%) of tongue cancer according to tumor size



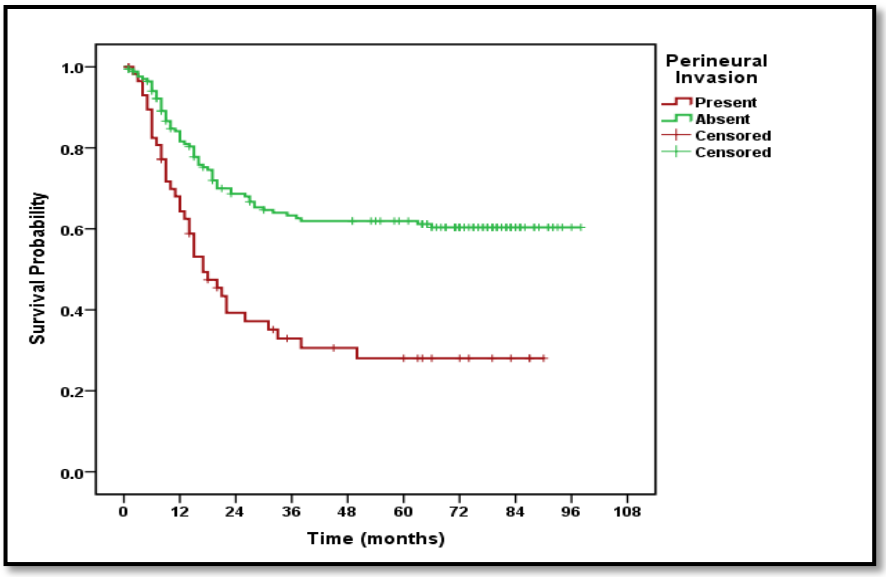
5.5.12 Survival according to Perineural invasion (PNI) (n=229): Presence of perineural invasion on histology was found to significantly affect the survival adversely. Patients with PNI had 5 yr survival of only 28.0% as compared to 61.2% in those patients without PNI (table 5.5.12) (Fig. 5.5.11).

Table 5.5.12: Observed Survival rate (%) of tongue cancer according Perineural invasion

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Perineural extension (n=229)							
Absent	170	81.6	68.7	63.3	61.9	61.2	<0.001
Present	59	64.3	39.3	32.9	30.6	28.0	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						<0.001
Present	2.43 (1.62- 3.65)						

**Calculated using Log Rank Test*

Figure 5.5.11: Observed survival rate (%) of tongue cancer according to perineural invasion



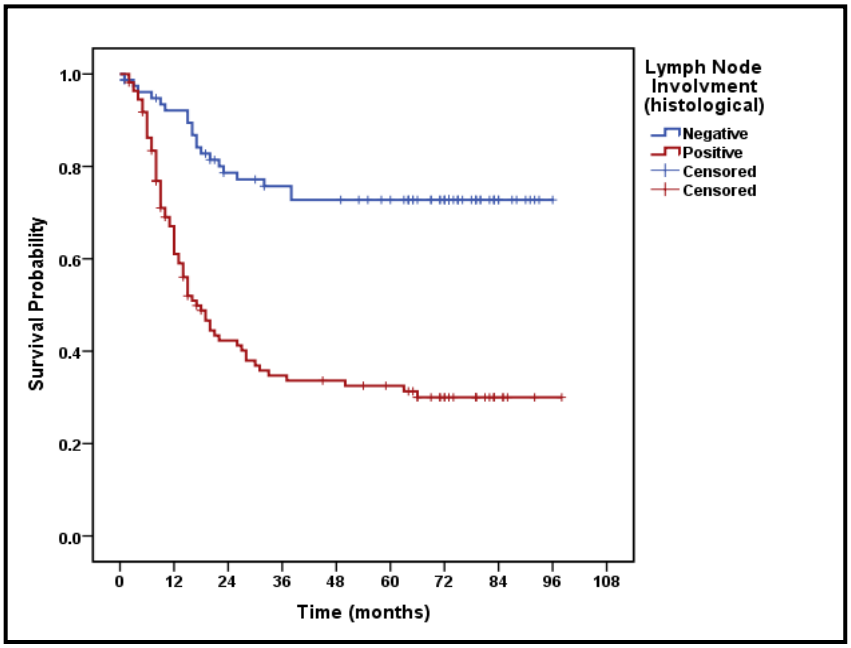
5.5.13 Survival according to histopathological Lymph Node Involvement (n=189): 229 patients who underwent surgical treatment, neck dissection reports were available for 189 patients, out which 110 patients were found to be positive for nodal metastasis. 5yr survival for node negative and node positive patients was found to be 72.8% and 31.3% respectively (table 5.5.13)

Table 5.5.13: Observed survival rate (%) of tongue cancer according to histopathological lymph node involvement *(n=189)*

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Lymph Node involvement (n=*189*)							
Nodes Negative for metastasis	79	92.1	78.6	75.7	72.8	72.8	<0.001
Nodes Positive for metastasis	110	61.0	42.3	34.7	32.5	31.3	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Nodes Negative for metastasis	1						<0.001
Nodes Positive for metastasis	3.77 (2.29 – 6.23)						

**Calculated using Log Rank Test*

Figure 5.5.12: Observed survival rate (%) of tongue cancer according to histopathological lymph node involvement *(n=189)*



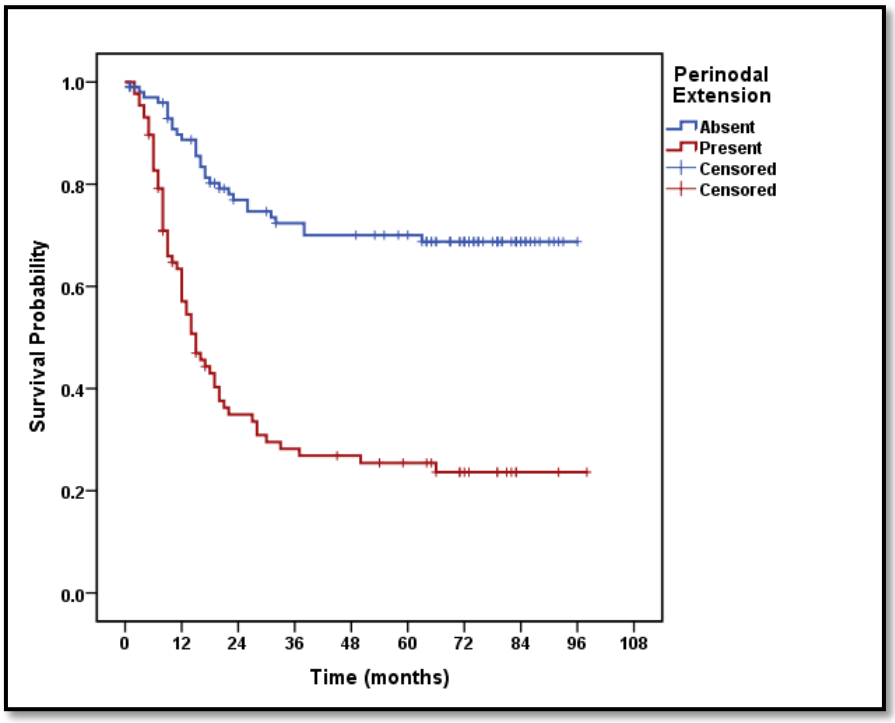
5.5.14 Survival according to Extra Capsular Spread (ECS) (n=189): Positive ECS was found in 224 patients, these patients were found to have significantly lower 5yr survival of 25.4% as compared to 68.8% in patients found negative for ECS (table 5.5.14) (Fig. 5.5.13).

Table 5.5.14: Observed survival rate (%) of tongue cancer according ECS

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Perinodal Extension (n=*189*)							
ECS negative	102	.88.7	76.9	72.4	70.0	68.8	<0.001
ECS positive	87	57.1	34.9	28.2	26.9	25.4	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
ECS negative	1						<0.001
ECS positive	3.92 (2.50 - 6.13)						

**Calculated using Log Rank Test*

Figure 5.5.13: Observed survival rate (%) of tongue cancer according to ECS



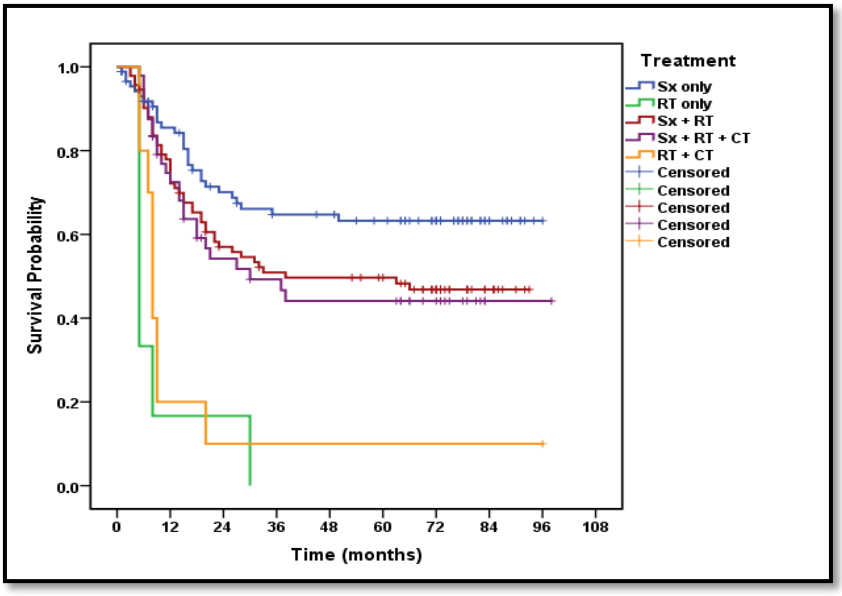
5.5.15 Survival according to Treatment: Surgery individually or in combination with Radiotherapy/ chemotherapy was the main modality of treatment. Out of 245 patients except for 16 cases, all other patients received surgery. These non surgically treated cases had the lowest 5yr survival i.e 0.0% and 10.0% for only radiotherapy, and chemotherapy plus radiotherapy respectively (Fig. 5.5.14). Out of the 229 surgically treated cases only surgically treated cases had the highest 5 yr survival of 63.3% and the patients who received all the three modalities of treatment namely Surgery, Radiotherapy and Chemotherapy had the lowest survival of 44.1% (table 5.5.15).

Table 5.5.15: Observed survival rate (%) of tongue cancer according to treatment

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Treatment							
Surgery only	89	85.5	70.1	64.7	64.7	63.3	<0.001
Radiotherapy only	6	16.7	16.7	0.00	0.00	0.00	
Surgery + Radiotherapy	92	72.2	57.0	50.9	49.7	48.3	
Surgery + Radiotherapy + Chemotherapy	48	72.5	.542	46.7	44.1	44.1	
Radiotherapy + Chemotherapy	10	20.02	10.0	10.0	10.0	10.0	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Surgery only	1						
Radiotherapy only	8.86 (3.63 – 21.67)						<0.001
Surgery + Radiotherapy	1.59 (1.00 – 2.54)						0.04
Surgery + Radiotherapy + Chemotherapy	1.73 (1.01 – 2.96)						0.04
Radiotherapy + Chemotherapy	5.72 (2.68 – 12.21)						<0.001

**Calculated using Log Rank Test*

Figure 5.5.14: Observed survival rate (%) of tongue cancer according to treatment



5.2.18 Multifactorial analysis for determining independent prognostic factors for overall survival of tongue cancer:

All the factors which were found to influence overall survival in univariate analysis, such as age (≥ 40yrs), presence of comorbidity, overall stage, lymph node involvement, histological tumor size, tumor differentiation, bone infiltration, perineural invasion, extra capsular spread and treatment modality were considered for further multifactorial analysis. However, as overall TNM stage includes tumor size and lymph node involvement, in order to avoid interaction between these factors two seperate models were developed, one with overall stage and other with tumor size and lymph node involvement, keeping all the other variables same in both the models. The results showed that presence of comorbidity (HR = 3.04, 95% CI = 1.94 - 4.78; p<0.001), poor tumor differentiation (HR = 1.99, 95% CI = 1.24 – 3.18; p <0.001), perineural invasion (HR = 1.90, 95% CI = 1.23 - 2.95; p <0.001), extra capsular spread (HR = 2.96, 95% CI = 1.83 - 4.80; p <0.001), advanced TNM stage (HR = 1.79, 95% CI = 1.09 - 2.95; p= 0.02) (table 5.5.18), lymph node involvement (HR = 1.76, 95% CI = 1.13 – 2.91; p<0.001) and tumor size of more than 4cms (HR = 2.77, 95% CI = 1.39 – 5.49; p <0.001) (table 5.5.17) were found to be independent predictors for poor overall survival of tongue cancer patients.

Table 5.5.16: Univariate and multifactorial analysis of prognostic factors for overall survival in patients with tongue cancer

Model - 1

Parameter	No. of cases	Univariate		Multifactorial	
		HR (95% CI)	p value	HR (95% CI)	p value
Age (< 40 yrs)	59	1			
Age (≥ 40 yrs)	186	2.42 (1.61 – 3.65)	<0.001	--	0.11
Comorbidity (Absent)	155	1		**1**	
Comorbidity (Present)	74	1.66 (1.13 – 2.45)	0.01	**3.04 (1.94 - 4.78)**	**<0.001****
Well/ Moderately Differentiated/ Unknown	172	1		**1**	
Poorly Differentiated	57	2.42 (1.61 – 3.65)	<0.001	**1.99 (1.24 – 3.18)**	**<0.001****
Early Stage (TNM I &II)	119	1		**1**	
Advanced Stage (TNM III &IV)	126	3.25 (2.16 – 4.88)	0.01	**1.79 (1.09 – 2.95)**	**0.02****
Perineural invasion (Absent)	158	1		**1**	
Perineural invasion (Present)	59	2.43 (1.62- 3.65)	<0.001	**1.90 (1.23 - 2.95)**	**<0.001****
ECS (Absent)	102	1		**1**	
ECS (Present)	87	3.92 (2.50 - 6.13)	<0.001	**2.96 (1.83 - 4.80)**	**<0.001****
Treatment				--	0.97
Surgery only	89	1			
Radiotherapy only	6	8.86 (3.63 – 21.67)	<0.001		
Surgery + Radiotherapy	92	1.59 (1.00 – 2.54)	0.04		
Surgery + Radiotherapy + Chemotherapy	48	1.73 (1.01 – 2.96)	0.04		
Radiotherapy + Chemotherapy	10	5.72 (2.68 – 12.21)	<0.001		

§ Abbreviations: HR, hazard ratio; CI, confidence interval
** Significant (p value <0.05)

Table 5.5.17: Univariate and multifactorial analysis of prognostic factors for overall survival in patients with tongue cancer

Model - 2

Parameter	No. of cases	Univariate		Multifactorial	
		HR (95% CI)	p value	HR (95% CI)	p value
Age (< 40 yrs)	59				
Age (≥ 40 yrs)	186	1.83 (1.13 – 2.97)	0.01	--	0.11
Comorbidity (Absent)	155	1.66 (1.13 – 2.45)	0.01	**1**	
Comorbidity (Present)	74			**3.19 (2.02 - 5.04)**	**<0.001****
Well/ Moderately Differentiated/ Unknown	172	2.42 (1.61 – 3.65)	<0.001	**1**	
Poorly Differentiated	57			**1.95 (1.23 – 3.11)**	**<0.001****
Tumor Size					
< 2cms	80	1		1	
2- 4 cms	109	2.69 (1.61 – 4.50)	<0.001	1.50 (0.81 – 2.77)	**0.19**
> 4cms	40	4.76 (2.64 – 8.56)	<0.001	**2.77 (1.39 – 5.49)**	**<0.001****
Lymph node (Absent)	142	1		**1**	
Lymph node (Present)	103	2.63 (1.81 – 3.82)	<0.001	**1.76 (1.13 – 2.91)**	**0.02****
Perineural invasion (Absent)	158	2.43 (1.62- 3.65)	<0.001	**1**	
Perineural invasion (Present)	59			**1.85 (1.19 - 2.85)**	**<0.001****
ECS (Absent)	102	3.92 (2.50 - 6.13)	<0.001	**1**	
ECS (Present)	87			**3.19 (1.99 - 5.13)**	**<0.001****
Treatment				--	0.88
Surgery only	89	1			
Radiotherapy only	6	8.86 (3.63 – 21.67)	<0.001		
Surgery + Radiotherapy	92	1.59 (1.00 – 2.54)	0.04		
Surgery + Radiotherapy + Chemotherapy	48	1.73 (1.01 – 2.96)	0.04		
Radiotherapy + Chemotherapy	10	5.72 (2.68 – 12.21)	<0.001		

§ Abbreviations: HR, hazard ratio; CI, confidence interval, ** Significant (p value <0.05)

Cheek Mucosa and Other Sites in Oral Cavity (Except Tongue)

5.6 Survival Analysis of Cheek Mucosa and Other Sites In Oral Cavity (n=481)

5.6.1 Out of the total 726 oral cancer cases, 245 cases were of tongue cancer which has been analyzed separately and results have been presented in section 5.5. The remaining 481 cases which include cheek mucosa and other sites in the oral cavity were analyzed together as one group and results of the same are presented in succeeding paragraphs. The site wise breakdown of the cases analyzed in this section are as follows (table 5.6.1).

Table 5.6.1: Distribution of cases as per subsites

Sl. No.	Subsite (ICD code as per ICD-10)	Specific site (nomenclature as per AJCC manual 7th edition) with ICD-10 codes	Specific site No.	Subsite Total (%)
1.	**Lip (C00) Excludes skin of lip**	Mucosa of Upper lip (C00.3)	2	**22 (4.5)**
		Mucosa of Lower lip (C00.4)	20	
2.	**Gum (C03)**	Upper Gum (C03.0)	14	**112 (23.3)**
		Lower Gum (C03.1)	97	
		Gum, unspecified (C03.9)	1	
3.	**Hard Palate (C05.0)**	Hard Palate (C05.0)	20	**20 (4.1)**
4.	**Other and Unspecified parts of mouth (C06)**	Cheek Mucosa (C06.0)	232	**232 (48.2)**
		Vestibule of mouth (C06.1)	74	**74 (15.3)**
		Retromolar Area (C06.2)	21	**21 (4.3)**
Total				**481 (100%)**

5.6.2 Overall Survival of Cheek Mucosa: At the end of follow-up (31st Dec 2014) out of the 481 patients, 214 (44.5 %) patients had expired, and 267 (55.5%) were censored. The median follow-up period was 36 months (range, 1 to 103 months). The 5-year Overall survival of the cohort calculated by using actuarial method was found to be 52% (table 5.6.2).

Table 5.6.2: Overall survival of cheek mucosa cancer

Total Number	Survival in percentage				
	1 Yr	2 Yr	3 Yr	4 Yr	5 Yr
481	79	64	60	55	52

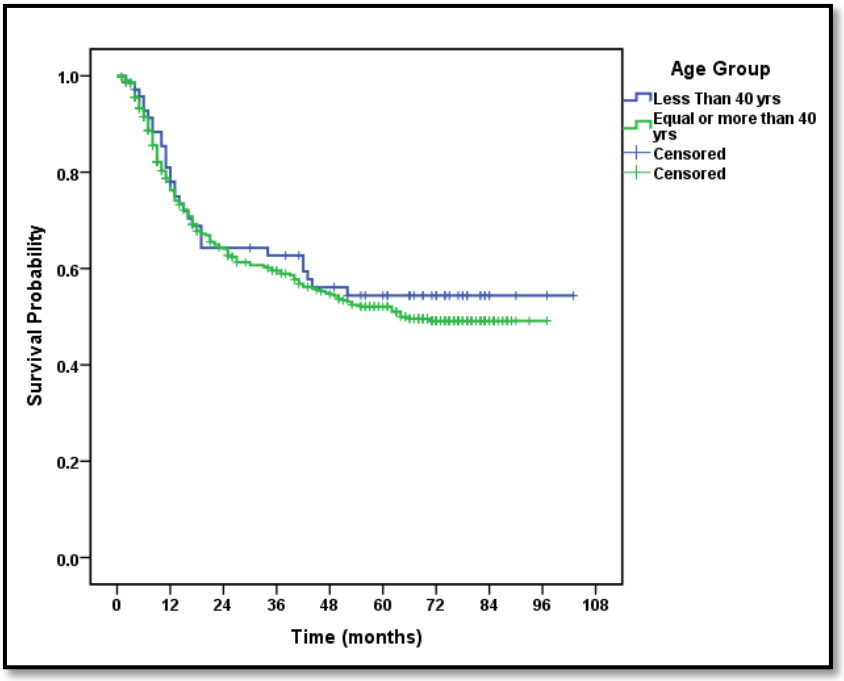
5.6.3 Survival according to Age: Patients were categorized according to several cut-offs of age at registration and its effect on survival was analyzed using Kaplan-Meier curves and the log-rank test. The difference in 5 yr overall survival rate between age group less than 40 yrs, 40-49, 50-59, 60-69 and more than 70 yrs was not found to be statistically significant (table 5.6.3). Similarly, no significant difference in 5 yr survival was observed in age groups formed by taking 40 yrs as a cut-off (p= 0.53) (Fig. 5.6.1).

Table 5.6.3: Observed survival rate of cheek mucosa cancer according to age

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Age (years), Median – 52 years (18-85 yrs)							
< 40	71	78.0	64.3	62.7	56.1	54.4	0.65
40 to 49	137	74.7	56.6	50.7	48.9	47.9	
50 to 59	136	79.6	71.2	65.2	58.7	54.6	
60 to 79	103	75.0	65.6	62.0	57.0	50.6	
≥ 70	34	72.6	63.1	59.8	56.3	52.3	
Age (as per cut-off of 40 yrs)							
< 40	71	78.0	64.3	62.7	56.1	54.4	0.53
≥ 40	410	76.2	64.1	59.5	54.6	52.1	

**Calculated using Log Rank Test*

Figure 5.6.1: Observed survival rate (%) of cheek mucosa cancer according to age



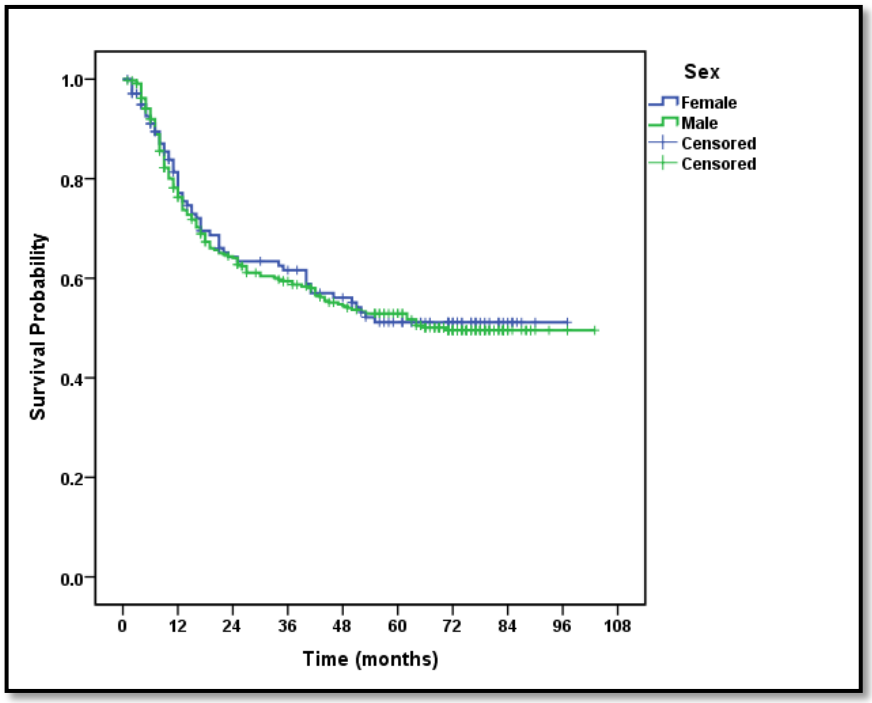
5.6.4 Survival according to Gender: The 5 yr survival rate for males and females was found to be 51.7% and 52.1% respectively (table 5.6.4), which was not significantly different for each other (p=0.81) (Fig. 5.6.2).

Table 5.6.4: Observed survival rate (%) of cheek mucosa cancer according to gender

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Gender							
Male	342	76.3	64.1	59.4	54.4	51.7	0.81
Female	139	77.1	63.4	61.6	56.1	52.1	

**Calculated using Log Rank Test*

Figure 5.6.2: Observed survival rate (%) of cheek mucosa cancer according to gender



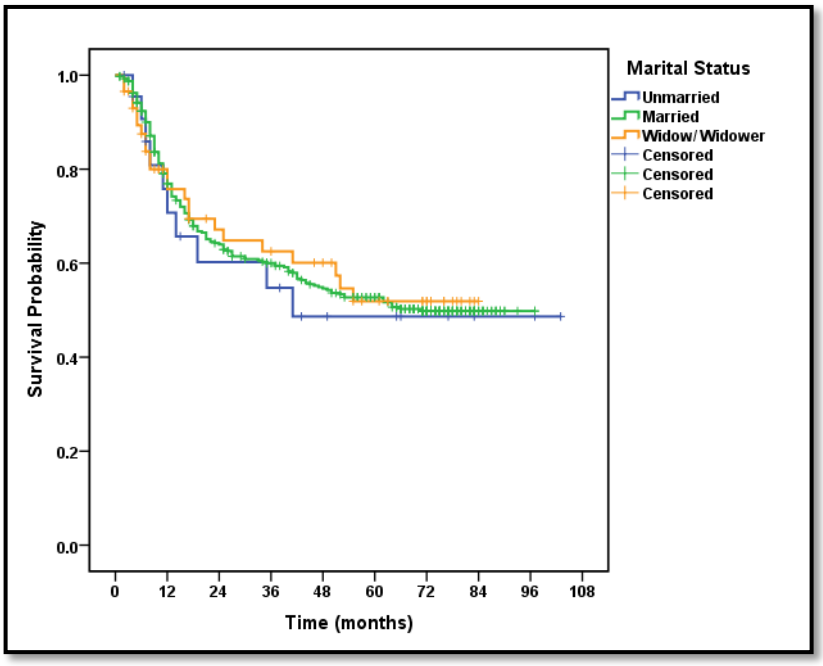
5.6.5 Survival according to Marital Status: The patients were divided into three categories as per their marital status reported at the time of registration. No significant (p=0.92) difference in survival was observed between the three groups namely unmarried, married or widow/ widower (table 5.6.5) (Fig. 5.6.3).

Table 5.6.5: Observed survival rate (%) of cheek mucosa cancer according to marital status

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Marital Status							
Unmarried	23	70.7	65.7	54.7	48.7	48.7	0.92
Married	400	76.9	64.0	59.4	54.6	51.7	
Widow/ widower	58	75.8	.67.1	62.5	60.1	51.9	

**Calculated using Log Rank Test*

Figure 5.6.3: Observed survival rate (%) of cheek mucosa cancer according to marital status



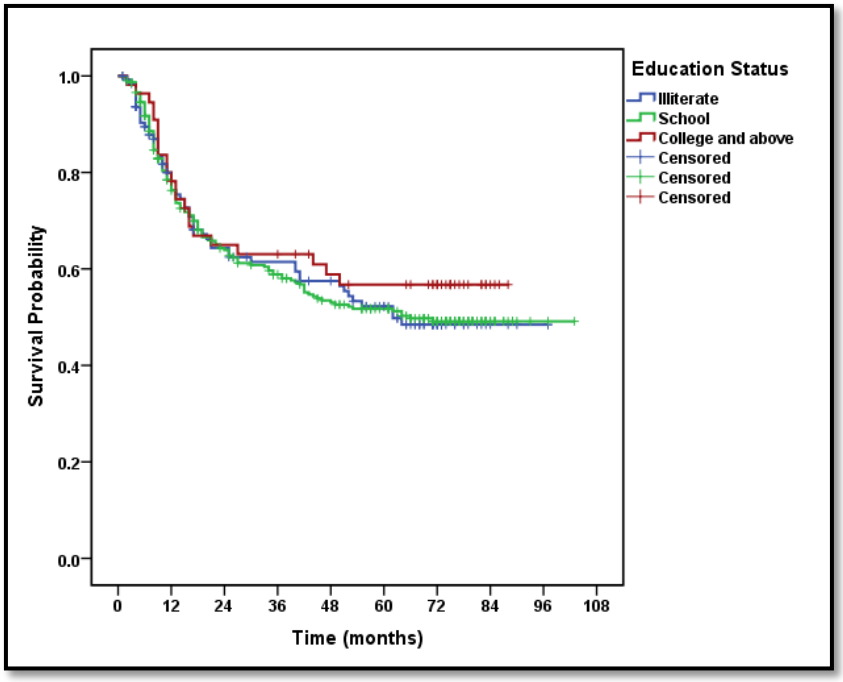
5.6.6 Survival according to Educational Status: The 5yr survival rate was found to be highest for patients with educational qualification of college and above (56.7%), followed by those who had done any level of schooling (51.2%) and lowest survival rate was found to be of illiterate (49.8%) patients (table 5.6.6). However, this difference in 5yr survival between the three levels of education failed to attain statistical significance (p=0.68) (Fig. 5.6.4).

Table 5.6.6: Observed survival rate (%) of cheek mucosa cancer according to education

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Education Status							
Illiterate	130	76.3	64.3	61.5	57.5	49.8	0.68
Schooling	296	76.3	63.9	58.9	53.0	51.2	
College and above	55	78.2	65.0	60.9	58.8	56.7	

**Calculated using Log Rank Test*

Figure 5.6.4: observed survival rate (%) of cheek mucosa cancer according to education status



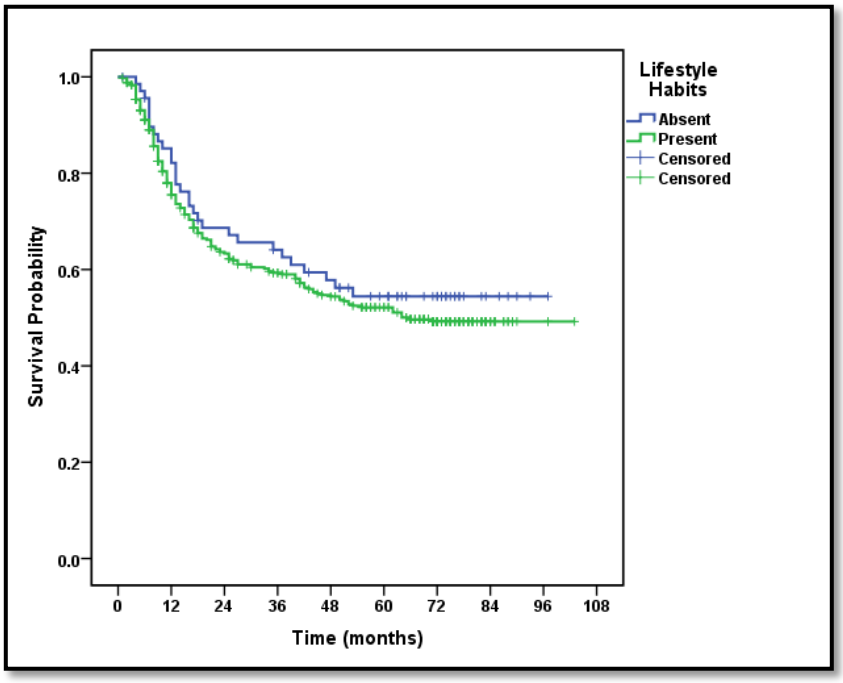
5.6.7 Survival according to Lifestyle Habits: Patients having habit of any form/ type of tobacco or alcohol were grouped in one category. Patients having lifestyle habit were found to have a 5 yr survival of 51.1 % and those without any had a 5 yr survival of 54.4% (table 5.6.7). However, this difference not statistically significant (p= 0.45) (Fig. 5.6.5).

Table 5.6.7: Observed survival rate (%) of cheek mucosa cancer according to presence of any habit (including smoking, any type of tobacco chewing and alcohol consumption)

Factor	Total Number	Survival in percentage					p Value *
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Habit							
Absent	65	82.1	67.1	62.5	56.2	54.4	0.45
Present	164	75.5	63.3	59.0	54.4	51.1	

**Calculated using Log Rank Test*

Figure 5.6.5: Observed survival rate (%) of cheek mucosa cancer according to presence of lifestyle habit



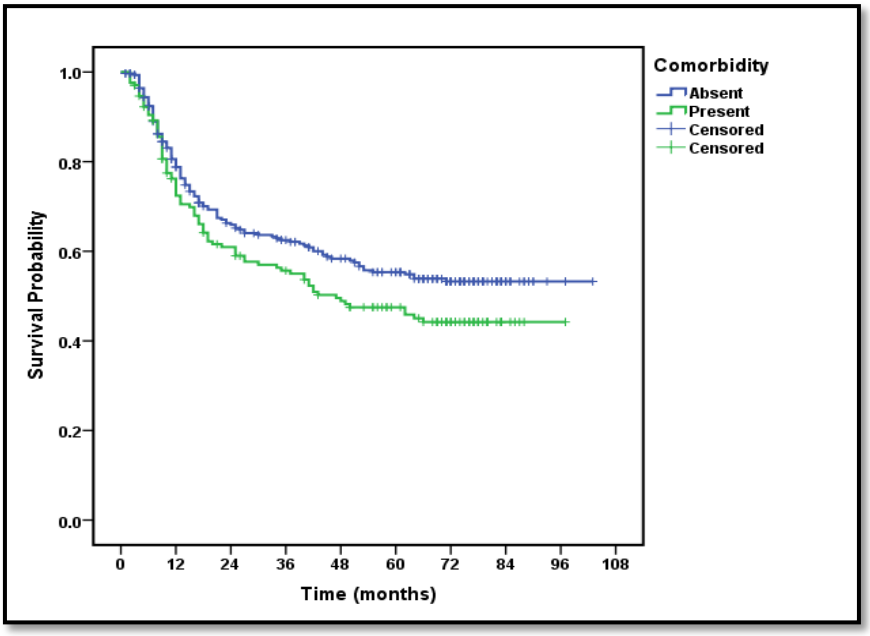
5.6.8 Survival according to Comorbidity: Cheek mucosa cancer patients having a concomitant comorbidity (Hypertension, Diabetes mellitus, Heart Disease, Asthma and HIV) were found to have significantly lower survival (45.9%) as compared to patients without any comorbidity (55.3%) (Fig. 5.6.6). However, this difference in survival rates between the two groups failed to attain statistical significance (p=0.07) (table 5.6.8).

Table 5.6.8: Observed survival rate (%) of cheek mucosa according to presence of comorbidity

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Comorbidity							
Absent	312	78.8	65.9	62.1	58.4	55.3	0.07
Present	169	72.4	59.0	55.0	48.9	45.9	

**Calculated using Log Rank Test*

Figure 5.6.6 : Observed survival rate (%) of Cheek Mucosa cancer according to presence of comorbidity



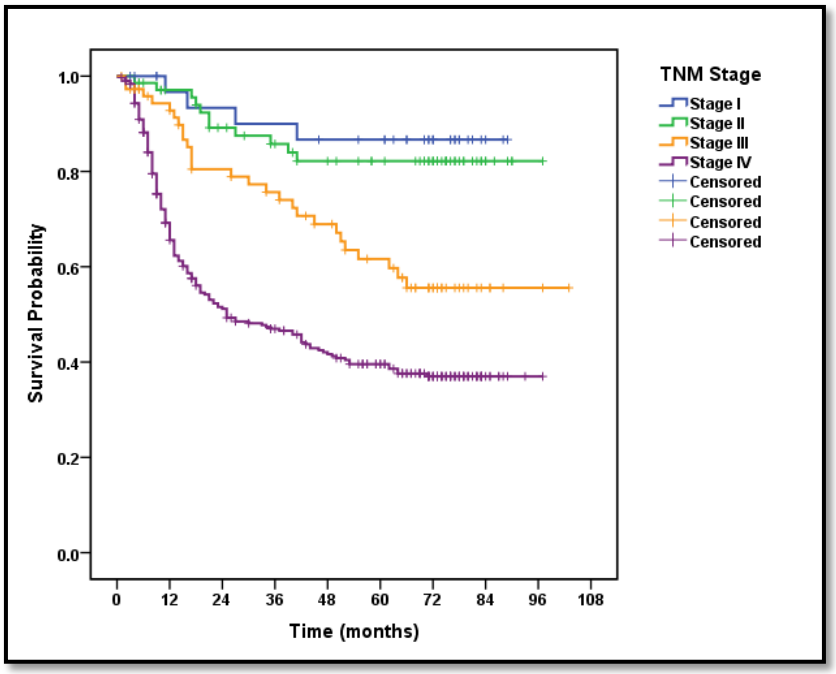
5.6.9 Survival according to TNM staging: TNM stage was found to significantly associated with overall survival (p<0.001) (Fig. 5.6.9). Stage IV had the lowest 5 yr survival rate of 38.6% and stage I had the highest survival rate of 86.7% (table 5.6.7).

Table 5.6.9: Observed survival rate (%) of cheek mucosa according to TNM Stage

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
TNM Stage							
I	34	96.7	90.0	90.0	86.7	86.7	<0.001
II	70	97.1	892	84.0	82.2	82.2	
III	74	92.8	78.9	74.0	68.9	59.7	
IV	303	65.6	51.2	47.0	41.7	38.6	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
I	1						
II	1.37 (0.43 – 4.32)						0 .58
III	3.60 (1.26 – 10.29)						0.01
IV	7.23 (2.68 – 19.50)						<0.001

**Calculated using Log Rank Test*

Figure 5.6.7: Observed survival rate (%) of cheek mucosa cancer according to TNM Stage



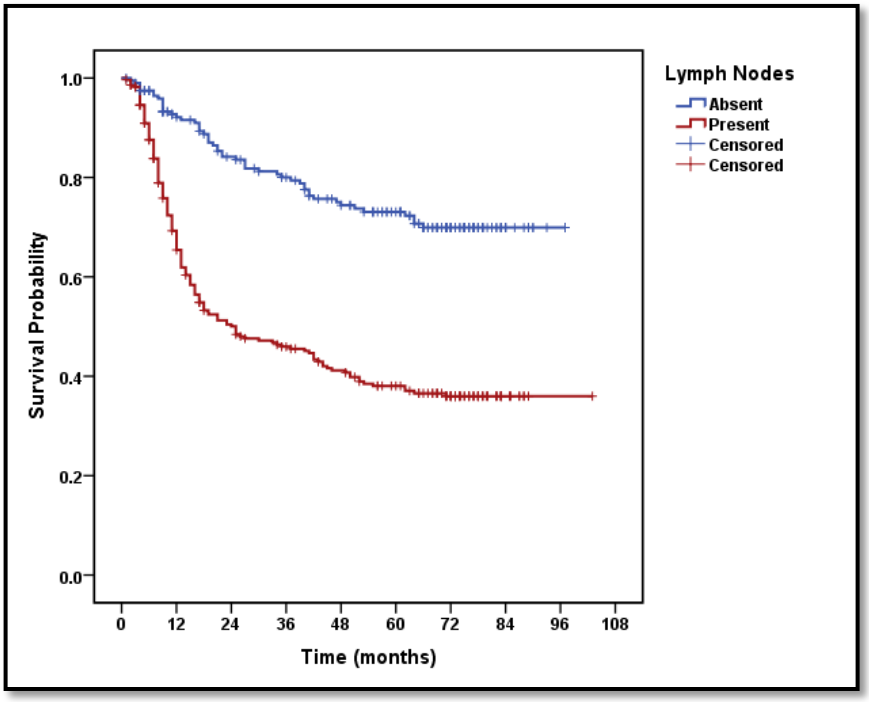
5.6.10 Survival according to Lymph Node Involvement: Clinical lymph node status was found to be significantly associated with overall survival (Fig. 5.6.8). Patients with lymph node involvement had poorer survival as compared to node negative (N0) patients (table 5.6.10).

Table 5.6.10: Observed survival rate (%) of cheek mucosa cancer according to clinical nodal status

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Lymph Node Involvement (Clinical)							
Absent	199	92.1	83.6	79.4	74.4	72.3	<0.001
Present	282	65.4	50.0	45.5	40.7	37.1	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						
Present	3.11 (2.27 – 4.27)						<0.001

**Calculated using Log Rank Test*

Figure 5.2.8: Observed survival rate (%) of cheek mucosa cancer according to clinical lymph node status



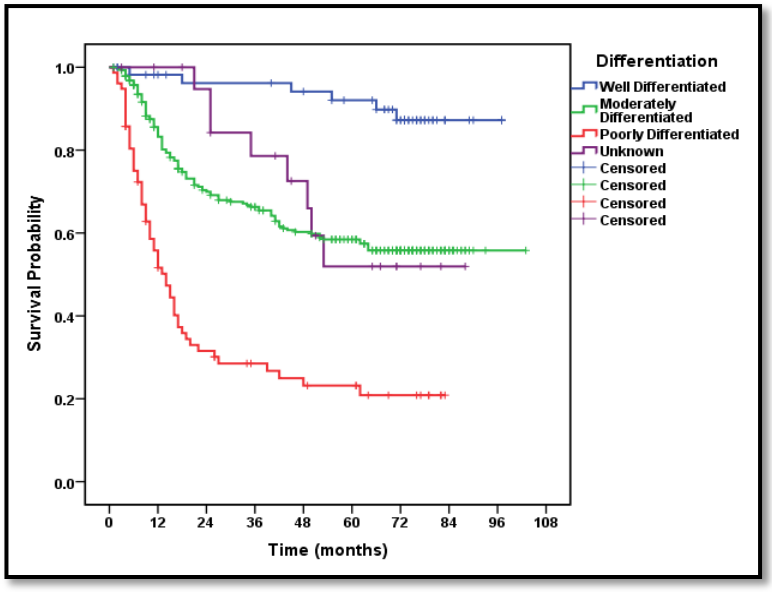
5.6.11 Survival according to Tumor Differentiation: Out of the 481 patients 39 patients did not receive surgical treatment hence their tumor differentiation could not be ascertained due to non-availability of their histopathological reports. Patients having Poorly differentiated tumor were found to have the worst 5yr survival of 20.9% , whereas well and moderately differentiated tumors had better survival of 92.0% and 57.4% respectively (table 5.6.11) (Fig. 5.6.9). In addition, tumor differentiation of 22 patients was not mentioned in the histopathological reports hence a separate category "Unknown differentiation"was created and taken into consideration for survival analysis. The 5yr survival rate of these patients was found to be 51.9%.

Table 5.6.11: Observed survival rate (%) of cheek mucosa cancer according to tumor differentiation

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Differentiation (n=442)							
Well Differentiated	59	98.2	96.2	96.2	94.1	92.0	<0.001
Moderately Differentiated	284	83.2	69.9	66.3	60.2	57.4	
Poorly Differentiated	77	51.6	31.5	28.5	23.2	20.9	
Unknown	22	94.7	84.2	78.6	66.0	51.9	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Well Differentiated	1						
Moderately Differentiated	4.75 (2.08 – 10.81)						<0.001
Poorly Differentiated	14.85 (6.37 – 34.58)						<0.001
Unknown	3.91 (1.35 – 11.29)						0.01

**Calculated using Log Rank Test*

Figure 5.6.9: Observed survival rate (%) of cheek mucosa cancer to tumor differentiation (n=442)



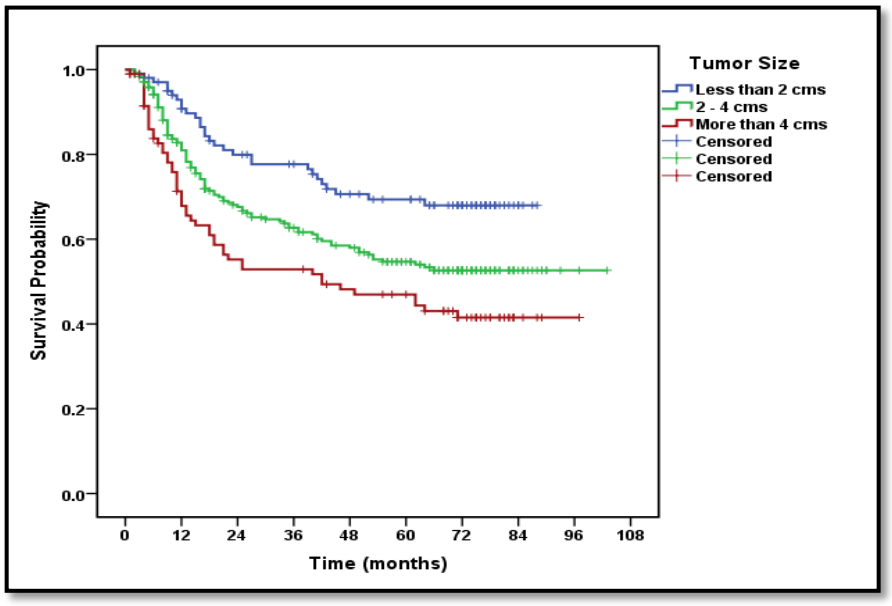
5.6.12 Survival according to Tumor size (Histopathological): 5 yr survival rate of oral cavity cancer patients was found to be significantly associated with size of the primary tumor (Fig. 5.6.10). Patients with tumor size of more than 4cms had poorer prognosis as compared to patients with smaller size tumors (table 5.6.12).

Table 5.6.12: Observed survival rate (%) of cheek mucosa cancer according as per tumor size

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Size in greatest dimension (n=442)							
2 cms or less	103	90.8	79.9	77.7	70.6	69.4	<0.001
2.1 – 4 cms	242	80.9	67.6	63.7	58.0	54.0	
More than 4cms	97	67.8	55.2	52.9	47.0	44.4	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
2 cms or less	1						
2.1 – 4 cms	1.70 (1.27 – 2.57)						0.01
More than 4cms	2.40 (1.52 – 3.79)						<0.001

**Calculated using Log Rank Test*

Figure 5.6.10: Observed survival rate (%) of cheek mucosa cancer according to tumor size



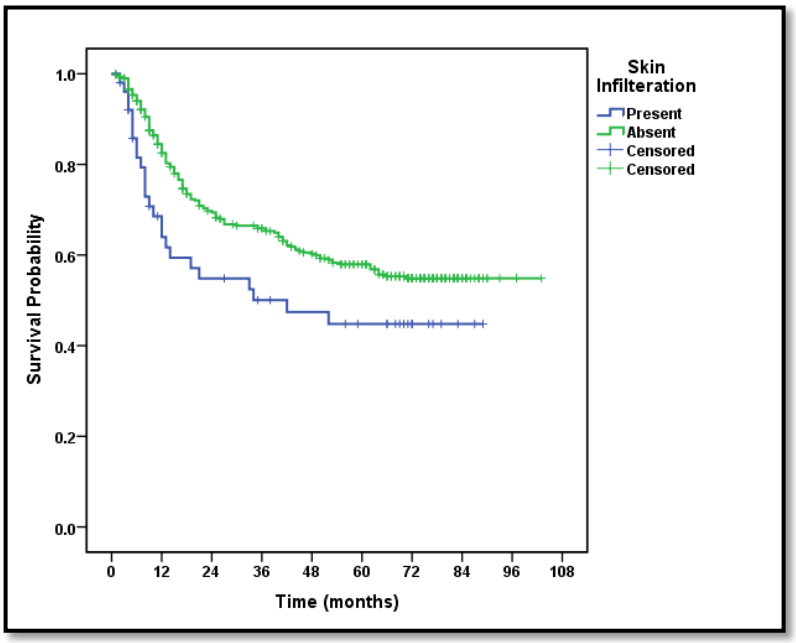
5.6.13 Survival according to skin infiltration: 5 yr survival of patients having skin infiltration was found to be 44.8%, which was significantly (p <0.001) lower than those not having skin infiltration (57.9%) (table 5.6.13) (Fig. 5.6.11).

Table 5.6.13: Observed survival rate (%) of cheek mucosa r according to skin infiltration

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Skin Infiltration (n=442)							
Absent	390	82.5	69.4	65.9	60.2	57.9	0.03
Present	52	64.0	54.8	50.1	47.4	44.8	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						0.04
Present	1.55 (1.02 – 2.37)						

**Calculated using Log Rank Test*

Figure 5.6.11: Observed survival rate (%) of cheek Mucosa cancer according to skin infiltration



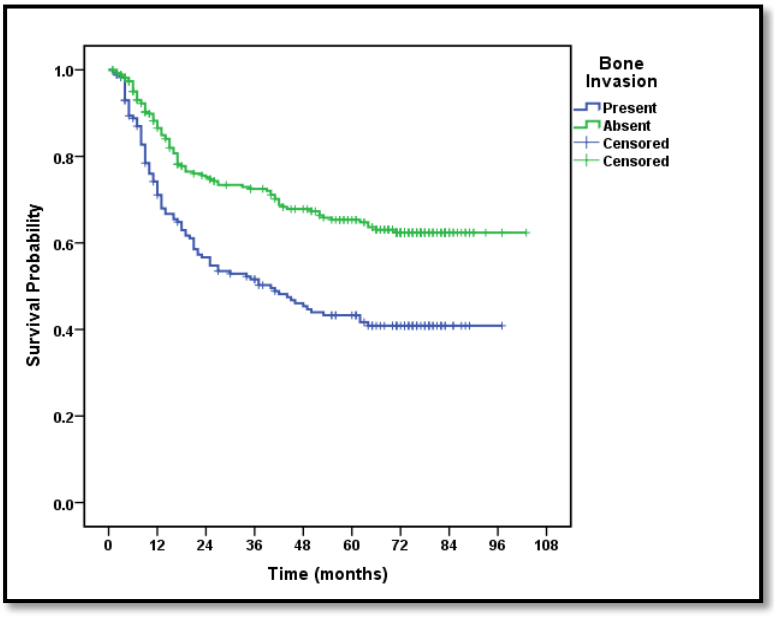
5.6.14 Survival according to bone infiltration: Patients with bone infiltration on histology were found to have significantly lower survival (p<0.001) as compared to patients without any bone involvement (Fig. 5.6.12). On univariate analysis cases showing presence of bone involvement were found to have unadjusted hazard of 1.96 (1.46- 2.63) of outcome as compared to those without evidence bone infiltration (table 5.6.14).

Table 5.6.14: Observed survival rate (%) of cheek mucosa according to bone infiltration

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Bone Infiltration (n=442)							
Absent	269	86.6	75.2	72.5	67.8	64.8	<0.001
Present	173	71.1	56.7	51.6	45.4	41.7	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						<0.001
Present	1.96 (1.46- 2.63)						

**Calculated using Log Rank Test*

Figure 5.6.12: Observed survival rate (%) of cheek mucosa cancer according as per bone infiltration



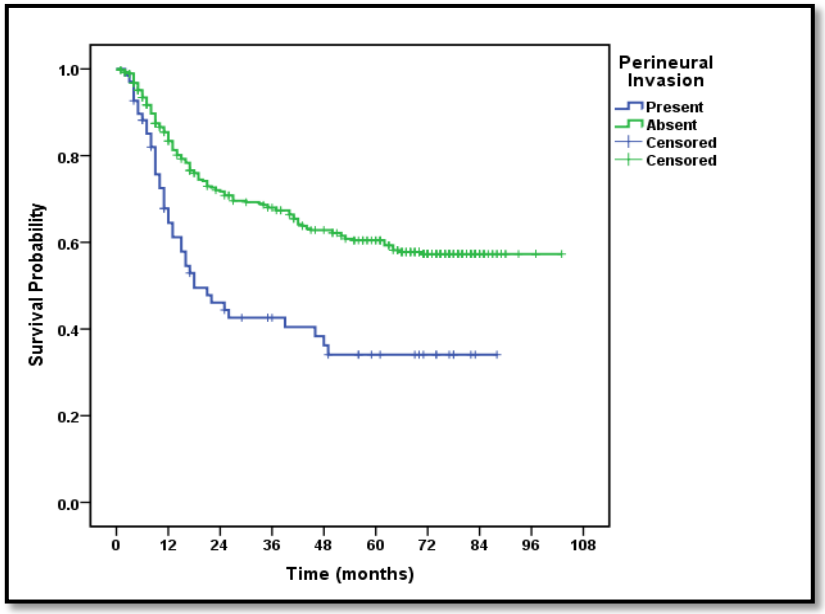
5.6.15 Survival according to Perineural Invasion (PNI): Presence of perineural invasion on histology was found to significantly affect the survival adversely. Patients with PNI had 5yr survival of only 34.1% as compared to 59.3% in patients without PNI (table 5.6.15) (Fig. 5.6.13).

Table 5.6.15: Observed survival rate (%) of cheek mucosa according perineural invasion

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Perineural extension (n=442)							
Absent	374	83.4	71.7	67.4	62.8	59.3	<0.001
Present	68	64.5	44.4	42.6	36.2	34.1	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Absent	1						<0.001
Present	2.11 (1.48- 3.06)						

**Calculated using Log Rank Test*

Figure 5.6.13: Observed survival rate (%) of cheek mucosa cancer according to perineural invasion



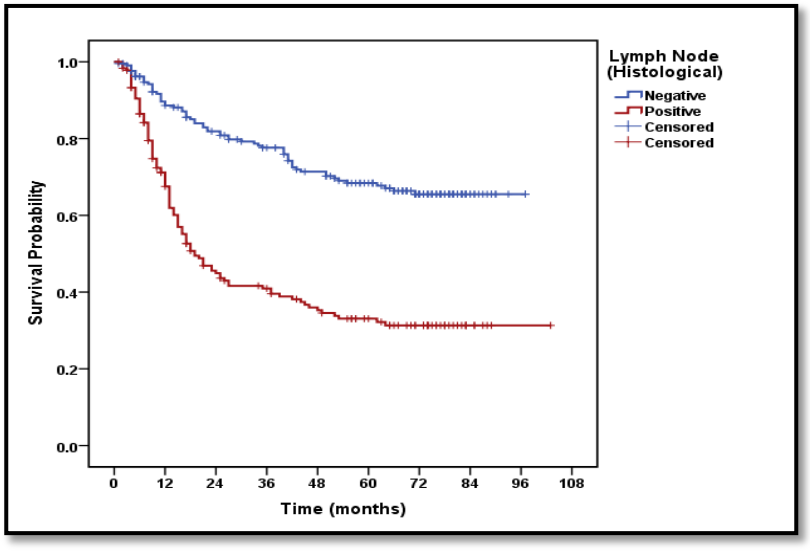
5.6.16 Survival according to histopathological Lymph Node Involvement: 442 patients who underwent surgical treatment, neck dissection reports were available for 395 patients, out of which 181 patients were positive for nodal metastasis. 5 yr survival for node negative and node positive patients was found to be 68.4% and 32.2% respectively (table 5.6.16).

Table 5.2.16: Observed survival rate (%) of cheek mucosa cancer according to histopathological lymph node involvement

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Lymph Node involvement (n= 395)							
Nodes Negative for metastasis	214	88.6	80.8	77.6	71.4	68.4	<0.001
Nodes Positive for metastasis	181	67.5	44.9	40.9	35.3	32.2	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Nodes Negative for metastasis	1						<0.001
Nodes Positive for metastasis	3.01 (2.21 – 4.11)						

**Calculated using Log Rank Test*

Figure 5.6.14: Observed survival rate (%) of cheek mucosa cancer according to histopathological lymph node involvement



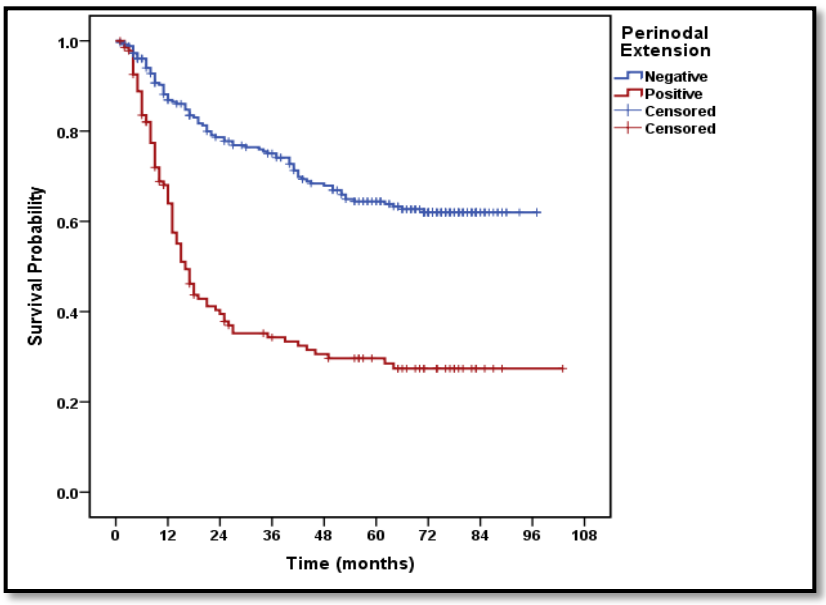
5.6.17 Survival according to Extra Capsular Spread (ECS): Positive ECS was found in 137, these patients were found to have significantly lower 5 yr survival of 28.5% as compared to 64.4% in patients found negative for ECS (table 5.6.17) (Fig. 5.6.15).

Table 5.6.17: Observed survival rate (%) of cheek mucosa cancer according to extra capsular spread

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Extra Capsular Spread (n=395)							
ECS negative	258	86.9	77.8	74.1	67.9	64.4	<0.001
ECS positive	137	64.0	37.8	34.3	30.6	28.5	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
ECS negative	1						<0.001
ECS positive	3.03 (2.25 - 4.10)						

**Calculated using Log Rank Test*

Figure 5.6.15: Observed survival rate (%) of cheek mucosa cancer according as per extra capsular spread



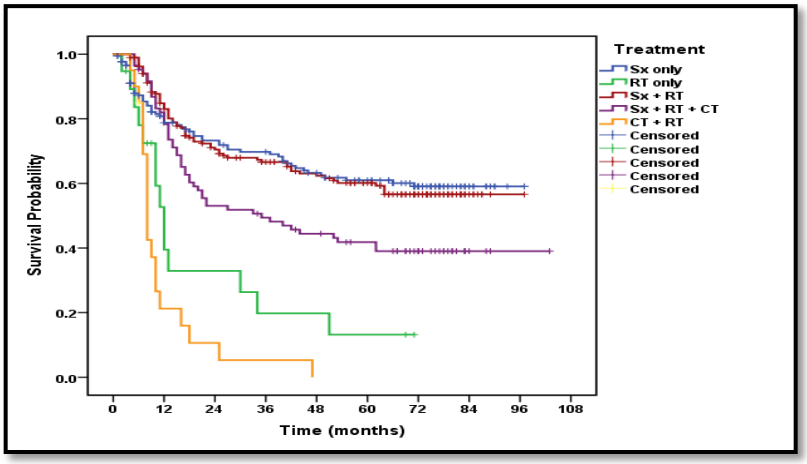
5.6.18 Survival according to Treatment: Surgery individually or in combination with Radiotherapy/ chemotherapy was the main modality of treatment. Out of 481 patients except for 39 cases, all other patients received surgery. These non-surgically treated cases had the lowest 5yr survival i.e 13.2% and 0.00%, for only radiotherapy, and chemotherapy plus radiotherapy respectively (Fig. 5.6.16). Out of the 442 surgically treated cases, only surgically treated cases had the highest 5 yr survival of 61.0% and the patients who received all the three modalities of treatment namely Surgery, Radiotherapy and Chemotherapy had the lowest survival of 39.0% (table 5.6.18).

Table 5.6.18: Observed survival rate (%) of cheek mucosa cancer according to treatment

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Treatment							
Surgery only	173	78.8	73.3	69.0	63.3	61.0	<0.001
Radiotherapy only	19	39.5	.32.9	19.8	19.8	13.2	
Surgery + Radiotherapy	185	83.0	70.5	66.6	62.3	59.3	
Surgery + Radiotherapy + Chemotherapy	84	78.4	53.0	49.4	44.4	39.0	
Radiotherapy + Chemotherapy	20	21.2	10.6	05.3	00.0	00.0	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Surgery only	1						
Radiotherapy only	3.61 (2.01 – 6.48)						<0.001
Surgery + Radiotherapy	1.00 (0.71 – 1.42)						0.96
Surgery + Radiotherapy + Chemotherapy	1.64 (1.12 – 2.38)						<0.001
Radiotherapy + Chemotherapy	6.53 (3.84 – 11.09)						<0.001

**Calculated using Log Rank Test*

Figure 5.6.16: Observed survival rate (%) of cheek mucosa cancer according to treatment



5.6.17 Multifactorial analysis for independent prognostic factors for overall survival:

All the factors which were found to influence overall survival in univariate analysis, such as, overall stage, lymph node involvement, histological tumor size, tumor differentiation, bone infiltration, perineural invasion, extra capsular spread and treatment modality were considered for further multifactorial analysis. However, as overall TNM stage includes tumor size and lymph node involvement, in order to avoid interaction between these factors two separate models were developed, one with overall stage and other with tumor size and lymph node involvement, keeping all the other variables same in both the models. The results showed that age (HR = 1.59, 95% CI = 1.02 – 2.48; p= 0.03) poor tumor differentiation (HR = 6.69, 95% CI = 2.79 – 16.05; p<0.001), perineural invasion (HR = 1.48, 95% CI = 1.02 - 2.14; p= 0.03), extra capsular spread (HR = 2.07, 95% CI = 1.48 – 2.90; p<0.001), advanced TNM stage (HR = 2.38, 95% CI = 1.33 – 4.23; p<0.001) (table 5.6.17), lymph node involvement (HR = 1.84, 95% CI = 1.27 – 2.69; p<0.001) and tumor size of more than 4 cms (HR = 1.73, 95% CI = 1.06 – 2.82; p= 0.02) (table 5.6.18) were found to be independent predictors for poor overall survival of cheek mucosa cancer patients.

Table 5.6.19: Univariate and multifactorial analysis of prognostic factors for overall survival in patients with cheek mucosa cancer

Model - 1

Parameter	No. of cases	Univariate		Multifactorial	
		HR (95% CI)	p value	HR (95% CI)	p value
Age (< 40 yrs)	71			1	
Age (≥ 40 yrs)	410	1.13 (0.76 – 1.66)	0.53	**1.59 (1.02 – 2.48)**	**0.03****
Differentiation					
Well Differentiated	59	1		**1**	
Moderately Differentiated	284	4.75 (2.08 – 10.81)	<0.001	**2.88 (1.24 – 6.66)**	**0.01****
Poorly Differentiated	77	14.85 (6.37 – 34.58)	<0.001	**6.69 (2.79 – 16.05)**	**<0.001****
Unknown	22	3.91 (1.35 – 11.29)	0.01	2.05 (0.70 – 6.00)	0.18
Early Stage (TNM I &II)	104	5.06 (2.99 – 8.57)	0.01	**1**	
Advanced Stage (TNM III &IV)	377			**2.38 (1.33 – 4.23)**	**<0.001****
Skin Infiltration (Absent)	390				
Skin Infiltration (Present)	52	1.55 (1.02 – 2.37)	0.04	**--**	0.14
Bone Infiltration (Absent)	269				
Bone Infiltration (Present)	173	1.96 (1.46 - 2.63)	<0.001	**--**	0.18
Perineural invasion (Absent)	374			**1**	
Perineural invasion (Present)	68	2.11 (1.48- 3.06)	<0.001	**1.48 (1.02 - 2.14)**	**0.03****
ECS (Absent)	258			**1**	
ECS (Present)	137	3.03 (2.25 - 4.10)	<0.001	**2.07 (1.48 – 2.90)**	**<0.001****
Treatment				--	0.84
Surgery only	173	1			
Radiotherapy only	19	3.61 (2.01 – 6.48)	<0.001		
Surgery + Radiotherapy	185	1.00 (0.71 – 1.42)	0.96		
Surgery + Radiotherapy + Chemotherapy	84	1.64 (1.12 – 2.38)	<0.001		
Radiotherapy + Chemotherapy	20	6.53 (3.84 – 11.09)	<0.001		

§ Abbreviations: HR, hazard ratio; CI, confidence interval, ** Significant (p value <0.05)

Table 5.6.20: Univariate and multifactorial analysis of prognostic factors for overall survival in patients with Cheek Mucosa cancer

Model - 2

Parameter	No. of cases	Univariate		Multifactorial	
		HR (95% CI)	p value	HR (95% CI)	p value
Age (< 40 yrs)	71			1	
Age (≥ 40 yrs)	410	1.13 (0.76 – 1.66)	0.53	**1.59 (1.02 – 2.48)**	**0.03****
Differentiation					
Well Differentiated	59	1		**1**	
Moderately Differentiated	284	4.75 (2.08 – 10.81)	<0.001	**3.24 (1.40 – 7.50)**	**<0.001****
Poorly Differentiated	77	14.85 (6.37 – 34.58)	<0.001	**7.62 (3.17 – 18.29)**	**<0.001****
Unknown	22	3.91 (1.35 – 11.29)	0.01	1.97 (0.67 – 5.78)	0. 21
Tumor Size					
<2cms	103	1		1	
2- 4 cms	242	1.70 (1.27 – 2.57)	0.01	1.27 (0.82 – 1.98)	0.27
> 4cms	97	2.40 (1.52 – 3.79)	<0.001	**1.73 (1.06 – 2.82)**	**0.02**
Lymph node Involvment (Absent)	199	3.11 (2.27 – 4.27)	<0.001	**1**	
Lymph node Involvment (Present)	282			**1.84 (1.27 – 2.69)**	**<0.001****
Skin Infiltration (Absent)	390				
Skin Infiltration (Present)	52	1.55 (1.02 – 2.37)	0.04	--	0.25
Bone Infiltration (Absent)	269				
Bone Infiltration (Present)	173	1.96 (1.46 - 2.63)	<0.001	--	0.25
Perineural invasion (Absent)	374			**1**	
Perineural invasion (Present)	68	2.11 (1.48- 3.06)	<0.001	**1.38 (1.01 - 2.00)**	**0.04****
ECS (Absent)	258			**1**	
ECS (Present)	137	3.03 (2.25 - 4.10)	<0.001	**1.87 (1.32 – 2.65)**	**<0.001****
Treatment				--	0.08
Surgery only	173	1			
Radiotherapy only	19	3.61 (2.01 – 6.48)	<0.001		
Surgery + Radiotherapy	185	1.00 (0.71 – 1.42)	0.96		
Surgery + Radiotherapy + Chemotherapy	84	1.64 (1.12 – 2.38)	<0.001		
Radiotherapy + Chemotherapy	20	6.53 (3.84 – 11.09)	<0.001		

§ Abbreviations: HR, hazard ratio; CI, confidence interval, ** Significant (p value <0.05)

Laboratory Parameters

5.7.1 Distribution of laboratory parameters: In the recent past, there have been a number of publications suggesting the role of various hematological parameters in cancer survival. Hence, pretreatment levels of hemoglobin, red cell distribution width percentage (RDW) total white blood cell count (WBC), absolute neutrophil, lymphocyte and monocyte counts were obtained from the hospital electronic medical record system. Out of total 726 cases, pretreatment counts for the above mentioned selected parameters were available for only 498 cases. Basic descriptive analysis of these parameters including their minimum and maximum values is presented in table 5.7.1. For the purpose survival analysis all the continuous variables were converted to categorical variable by taking their median values as cut-off's, except for hemoglobin for which 12gm% was taken as a cut-off.

Table 5.7.1: Descriptive data of hematological parameters

Sl No.	Parameter	Mean ± SD	Median	Minimum	Maximum
1.	Hemoglobin (g/dL)	12.99 ± 2.16	13.25	6.11	18.50
2.	RDW (%)	14.13 ± 2.26	13.65	10.70	26.70
4.	WBC (10^9/L)	8.82 ± 3.26	8.20	4.13	26.70
5.	Neutrophil (10^9/L)	5.68 ± 2.87	5.00	1.10	22.18
6.	Lymphocyte (10^9/L)	1.99 ± 0.72	1.95	0.24	5.46
7.	Monocyte (10^9/L)	0.57 ± 0.23	0.52	0.073	1.60
8.	Neutrophil/ lymphocyte ratio (NLR)	3.67 ± 4.29	2.50	0.76	45.10

§ Abbreviations: SD, Standard deviation

5.7.2 Survival Analysis (n= 498):

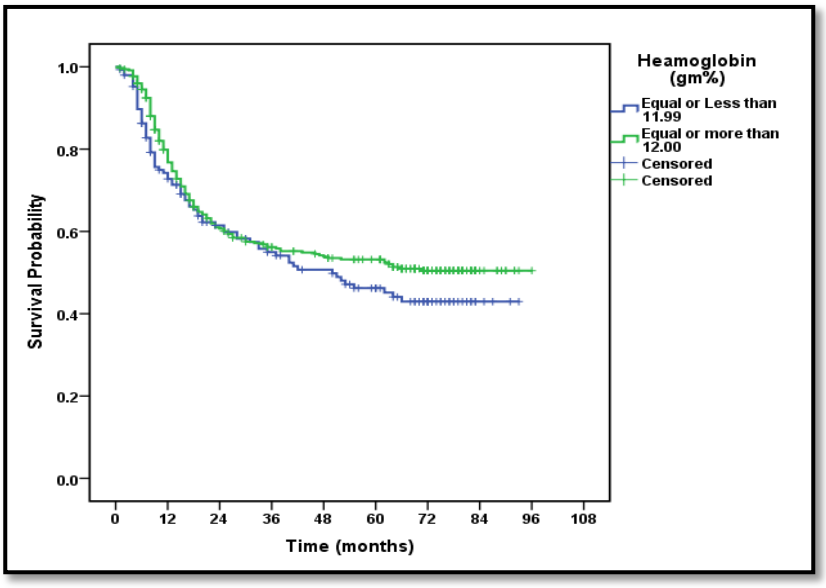
5.7.2.1 Survival according to heamoglobin levels: In order to access the effect of heamoglobin on survival, oral cancer patients were divided into two groups first by taking median value of 13.25 gm% as a cut-off and then also by taking 12gm% as a cut-off (table 5.7.2.1). However, in both the settings the survival was not found to be significantly different between two comparison groups (table 5.7.2.1) (Fig 5.7.2.1)

Table 5.7.2.1: Observed survival rate (%) according to heamoglobin levels

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
Heamoglobin (Median 13.25 gm%)							
Heamoglobin (≤ 13.24)	249	71.2	60.4	55.2	51.2	47.4	0.13
Heamoglobin (≥ 13.25)	249	80.0	61.5	56.6	54.3	53.8	
Heamoglobin (taking cut-off of 12 gm%)							
Heamoglobin (≤ 11.99)	148	72.8	61.4	55.0	49.8	45.1	0.16
Heamoglobin (≥ 12.00)	350	76.8	60.7	55.9	53.9	52.4	

**Calculated using Log Rank Test*

Figure 5.7.2.1: Observed survival rate (%) of oral cancer according to heamoglobin levels



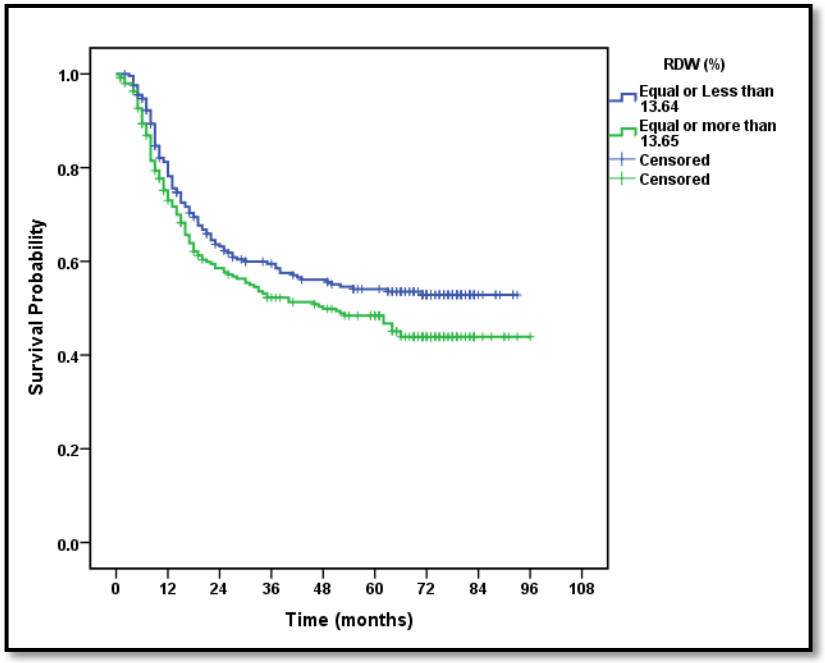
5.7.2.1 Survival according to Red cell distribution width (%) (RDW): A RDW (%) of 13.65 was considered as a cut-off for survival analysis. Patients with lower RDW were found to have 5yr survival of 54.1% and those with higher RDW(%) were found to have survival of 48.4% (table 5.7.2.2). However, this difference failed to attain statistical significance (p=0.06) (fig. 5.7.2.2)

Table 5.7.2.2: Observed Survival rate (%) according to Red Cell Distribution Width (RDW) percentage

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Red Cell Distribution Width (RDW), %							
RDW (≤ 13.64)	249	81.2	63.2	59.5	56.1	54.1	0.06
RDW (≥ 13.65)	249	73.0	58.6	52.3	49.9	48.4	

**Calculated using Log Rank Test*

Figure 5.7.2.2: Observed Survival rate (%) of oral cancer according to red cell distribution width (RDW) percentage



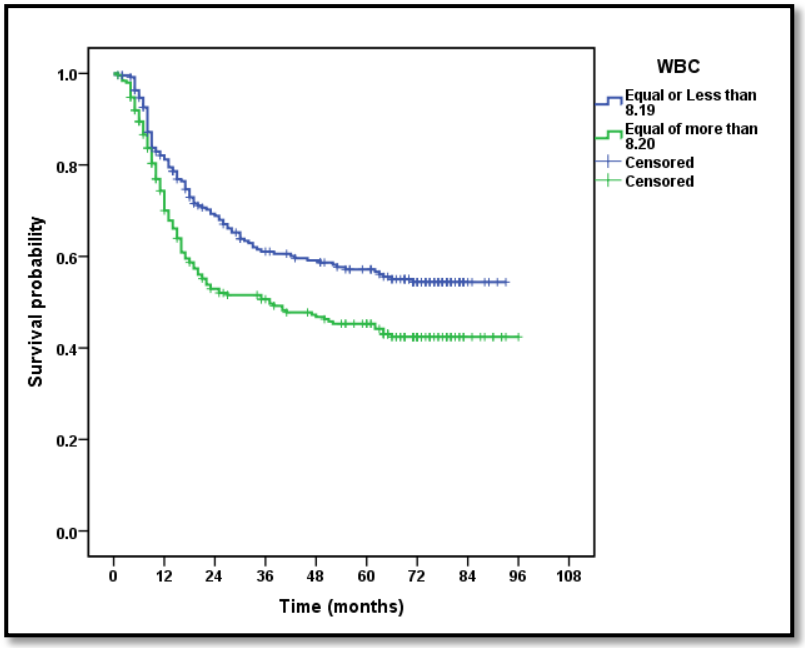
5.7.2.3 Survival according to White Blood Cell Count (WBC): Patients' with lower WBC count were found to have significantly (p<0.001) (fig. 5.7.2.3) better 5 yr survival (57.2%) as compared to patients with higher WBC counts (44.2%) (table 5.7.2.3).

Table 5.7.2.3: Observed survival rate (%) according to white blood cell count (WBC)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
White Blood Cell Count (10^9/L)							
WBC (≤ 8.19)	248	81.2	68.9	61.1	59.1	57.2	<0.001
WBC (≥ 8.20)	250	70.0	52.9	50.6	46.8	44.2	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
WBC (≤ 8.19)	1						<0.001
WBC (≥ 8.20)	1.46 (1.13- 1.89)						

**Calculated using Log Rank Test*

Figure 5.7.2.3: Observed survival rate (%) of oral cancer according to white blood cell count (WBC)



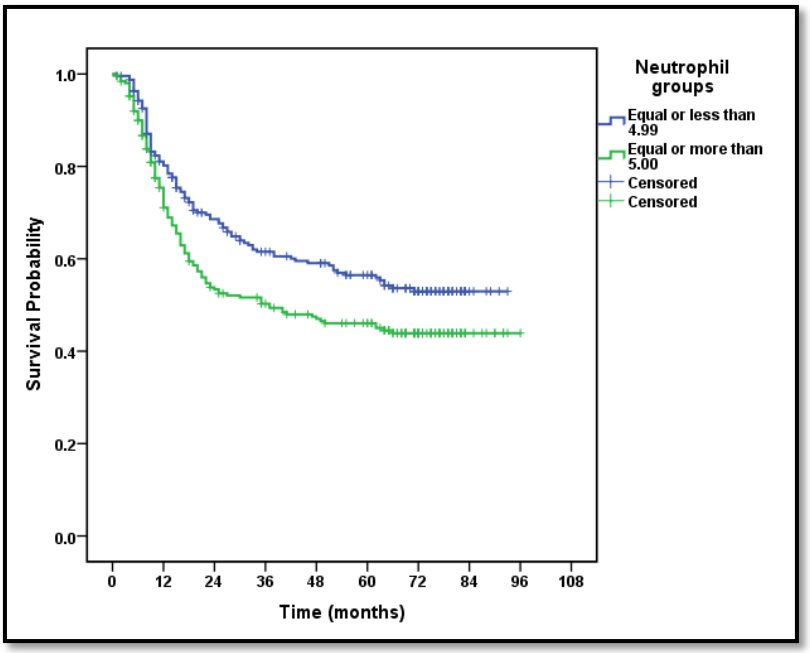
5.7.2.4 Survival according to Neutrtophil count: An absolute neutrophil count of 4.99 (10^9/L) was taken as a cut-off for dividing neutrophil count into a categorical variable. Patients having lower neutrophil count were found to have significantly (p=0.01) (fig. 5.7.2.4) better 5 yr survival (56.5%) as compared to patients with higher neutrtophil count (46.1%) (table 5.7.2.4).

Table 5.7.2.4: Observed survival rate (%) according to neutrtophil count

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Neutrophil Count (10^9/L)							
Neutrophil (≤ 4.99)	246	80.2	68.6	61.5	59.1	56.5	0.01
Neutrophil (≥ 5.00)	254	75.4	53.4	50.3	47.0	46.1	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Neutrophil (≤ 4.99)	1						0.01
Neutrophil (≥ 5.00)	1.37 (1.05 -1.77)						

**Calculated using Log Rank Test*

Figure 5.7.2.4: Observed survival rate (%) of oral cancer according to neutrtophil count



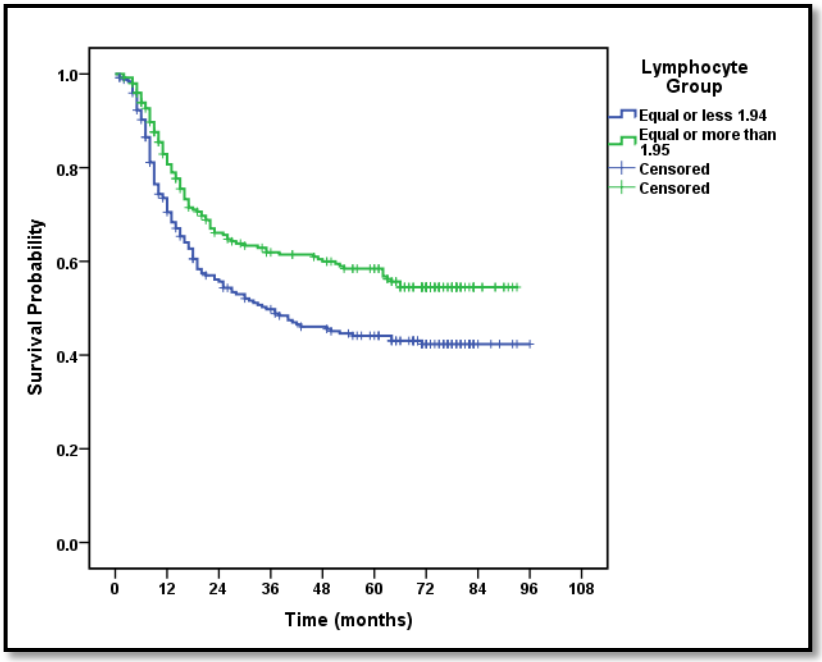
5.7.2.5 Survival according to Lymphocyte count: Absolute Lymphocyte count was found to be inversely related to survival. Patients having lower lymphocyte count were found to have significantly (p<0.001) (fig. 5.7.2.5) poorer 5 yr survival (44.1%) as compared to patients with higher lymphocyte count (58.4%) (table 5.7.2.5).

Table 5.7.2.5: Observed survival rate (%) according to lymphocyte count

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
Lymphocyte Count (10^9/L)							
Lymphocyte (≤ 1.94)	249	70.5	55.7	49.8	46.1	44.1	<0.001
Lymphocyte (≥ 1.95)	249	80.7	66.1	61.9	60.0	58.4	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Lymphocyte (≥ 1.95)	1						<0.001
Lymphocyte (≤ 1.94)	1.46 (1.13 - 1.89)						

**Calculated using Log Rank Test*

Figure 5.7.2.5: Observed survival rate (%) of oral cancer according to lymphocyte count



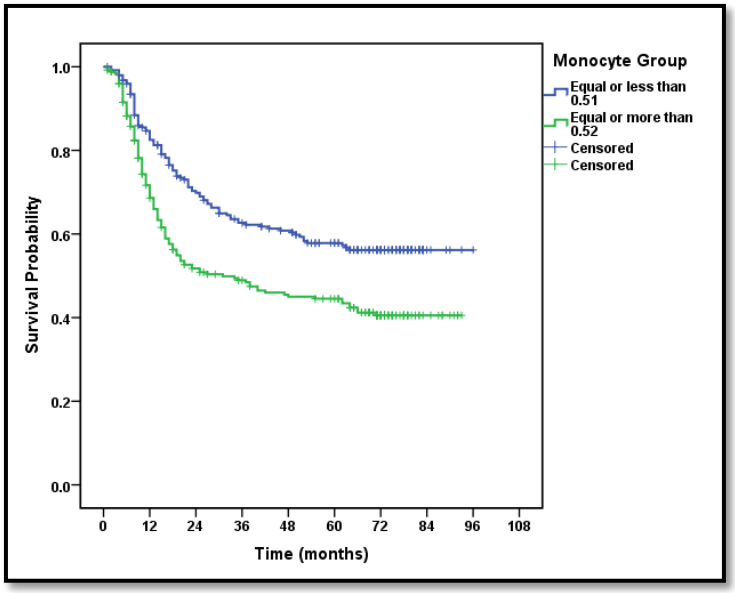
5.7.2.6 Survival according to Monocyte count: Absolute monocyte count was found to be significantly ($p<0.001$) associated with survival. Patients with lower monocyte count were found to have better 5 yr survival (57.8%) as compared to patients with higher monocyte count (43.4%) (table 5.7.2.6) (fig. 5.7.2.6).

Table 5.7.2.6: Observed survival rate (%) according to monocyte count

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Monocyte Count (10^9/L)							
Monocyte (≤ 0.51)	249	82.5	69.9	62.7	60.8	57.8	<0.001
Monocyte (≥ 0.52)	249	68.6	51.7	48.9	45.0	43.4	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Monocyte (≤ 0.51)	1						<0.001
Monocyte (≥ 0.52)	1.63 (1.25- 2.11)						

**Calculated using Log Rank Test*

Figure 5.7.2.6: Observed survival rate (%) of oral cancer according to monocyte count



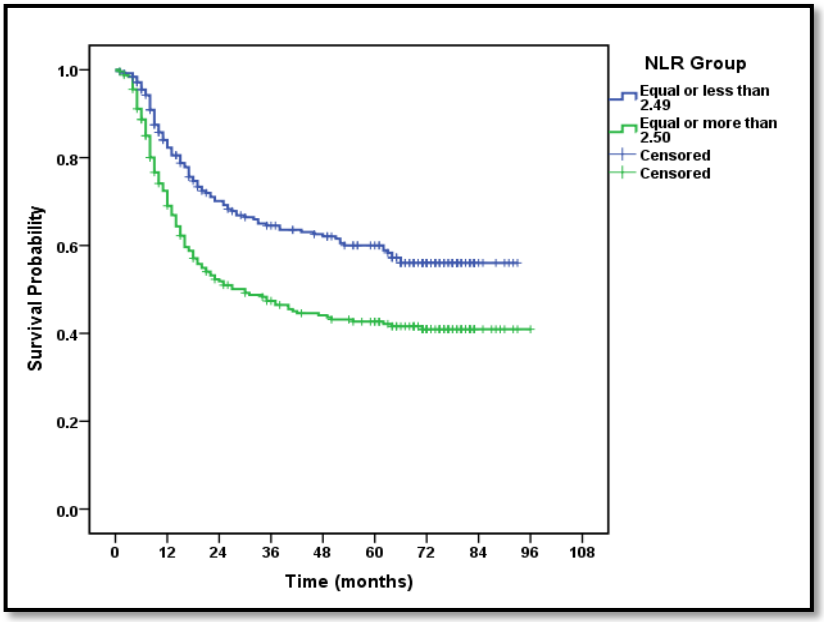
5.7.2.7 Survival according to Neutrtophil/ Lymphocyte ratio (NLR): The absolute neutrophil count was divided by absolute lymphocte count to calculate NLR. A median value of 2.49 was taken as a cut-off for converting NLR into a categorical variable. Patients having lower NLR were found to have significantly ($p< 0.05$) (fig. 5.7.2.7) better 5 yr survival (60.2%) as compared to patients with higher NLR (41.3%) (table 5.7.2.7).

Table 5.7.2.7: Observed survival rate (%) according to neutrtophil/ lymphocyte ratio:

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
Neutrophil Lymphocyte ratio							
NLR (≤ 2.49)	248	83.6	71.7	65.9	63.4	60.2	<0.001
NLR (≥ 2.50)	250	68.0	50.8	46.4	43.2	41.3	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
NLR (≤ 2.49)	1						<0.001
NLR (≥ 2.50)	1.77 (1.36- 2.31)						

**Calculated using Log Rank Test*

Figure 5.7.2.7: Observed survival rate (%) of oral cancer according to NLR



5.7.2.8 Multifactorial analysis for independent prognostic factors for overall survival:

All the heamatological factors which were found to influence overall survival in univariate analysis, viz. Total WBC, neutrophil count, lymphocyte count, monocyte count and NLR were considered for further multifactorial analysis. In addition, other clinical and histological factors which were found to significantly affect overall survival in section 5.2 (table Table 5.2.18), were included in multifactorial analysis. The results showed that higher NLR level (HR = 1.40, 95% CI = 1.03 – 1.90; p= 0.02), monocyte count (HR = 1.45, 95% CI = 1.08 – 1.96; p= 0.01). In addition, presence of comorbidity, poor differentiation, advanced stage disease, extra capsular spread and perineural invasion were also found to be independent predictors for poor overall survival of oral cavity cancer patients (table 5.7.2.8).

5.7.2.8 : Multifactorial analysis of prognostic factors for overall survival in oral cavity cancer for heamatological factors

	No. of	Univariate		Multifactorial	
Parameter	**cases**	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Age (< 40 yrs)	91	1		1	
Age (≥ 40 yrs)	407	1.26 (0.89 – 1.78)	0.18	--	0.09
Comorbidity Present	326	1		**1**	
Comorbidity Absent	172	1.44 (1.11 - 1.86)	<0.001**	**1.60 (1.18 - 2.17)**	**<0.001****
Differentiation					
Well Differentiated	49	1		**1**	
Moderately Differentiated	290	3.32 (1.55 – 7.12)	<0.001	2.00 (0.91 – 4.39)	0.08
Poorly Differentiated	94	7.97 (3.64 – 17.45)	<0.001	**3.85 (1.69 – 8.78)**	**<0.001****
Unknown	22	2.63 (0.95– 7.28)	0.06	1.28 (0.45 – 3.66)	0.13
Early Stage (I &II)	148	1		**1**	
Advanced Stage (III & IV)	350	3.97 (2.71 – 5.84)	<0.001**	**2.12 (1.35 - 3.34)**	**<0.001****
Bone Infiltration (Absent)	325	1			
Bone Infiltration (Present)	120	1.67 (1.25- 2.23)	<0.001**		0.75
Perineural invasion (Absent)	375	1		**1**	
Perineural invasion (Present)	80	2.22 (1.61- 3.07)	<0.001**	**1.69 (1.20 - 2.37)**	**<0.001****
ECS (Absent)	247	1		**1**	
ECS (Present)	151	3.25 (2.42 - 4.36)	<0.001**	**2.87 (2.08 – 3.97)**	**<0.001****
WBC ≤ 8.19 10^9/L	248	1			
WBC ≥ 8.20 10^9/L	252	1.46 (1.13- 1.89)	<0.001**		0.82
Neutrophil ≤ 4.9910^9/L	246	1			
Neutrophil ≥ 5.00 10^9/L	254	1.37 (1.05 -1.77)	0.01		0.16
Lymphocyte ≤ 1.94 10^9/L	249	1			
Lymphocyte ≥ 1.95 10^9/L	249	1.46 (1.13 - 1.89)	<0.001**		0.73
Monocyte ≤ 0.51 10^9/L	247	1		**1**	
Monocyte ≥ 0.52 10^9/L	251	1.63 (1.25- 2.11)	0.01**	**1.45 (1.08 – 1.96)**	**0.01****
NLR ≤ 2.49	248	1		**1**	
NLR ≥ 2.50	252	1.77 (1.36- 2.31)	<0.001**	**1.40 (1.03 – 1.90)**	**0.02****
Treatment				--	0.06
Surgery only	171	1			
Radiotherapy only	19	5.11 (2.94 – 8.90)	<0.001		
Surgery + Radiotherapy	187	1.28 (0.92 – 1.78)	0.14		
Surgery + Radiotherapy + Chemotherapy	97	1.56 (1.08 – 2.26)	0.01		
Radiotherapy + Chemotherapy	24	5.78 (3.52 – 9.49)	<0.001		

Laboratory Parameters in Early Stage (TNM Stage I and II)

5.7.3.1 Distribution of laboratory parameters in early stage disease: Out of total 223 patients with early stage disease, pretreatment counts for hemoglobin, red cell distribution width percentage (RDW), total white blood cell count (WBC), absolute neutrophil, lymphocyte and monocyte counts parameters were available for only 148 cases. Basic descriptive analysis of these parameters including their minimum and maximum values is presented in table 5.7.3.1.

Table 5.7.3.1: Descriptive data of laboratory parameters in early stage disease

Sl No.	Parameter	Mean ± SD	Median	Minimum	Maximum
1.	Hemoglobin (g/dL)	13.42 ± 2.08	13.60	6.50	18.50
2.	RDW (%)	14.11 ± 2.38	13.55	10.70	26.70
3.	WBC (10^9/L)	8.27 ± 3.21	7.47	4.45	26.70
4.	Neutrophil (10^9/L)	5.02 ± 2.57	4.49	1.92	20.22
5.	Lymphocyte (10^9/L)	2.09 ± 0.72	2.06	0.25	5.07
6.	Monocyte (10^9/L)	0.52 ± 0.18	0.48	0.07	1.26
7.	Neutrophil/ lymphocyte ratio (NLR)	3.01 ± 3.50	2.17	0.75	26.23

5.7.3.2 Survival according to various laboratory parameters: All the selected laboratory parameters namely hemoglobin, red cell distribution width percentage (RDW), total white blood cell count (WBC), absolute neutrophil, lymphocyte and monocyte counts and NLR were not found to be significantly ($p > 0.05$) associated with survival of earl stage oral cancer patients (5.7.3.2)

Table 5.7.3.2: Observed survival rate (%) of early stage cancer according to selected laboratory parameters

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
Heamoglobin (gm%)							
Heamoglobin (≤ 11.99)	30	93.3	89.6	85.3	80.8	80.8	0.62
Heamoglobin (≥ 12.00)	118	93.1	82.1	78.1	77.0	77.0	
Red Cell Distribution Width (RDW), %							
RDW (≤ 13.64)	77	93.4	84.9	.83.3	81.7	79.9	0.49
RDW (≥ 13.65)	71	92.9	82.0	75.6	75.6	75.6	
White Blood Cell Count (10^9/L)							
WBC (≤ 8.19)	85	91.7	82.8	77.5	77.5	75.9	0.52
WBC (≥ 8.20)	63	95.2	84.5	82.5	80.4	80.4	
Neutrophil Count (10^9/L)							
Neutrophil (≤ 4.99)	89	.92.0	85.7	81.6	81.6	80.0	0.49
Neutrophil (≥ 5.00)	59	94.9	80.5	76.6	74.7	74.7	
Lymphocyte Count (10^9/L)							
Lymphocyte (≤ 1.94)	61	86.4	73.1	73.1	73.1	73.1	0.28
Lymphocyte (≥ 1.95)	87	94.2	84.0	82.7	81.1	81.1	
Monocyte Count (10^9/L)							
Monocyte (≤ 0.51)	90	95.5	87.2	83.6	79.9	78.4	0.61
Monocyte (≥ 0.52)	58	89.5	77.6	77.6	77.6	776	
Neutrophil Lymphocyte ratio							
NLR (≤ 2.49)	96	91.6	82.2	78..5	78.5	770	0.68
NLR (≥ 2.50)	52	96.1	86.0	81.6	79.3	79.3	

**Calculated using Log Rank Test*

Laboratory Parameters in Advanced Stage (TNM Stage I and II)

5.7.4.1 Distribution of laboratory parameters in advanced stage disease: Out of total 503 patients with advanced stage disease, pretreatment counts for hemoglobin, red cell distribution width percentage (RDW), total white blood cell count (WBC), absolute neutrophil, lymphocyte and monocyte counts parameters were available for only 350 cases. Basic descriptive analysis of these parameters including their minimum and maximum values is presented in table 5.7.4.1.

Table 5.7.4.1: Descriptive data of laboratory parameters

Sl No.	Parameter	Mean ± SD	Median	Minimum	Maximum
1.	Hemoglobin (g/dL)	12.80 ± 2.17	13.10	6.11	17.80
2.	RDW (%)	14.14 ± 2.21	13.70	10.90	24.30
3.	WBC (10^9/L)	9.06 ± 3.27	8.40	4.13	26.70
4.	Neutrophil (10^9/L)	5.96 ± 2.94	5.17	1.10	22.18
5.	Lymphocyte (10^9/L)	1.95 ± 0.72	1.90	0.24	5.46
6.	Monocyte (10^9/L)	0.60 ± 0.25	0.54	0.07	1.60
7.	Neutrophil/ lymphocyte ratio (NLR)	3.95 ± 4.56	2.69	0.89	45.09

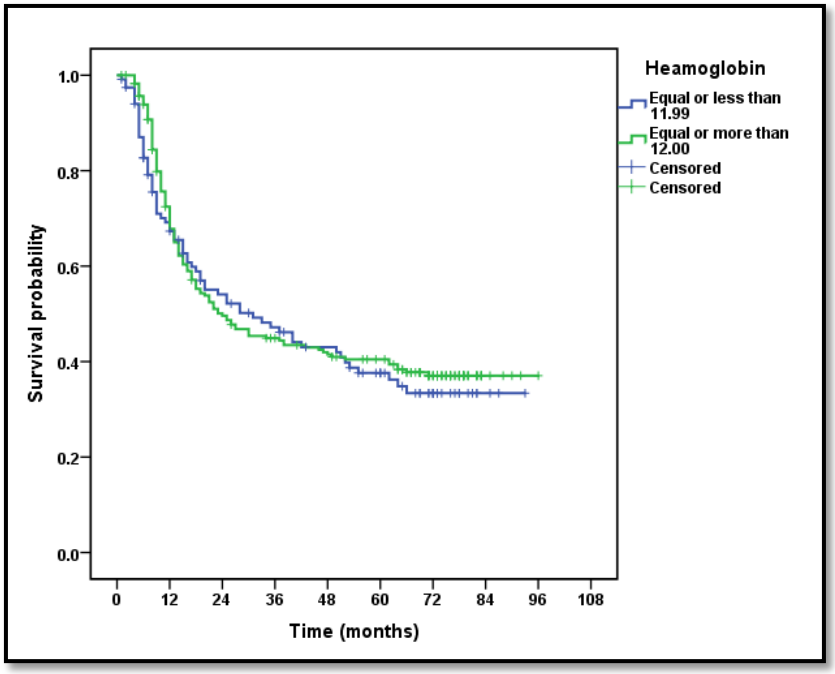
5.7.4.2 Survival according to heamoglobin levels: In order to access the effect of heamoglobin on survival of patients with advanced stage disease were divided them into two groups by taking 12gm% as a cut-off. Survival was not found to be significantly different between two comparison groups (table 5.7.4.2) (fig 5.7.4.1)

Table 5.7.4.2: Observed survival rate (%) of advanced stage oral cancer according to heamoglobin levels

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Heamoglobin							
Heamoglobin (≤ 11.99)	118	67.3	54.1	47.2	42.0	36.2	0.55
Heamoglobin (≥ 12.00)	232	67.8	49.6	44.4	41.5	39.4	

**Calculated using Log Rank Test*

Figure 5.7.4.1: Observed survival rate (%) of advanced stage oral cancer according to heamoglobin levels



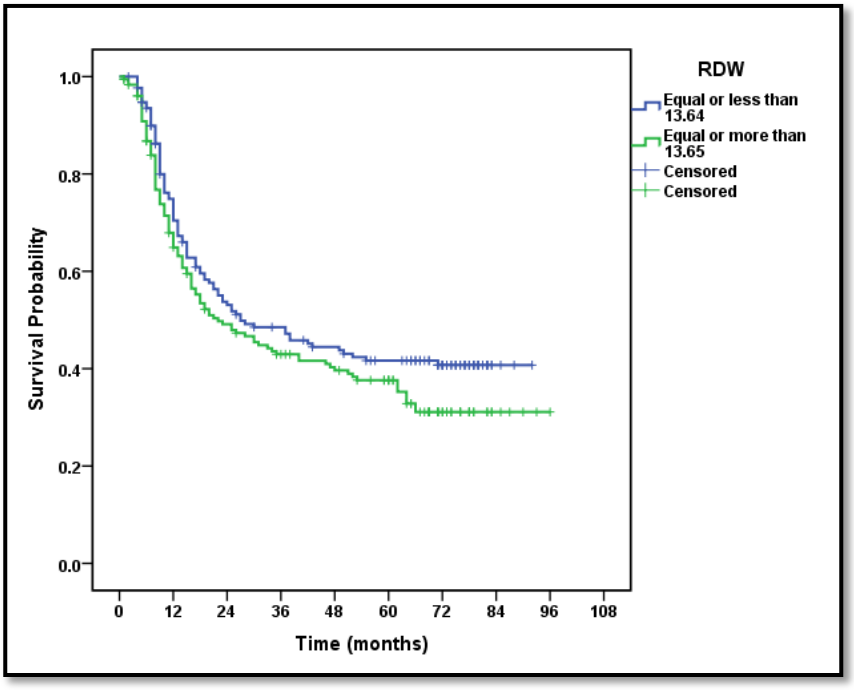
5.7.4.3 Survival according to Red cell distribution width (%) (RDW): Patients with lower RDW were found to have 5 yr survival of 41.7% and those with higher RDW(%) were found to have survival of 35.2% (table 5.7.2.2). However, this difference failed to attain statistical significance (p=0.10) (fig. 5.7.4.3) (fig 5.7.4.2)

Table 5.7.4.3: Observed survival rate (%) of advanced stage oral cancer according to red cell distribution width (RDW) percentage

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Red Cell Distribution Width (RDW), %							
RDW (≤ 13.64)	172	70.4	53.1	47.2	43.8	41.7	0.10
RDW (≥ 13.65)	178	6.49	49.1	42.9	39.6	35.2	

**Calculated using Log Rank Test*

Figure 5.7.4.2: Observed survival rate (%) of advanced stage oral cancer according to red cell distribution width (RDW) percentage



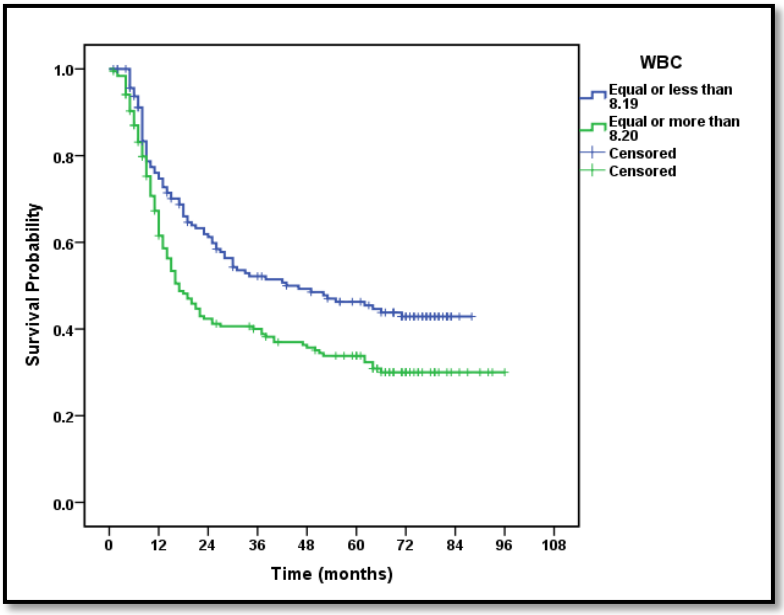
5.7.4.4 Survival according to White Blood Cell Count (WBC): Patients' with lower WBC count were found to have significantly (p<0.001) (fig. 5.7.4.3) better 5yr survival (45.5%) as compared to patients with higher WBC counts (32.3%) (table 5.7.4.4).

Table 5.7.2.4: Observed survival rate (%) of advanced stage oral cancer according to white blood cell count (WBC)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
White Blood Cell Count (10^9/L)							
WBC (≤ 8.19)	163	74.7	61.2	52.2	48.5	45.5	<0.001
WBC (≥ 8.20)	187	61.5	42.4	38.8	35.7	32.3	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
WBC (≤ 8.19)	1						<0.001
WBC (≥ 8.20)	1.48 (1.12- 1.96)						

**Calculated using Log Rank Test*

Figure 5.7.4.3: Observed survival rate (%) of oral cancer according to white blood cell count (WBC)



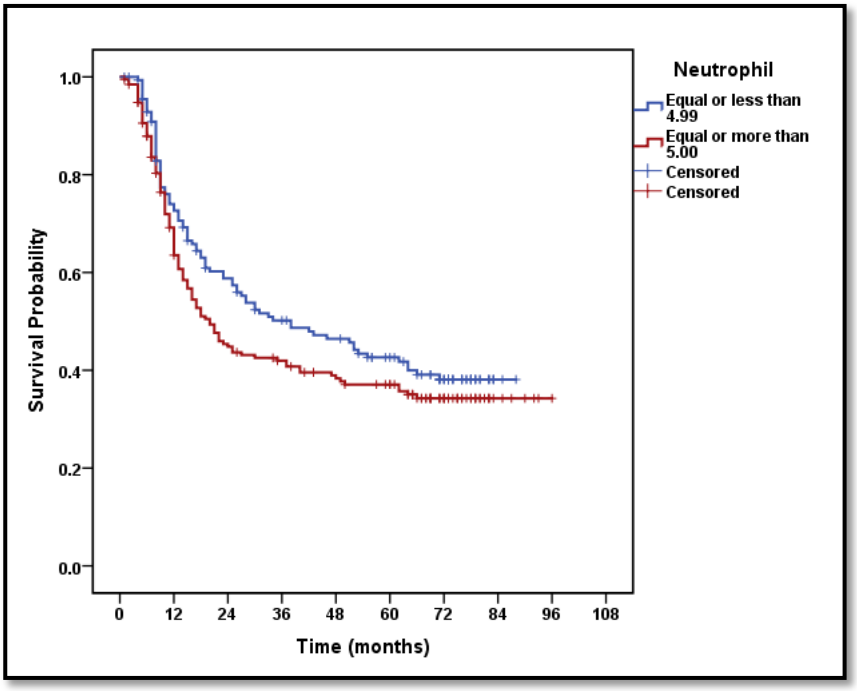
5.7.4.5 Survival according to Neutrtophil count: An absolute neutrophil count of 4.99 (10^9/L) was taken as a cut-off for dividing neutrophil count into a categorical variable. Patients having lower neutrophil count were found to have 5 yr survival (41.8%) as compared to patients with higher neutrtophil count (35.7%) (table 5.7.4.5) (fig 5.7.4.4). However, this difference between the two groups failed to achieve statistical significance (p= 0.15)

Table 5.7.4.5: Observed survival rate (%) of advanced stage oral cancer according to neutrtophil count

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Neutrophil Count (10^9/L)							
Neutrophil (≤ 4.99)	157	72.6	58.8	50.2	46.4	41.8	0.15
Neutrophil (≥ 5.00)	193	63.5	44.8	40.8	38.3	35.7	

**Calculated using Log Rank Test*

Figure 5.7.4.4: Observed survival rate (%) of advanced stage oral cancer according to neutrophil count



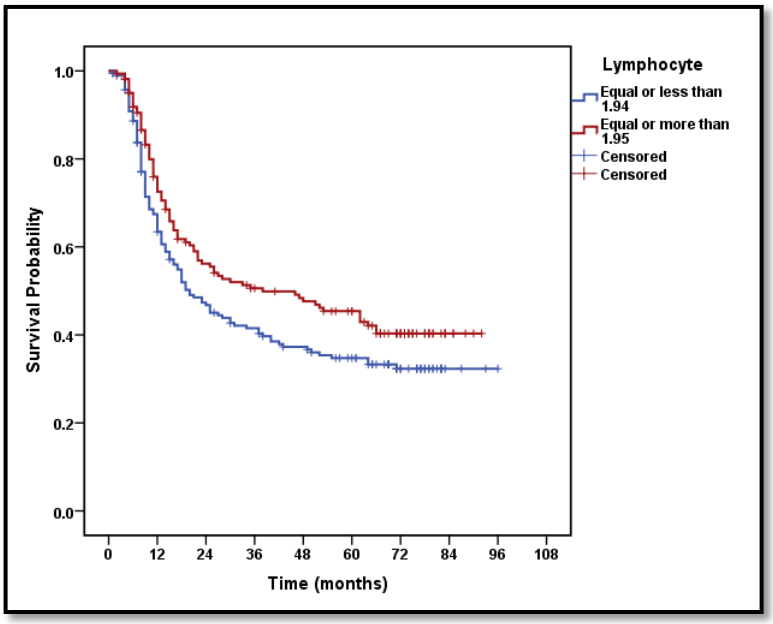
5.7.4.6 Survival according to Lymphocyte count: Absolute Lymphocyte count was found to be inversely related to survival. Patients having lower lymphocyte count were found to have significantly (p= 0.05) (fig. 5.7.4.5) poorer 5 yr survival (34.7%) as compared to patients with higher lymphocyte count (42.9%) (table 5.7.4.6) (fig 5.7.4.5) .

Table 5.7.4.6: Observed survival rate (%) of advanced stage oral cancer according to lymphocyte count

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
Lymphocyte Count (10^9/L)							
Lymphocyte (≤ 1.94)	188	63.4	46.8	40.3	36.7	34.7	0.05
Lymphocyte (≥ 1.95)	162	72.6	56.2	50.6	47.6	42.9	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Lymphocyte (≥ 1.95)	1						0.05
Lymphocyte (≤ 1.94)	1.31 (1.01 - 1.72)						

**Calculated using Log Rank Test*

Figure 5.7.4.5: Observed survival rate (%) of advanced stage oral cancer according to lymphocyte count



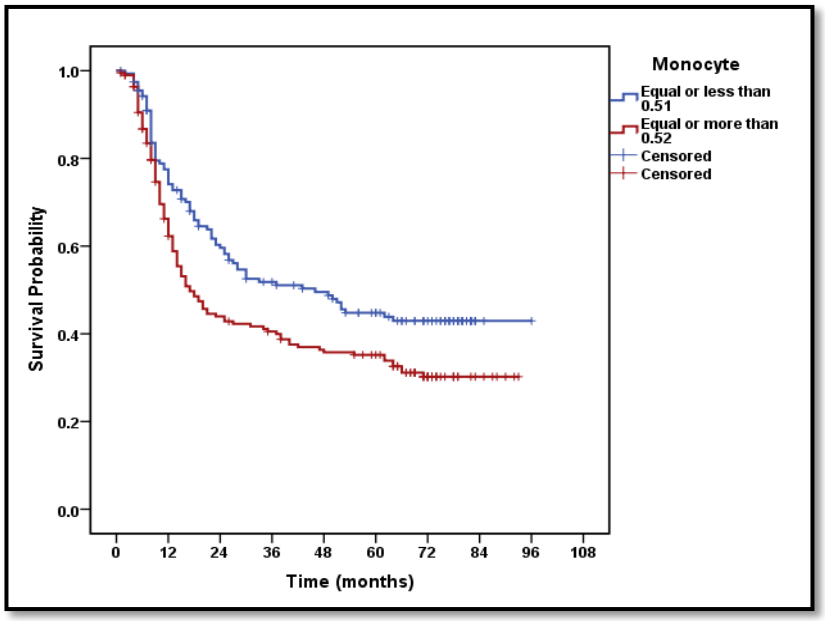
5.7.4.7 Survival according to Monocyte count: Absolute monocyte count was found to be significantly ($p<0.001$) associated with survival. Patients with lower monocyte count were found to have better 5 yr survival (43.9%) as compared to patients with higher monocyte count (33.9%) (table 5.7.4.7) (fig. 5.7.4.6).

Table 5.7.4.7: Observed survival rate (%) of advanced stage oral cancer according to monocyte count

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Monocyte Count (10^9/L)							
Monocyte (≤ 0.51)	157	74.1	59.6	51.1	48.8	43.9	<0.001
Monocyte (≥ 0.52)	193	62.3	44.0	40.5	35.8	33.9	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
Monocyte (≤ 0.51)	1						0.01
Monocyte (≥ 0.52)	1.44 (1.09 - 1.91)						

**Calculated using Log Rank Test*

Figure 5.7.4.6: Observed survival rate (%) of advanced stage oral cancer according to monocyte count



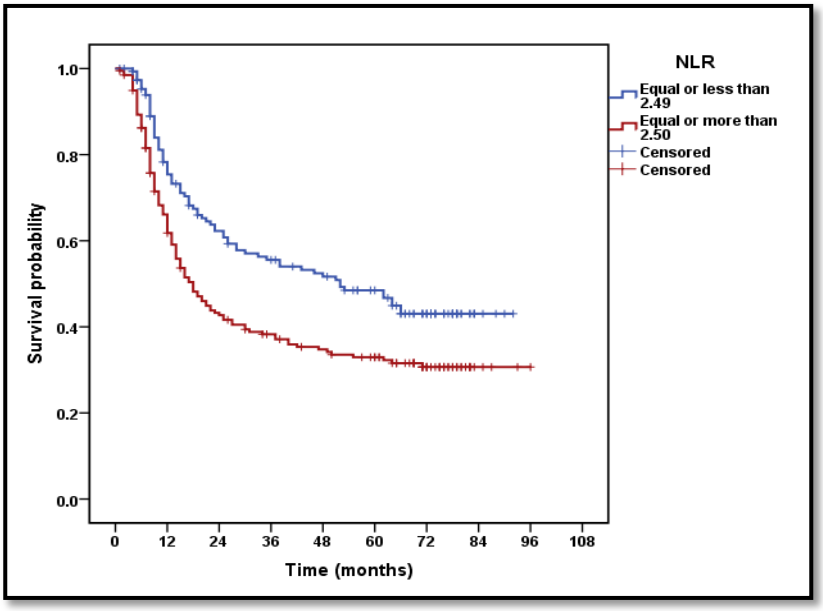
5.7.4.8 Survival according to Neutrtophil/ Lymphocyte ratio (NLR): The absolute neutrophil count was divided by absolute lymphocte count to calculate NLR. An overall median value of 2.49 was taken as a cut-off for dividing NLR into a categorical variable. Patients having lower NLR were found to have significantly (p<0.001) (fig. 5.7.4.7) better 5 yr survival (46.7%) as compared to patients with higher NLR (32.2%) (table 5.7.4.8).

Table 5.7.4.8: Observed survival rate (%) of advanced stage oral cancer according to neutrtophil/ lymphocyte ratio (NLR):

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4 Yr	5 Yr	
Neutrophil Lymphocyte ratio							
NLR (≤ 2.49)	152	.75.4	62.3	55.5	51.7	46.7	<0.001
NLR (≥ 2.50)	198	61.8	42.7	37.1	34.7	32.2	
Univariate analysis							
	Hazard Ratio (95% CI)						**p Value**
NLR (≤ 2.49)	1						<0.001
NLR (≥ 2.50)	1.66 (1.25 - 2.21)						

**Calculated using Log Rank Test*

Figure 5.7.4.7: Observed survival rate (%) of advanced stage oral cancer according to NLR



5.7.4.9 Multifactorial analysis for independent prognostic factors for overall survival:

All the heamatological factors which were found to influence overall survival in univariate analysis, such as, Total WBC, lymphocyte count, monocyte count and NLR were considered for further multifactorial analysis. In addition other clinical and histological factors which were found to significantly affect survival in advanced stage oral cancer in section 5.4 (table 5.4.14), were included in multifactorial analysis. The results showed that higher NLR level (HR = 1.69, 95% CI = 1.22 - 2.34; p=0.01), monocyte count (HR = 1.47, 95% CI = 1.06 - 2.02; p=0.02). In addition, age, presence of comorbidity, poor differentiation, histological lymph node involvement, extra capsular spread and perineural invasion were also found to be independent predictors for poor overall survival of advanced stage oral cancer patients (table 5.7.4.9).

Table 5.7.4.9: Multifactorial analysis of prognostic factors for overall survival in patients with of advanced stage oral cancer

	No. of cases	Univariate		Multifactorial	
Parameter		**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Age (< 40 yrs)	67	1		1	
Age (≥ 40 yrs)	283	1.21 (0.84 – 1.75)	0.28	**1.51 (1.06 - 2.15)**	**0.02****
Comorbidity Present	233	1		**1**	
Comorbidity Absent	117	1.39 (1.05 – 1.84)	0.02	**1.57 (1.14 – 2.17)**	**<0.001****
Differentiation					
Well Differentiated	27	1		1	
Moderately Differentiated	191	2.19 (1.02 – 4.74)	0.04	1.52 (0.68 – 3.37)	0.29
Poorly Differentiated	77	4.78 (2.17 – 10.53)	<0.001	**2.87 (1.25 – 6.58)**	**0.01****
Unknown	14	2.09 (0.75 – 5.78)	0.15	1.17 (0.41 – 3.35)	0.75
Tumor Size					0.33
< 2cms	53	1			
2- 4 cms	174	1.56 (0.98 – 2.48)	0.05		
> 4cms	82	1.99 (1.21 – 3.30)	<0.001		
Lymph node Absent (Histo)	132	1		**1**	
Lymph node Present (Histo)	169	2.67 (1.90 – 3.75)	<0.001	**1.70 (1.04 - 2.88)**	**0.04****
Bone Infiltration (Absent)	186	1			
Bone Infiltration (Present)	123	1.29 (1.01 - 1.58)	0.04		0.54
Perineural invasion (Absent)	247	1		**1**	
Perineural invasion (Present)	62	2.27 (1.61 - 3.19)	<0.001	**1.83 (1.28 - 2.62)**	**<0.001****
ECS (Absent)	171	1		**1**	
ECS (Present)	130	2.77 (2.02 - 3.79)	<0.001	**1.77 (1.07 – 2.90)**	**0.02****
WBC ≤ 8.19 10^9/L	163	1			
WBC ≥ 8.20 10^9/L	187	1.48 (1.12- 1.96)	<0.001	--	0.24
Lymphocyte ≤ 1.94 10^9/L	188	1			
Lymphocyte ≥ 1.95 10^9/L	162	1.31 (0.99 - 1.72)	0.05	--	0.80
Monocyte ≤ 0.51 10^9/L	157	1		**1**	
Monocyte ≥ 0.52 10^9/L	193	1.44 (1.09 - 1.91)	0.01	**1.47 (1.06 - 2.02)**	**0.01****
NLR ≤ 2.49	152	1		**1**	
NLR ≥ 2.50	198	1.66 (1.25 - 2.21)	<0.001	**1.69 (1.22 - 2.34)**	**<0.001****
Treatment				--	0.50
Surgery only	90	1		--	
Radiotherapy only	17	4.48 (2.52 – 7.97)	<0.001	--	
Surgery + Radiotherapy	136	0.88 (0.61 – 1.28)	0.51	--	
Surgery + Radiotherapy + Chemo	83	1.02 (0.68 – 1.51)	0.91	--	
Radiotherapy + Chemotherapy	24	3.39 (2.03 – 5.67)	<0.001		

Treatment Time

5.8.1 Time taken for diagnosis: Time period from registration of patient at Tata memorial Hospital to pathological confirmation of malignancy was taken as time to diagnosis. The median duration for diagnosis was 03 days (table 5.8.1). Majority of cases (87.1%) were diagnosed in less than 07 days and only 07 cases (1%) required more one month for diagnosis (table 5.8.2). The duration taken for diagnosis was divided into three categories for analyzing its effect on overall survival of patients (table 5.8.3). No significant difference in 5 yr survival rates was observed as per the time taken for diagnosis (figure 5.8.1).

Table 5.8.1: Time taken for diagnosis

Sl. No.	Time period from date of registration to date to diagnosis	Duration (days)
1.	**Median**	03
2.	**Minimum**	01
3.	**Maximum**	56

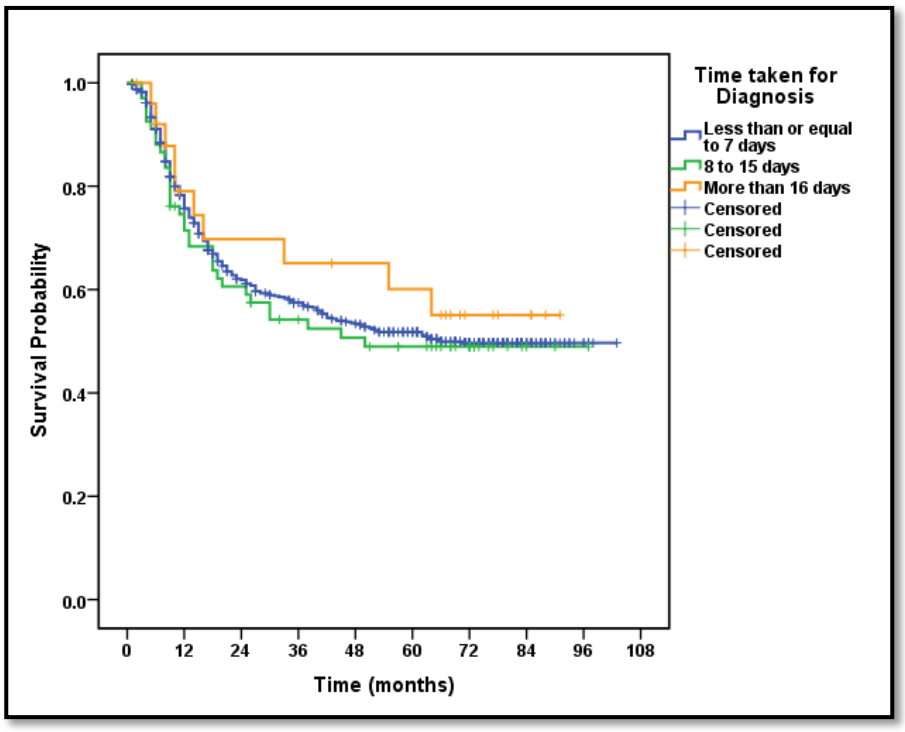
Table 5.8.2: Distribution of patients as per time taken for diagnosis

Sl. No.	Time taken for Diagnosis (days)	No. of patients (%)	Cumulative total (%)
1.	**≤ 7 days**	632 (87.1)	632 (87.1)
2.	**8 to 15 days**	68 (9.3)	700 (96.4)
3.	**16 to 30 days**	19 (2.6)	719 (99.0)
4.	**≥ 31 days**	07 (1.0)	726 (100)

Table 5.8.3: Observed survival rate (%) of oral cavity cancer according to time taken for diagnosis

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Time taken for diagnosis (Days)							
≤ 7 days	632	75.7	61.9	57.4	53.4	51.1	0.77
8 to 15 days	68	74.6	60.6	54.2	50.7	48.9	
≥ 16 days	26	79.0	69.7	65.1	60.1	55.1	

Figure 5.8.1: Observed survival rate (%) of oral cancer according to time taken for diagnosis



5.8.2 Time between diagnosis and commencement of treatment: Time period between pathological confirmation of malignancy and initiation any type of cancer directed treatment (CDT) i.e surgery or radiotherapy or chemotherapy, was considered as time taken for treatment commencement. The median duration for treatment initiation was 30 days (table 5.8.4). In majority of patients (80.9%) treatment was started within 60 days of pathological diagnosis of malignancy (table 5.8.5). The duration taken for treatment initiation was divided into four categories for analyzing its effect on overall survival of patients (table 5.8.5). No significant ($p<0.05$) difference in 5 yr survival rates was observed as per the time taken for commencement of cancer directed treatment (figure 5.8.2).

Table 5.8.4: Time taken to start cancer directed treatment

Sl. No.	Time period from date of diagnosis to date of start of cancer directed treatment	Duration (days)
1.	**Median**	30
2.	**Minimum**	01
3.	**Maximum**	188

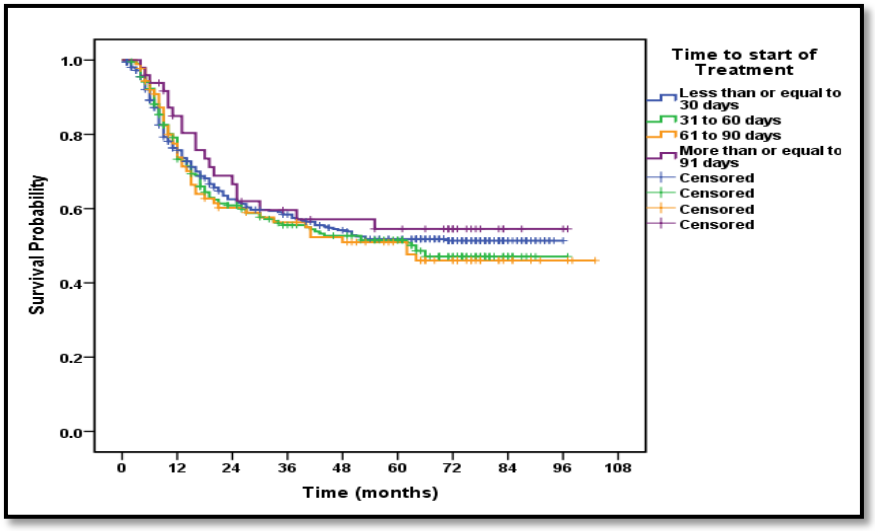
Table 5.8.5: Distribution of patients as per time taken to start cancer directed treatment

Sl. No.	Time taken for Diagnosis (days)	No. of patients (%)	Cumulative total (%)
1.	**≤ 30 days**	365 (50.3)	365 (50.3)
2.	**31 – 60 days**	222 (30.6)	587 (80.9)
3.	**61 - 90 days**	90 (12.4)	677 (93.3)
4.	**≥ 91 days**	49 (6.7)	726 (100)

Table 5.8.6: Observed survival rate (%) of oral cavity cancer according to time taken to start cancer directed treatment

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Time taken to start Cancer Directed treatment (Days)							
≤ 30 days	365	75.7	62.5	58.4	54.2	51.8	0.76
31 – 60 days	222	79.1	60.9	55.6	52.7	50.8	
61 - 90 days	90	77.5	60.2	56.3	51.0	47.7	
≥ 91 days	49	84.9	66.6	57.1	57.1	54.5	

Figure 5.8.2: Observed Survival rate (%) of oral cancer according to Time taken from diagnosis to start of Cancer Directed Treatment



5.8.3 Time taken from start of Cancer Directed treatment to completion: The median duration of treatment (all modalities together) was 30 days (table 5.8.7). The median, minimum and maximum duration taken for completion of each modality of treatment is provided in table 5.8.7. Irrespective of modality of treatment used 70% of patients completed treatment in less than 90 days, whereas in only surgically treated cases 93% cases completed treatment in less than 21 days. Multimodality treatment required more time, approximately 42% patients in surgery plus radiotherapy group required more than 90 days for treatment completion, similarly 60% of patients in surgery plus radiotherapy plus chemotherapy group required more than 90 days for treatment completion (table 5.8.8). The time taken for treatment completion was divided into four categories (≤ 60 days, 61 – 90 days, 91 - 120 days and ≥ 121 days) for analyzing its effect on overall survival of patients (table 5.8.9). Patients who had completed CDT in less than 60 days had the best 5 yr survival of 55.4% and patients who had undergone treatment for more than 121days had the worst 5yr survival of 36.6% (figure 5.8.3). However, this difference in survival failed to achieve statistical significance (p=0.12). In addition, we also took the global recommended 100 days as cut-off, but no significant difference (p=0.19) was observed in individuals who completed treatment within 100 days and those who completed in more than 100 days (table 5.8.10), (figure 5.8.4).

Table 5.8.7: Time taken from start of cancer directed treatment to completion

Time taken to complete CDT	Duration (days)					
	Sx Only (n= 262)	Sx + RT (n= 277)	Sx + RT + CT (n= 132)	RT only (n= 25)	RT + CT (n= 30)	Overall (n= 726)
Median	07	87	93	34	100	30
Minimum	01	42	48	21	47	01
Maximum	67	184	198	66	187	198

Table 5.8.8: Distribution of patients as per time taken for treatment (CDT) completion

Sl. No.	Time taken for CDT completion	No. of patients (%)	Cumulative total (%)
1.	**≤ 60 days**	313 (43.1)	313 (43.1)
2.	**61 – 90 days**	196 (27.0)	509 (70.1)
3.	**91 - 120 days**	159 (21.9)	668 (92.0)
4.	**≥ 121 days**	58 (8.0)	726 (100)
Only Surgically Treated cases (n=262)			
1.	**≤ 10 days**	195 (74.4)	195 (74.4)
2.	**10 – 20 days**	49 (18.7)	244 (93.1)
3.	**≥ 21 days**	18 (6.9)	262 (100)
Surgery and Radiotherapy Treated cases (n=277)			
1.	**≤ 90 days**	159 (57.4)	159 (57.4)
2.	**90 – 120 days**	96 (34.7)	255 (92.1)
3.	**≥ 121 days**	22 (7.9)	277 (100)
Surgery, Radiotherapy and Chemotherapy Treated cases (n=132)			
1.	**≤ 90 days**	53 (40.2)	53 (40.2)
2.	**90 – 120 days**	55 (41.7)	108 (81.9)
3.	**≥ 121 days**	24 (18.1)	277 (100)

Table 5.8.9: Observed Survival rate (%) of oral cavity cancer according to time taken to for completion of cancer directed treatment (CDT)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Time taken for CDT completion							
≤ 60 days	313	76.3	66.5	61.5	57.5	55.4	0.128
61 – 90 days	196	72.2	.55.8	51.6	49.1	47.7	
91 - 120 days	159	77.6	.63.7	59.5	55.8	52.6	
≥ 121 days	58	76.5	.56.5	48.7	40.6	36.6	

Figure 5.8.3: Observed Survival rate (%) of oral cancer according to Time taken for completion of CDT

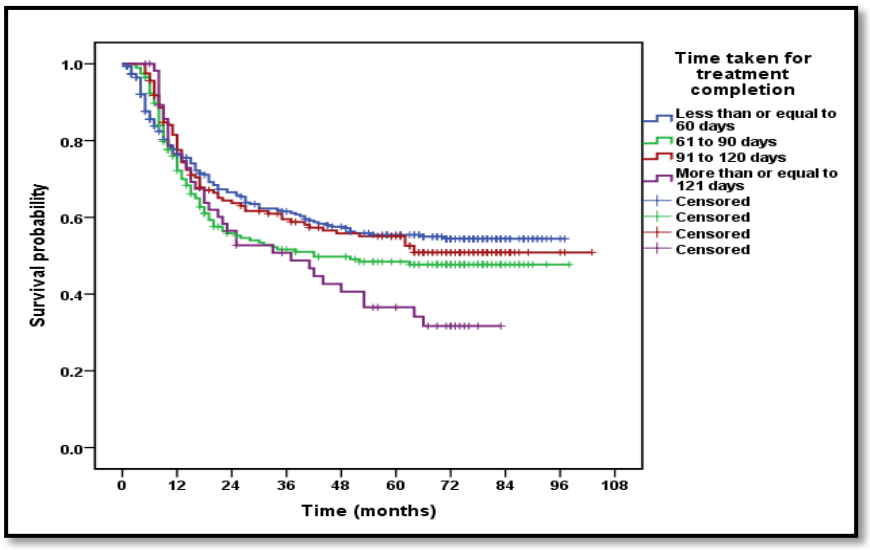
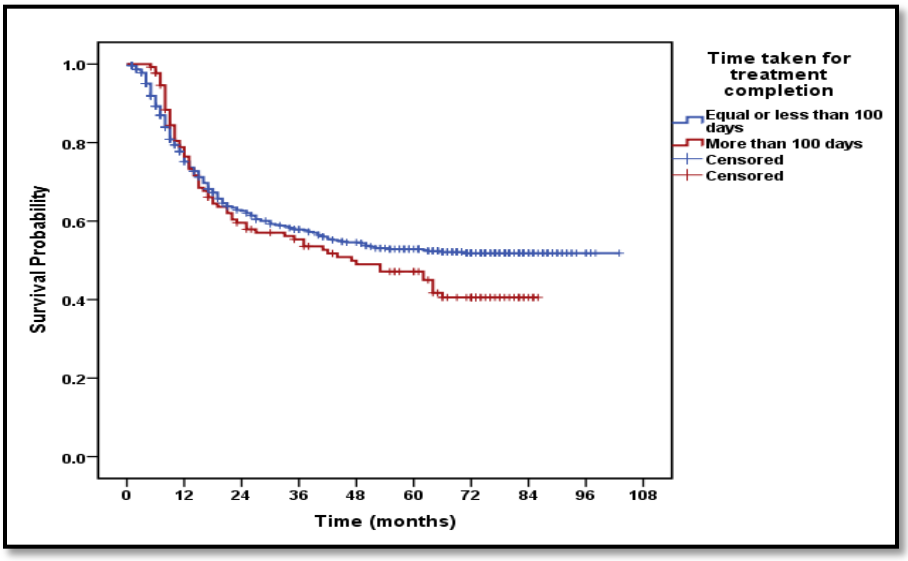


Table 5.8.10: Observed survival rate (%) of oral cavity cancer according to time taken to complete cancer directed treatment (taking a cut-off of 100 days)

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Time taken for CDT completion							
≤ 100 days	594	75.1	62.6	57.9	54.4	52.9	0.19
> 100 days	132	76.4	59.6	53.6	49.0	45.0	

Figure 5.8.4: Observed survival rate (%) of oral cancer according to time taken for CDT completion (taking a cut-off of 100 days)



5.8.3.1 Time taken from start of cancer directed treatment to completion as per stage: In order to further evaluate the effect of duration required for treatment completion on survival, patients were divided as per early and advanced disease, and impact of treatment duration was assessed in each category. Median treatment duration for patients with early stage disease was 10 days and for patients with advanced stage disease was 80 days (table 5.8.11). Treatment duration was found to have significant effect on survival of both early and advanced stage patients (fig 5.8.5 & 5.8.6). In early stage category patients having treatment duration of less than 10 days had better survival as compared to patients with treatment duration of more than 10 days, whereas in advanced stage diseases reverse was seen i.e patient with treatment duration of more than 80 days had better survival than patients with treatment duration of less than 80 days (table 5.8.12/ 14). Patients undergoing unimodality treatment in both categories (early and advanced stage) had lower treatment time as compared to patients given multimodality treatment (table 5.8.13/ 15).

Table 5.8.11: Time taken for treatment completion as per Stage

Sl. No.	Time taken for treatment completion	Duration (days)	
		Early Stage	Advanced Stage
1.	**Median**	10	80
2.	**Minimum**	01	1
3.	**Maximum**	180	198

Table 5.8.12: Observed survival rate (%) of early stage oral cavity cancer according to time taken to complete cancer directed treatment

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Time taken for CDT completion							
≤ 10 days	112	94.4	85.6	84.6	83.6	83.6	0.01
> 10 days	111	86.3	79.2	72.7	70.4	69.0	

Figure 5.8.5: Observed survival rate (%) of early stage oral cancer according to time taken for CDT completion

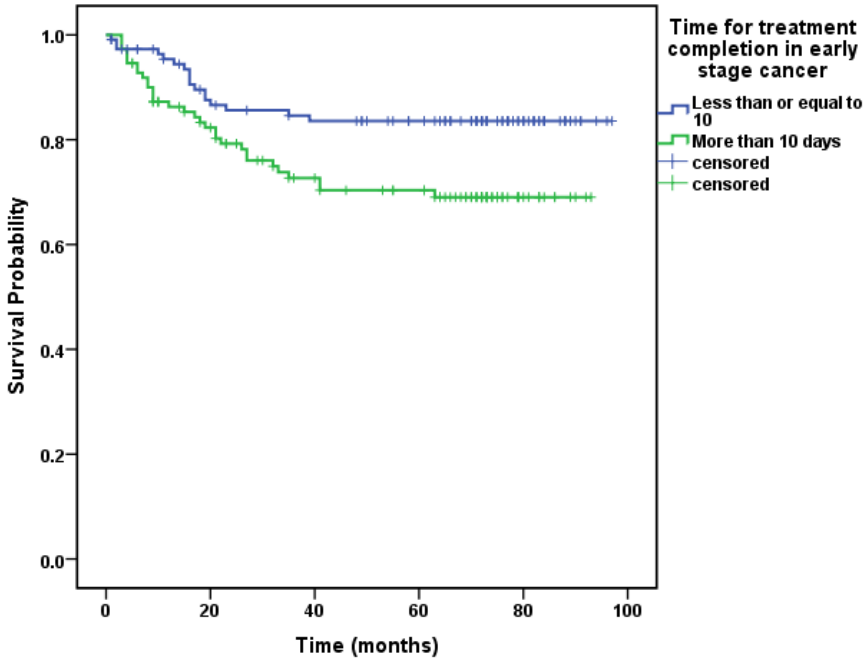


Table 5.8.13: Distribution of time taken for treatment completion in early stage cancer as per type of treatment

Time taken to complete CDT	Sx Only	RT only	Sx + RT	Sx + RT + CT	Overall (n= 223)
≤ 10 days	112	0	0	0	112
> 10 days	12	02	79	18	111

Table 5.8.14: Observed survival rate (%) of Advanced stage oral cavity cancer according to time taken to complete cancer directed treatment

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Time taken for CDT completion							
≤ 80 days	256	63.9	51.1	44.9	38.9	35.3	0.02
> 80 days	247	72.9	54.6	50.6	40.8	43.6	

Figure 5.8.6: Observed survival rate (%) of advanced stage oral cancer according to time taken for CDT completion

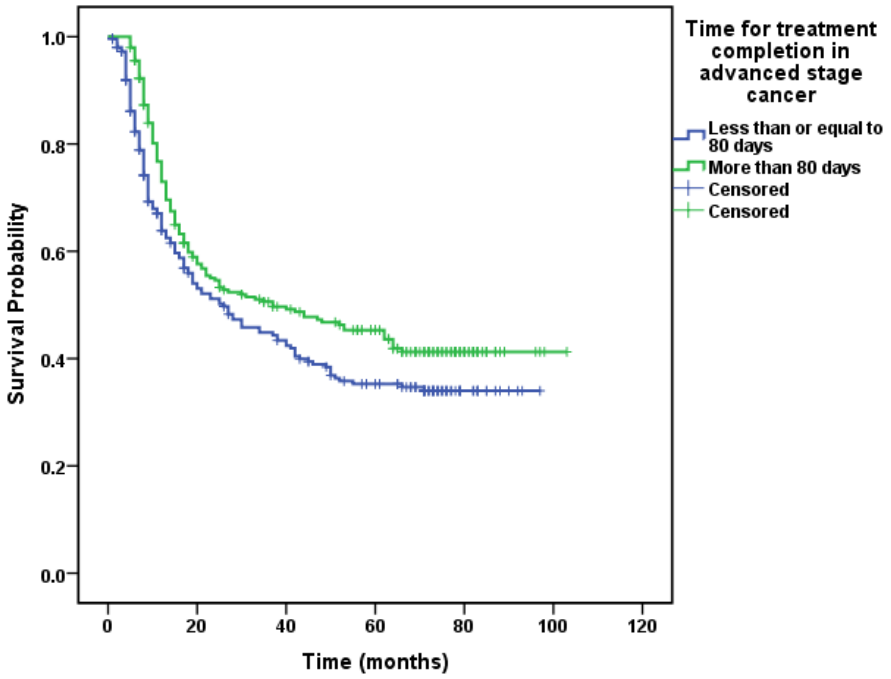


Table 5.8.15: Distribution of time taken for treatment completion in advanced stage cancer as per type of treatment

Time taken to complete CDT	Sx Only	RT only	Sx + RT	Sx + RT + CT	Rt + CT	Overall (n= 503)
≤ 80 days	138	23	64	21	10	256
> 80 days	00	00	134	93	20	247

5.8.4 Overall Treatment Time (OTT): Time period between registration of patient in Tata Memorial Hospital to completion of CDT, was considered as overall treatment time (OTT). The median OTT was 106 days (table 5.8.16). Almost half of the patients (48.1%) had OTT of more than 90 days and only 11% patients had OTT of more than 6months (> 180 days). The overall treatment time was divided into three categories for analyzing its effect on overall survival of patients (table 5.8.18). No significant (p=0.45) difference in 5 yr survival rates was observed as per OTT (figure 5.8.7).

Table 5.8.16: Overall treatment time (OTT)

Sl. No.	Overall treatment time	Duration (days)
1.	**Median**	106
2.	**Minimum**	5
3.	**Maximum**	317

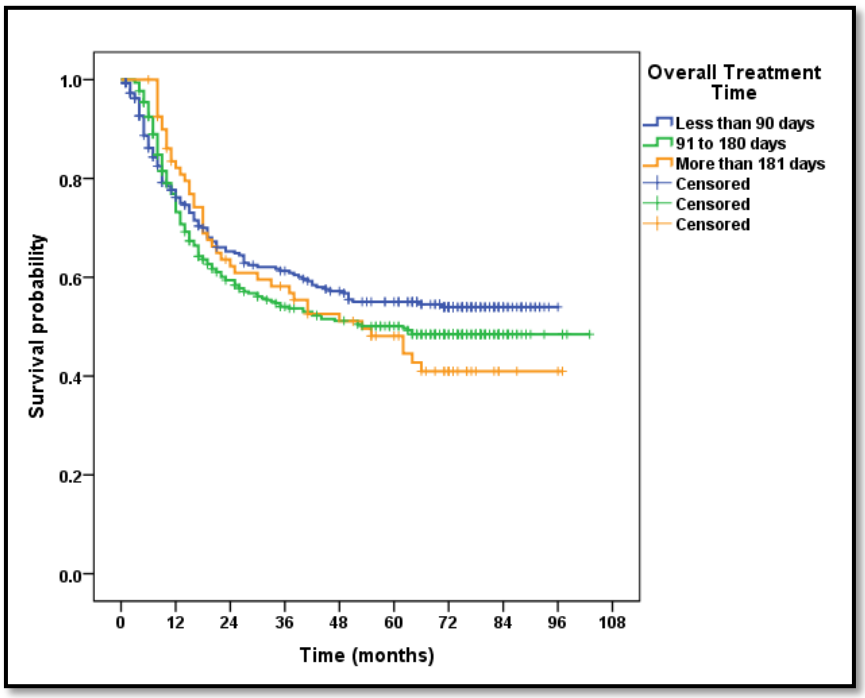
Table 5.8.17: Distribution of patients as per OTT

Sl. No.	OTT	No. of patients (%)	Cumulative total (%)
1.	**≤ 90 days**	296 (40.8)	296 (40.8)
2.	**91 – 180 days**	349 (48.1)	645 (88.9)
3.	**≥ 181 days**	81 (11.1)	726 (100)

Table No. 5.8.18: Observed survival rate (%) of oral cavity cancer according to OTT

Factor	Total Number	Survival in percentage					p Value*
		1 Yr	2 Yr	3 Yr	4Yr	5Yr	
Time taken for CDT completion							
≤ 90 days	296	76.2	65.3	60.9	57.2	54.5	0.45
91 – 180 days	349	73.2	59.4	53.7	51.2	49.7	
≥ 181 days	81	82.1	62.2	56.8	51.1	44.5	

Figure 5.8.7: Observed survival rate (%) of oral cancer according to OTT



5.9 Loss-adjusted survival (LAR): Loss adjusted survival rates were calculated by using method proposed by Ganesh (1995) (173). The proportion and risk (hazard ratio) of death and loss to follow-up at 5 years from the index date, by prognostic factors, are presented in Table 5.9.1. The proportion of patients lost to follow-up during the 5-year period was 18 %, and of dying was 43.9 %. The risk of loss to follow-up varied from 1.5-fold by age at diagnosis of more than 40 yrs and 1.1-fold by stage of disease. The risk of death increased 1.3-fold by age at diagnosis of more than 40 yrs, 1.3-fold by presence of comorbidity ($p<0.001$) and 3.3-fold with advanced stage of disease ($p=0.02$). The observed (actuarial) survival at 5 years was 52.0% (Table 5.9.2). During this period, 18.1% of cases were lost to follow-up; 7.6% in the first year, 5% of those remaining in the second and third years, and 5.5% of the remainder in the fourth and fifth years (Table 5.9.2). Adjustment for loss of follow-up gave an estimated survival of 51.2% at 5 years from index date, 0.8 % units less than the observed (actuarial) survival. This suggests that the patients who were lost to follow-up had a slightly higher mortality than assumed in the actuarial method of survival analysis, in which such deaths occur at the same rate as among those with complete follow-up. Table 5.9.2 also gives the estimate of loss-adjusted survival stage, adjusted for differential loss to follow-up by age and comorbidity.

Table 5.9.1: Number of cases, proportion and risk (Hazard ratio, HR) of death and loss to follow-up at 5 years from the index date (date of registration) and 95% confidence interval (CI) by factors studied

		Proportion at 5 years from index date		Hazard Ratio (HR) and 95% CI, (p value)	
Factors studied	**Number of cases**	**Lost (%)**	**Dead (%)**	**Lost HR[a]**	**Dead[b] HR**
All Cases	726	18.1	43.9	--	--
Age (< 40 yrs)	130	14.6	37.7	1	1
Age (≥ 40 yrs)	596	18.8	45.3	1.5 (0.9 – 2.6), (0.06)	1.3 (0.9 – 1.7), (0.08)
Comorbidity (absent)	479	19.8	40.1	1	1
Comorbidity (present)	247	14.6	51.4	0.7 (0.4 – 1.0), (0.12)	1.3 (1.1 – 1.6), (0.02)
Early Stage	223	21.1	21.1	1	1
Advanced Stage	503	16.7	54.1	1.1 (0.7 – 1.5), (0.60)	3.3 (2.4 – 4.5), (<0.001)

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

Table 5.9.2: Number of cases, proportion dead and lost to follow-up at varying intervals of time and 5-year cumulative absolute and loss-adjusted survival

	Survival in percentage									
	1 Yr		2 Yr		3 Yr		4 Yr		5 Yr	
All Cases										
Total No.	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**
726	21.1	7.6	14.2	2.9	4.1	2.1	3.0	1.8	1.5	3.7
Actuarial	78		62		57		54		52	
LAR*	77.1		61.8		56.9		53.2		51.2	
(*adjusted for age, stage and comorbidity)										
Early Stage										
Total No.	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**
223	8.5	6.7	8.1	4.5	3.1	3.1	1.3	1.8	0.0	4.9
Actuarial	91		82		79		77		77	
LAR*	90.8		81.6		77.8		76.1		76.1	
(*adjusted for age and comorbidity)										
Advanced Stage										
Total No.	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**
503	26.6	8.0	16.9	2.2	4.6	1.6	3.8	1.8	2.2	3.2
Actuarial	72		53		47		43		40	
LAR*	71.1		52.1		46.8		42.3		39.4	
(*adjusted for age and comorbidity)										

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. On an average 3000 patients attend the hospital daily for various cancer related investigation, treatment and follow-up. It has a well organized digital medical record system which comprehensively archives all patient details and provides sufficient opportunity for research. In India, though oral cavity is one of the leading sites of cancer, there is a dearth of studies describing the pattern of survival in oral 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 oral cancer survival in India is deficient and incomprehensive. Therefore, this study seeks to provide a holistic picture of overall survival and to also, identify and evaluate the impact of host characteristics and tumor related factors on survival of oral cavity cancer patients.

6.1 Overall Survival: A total of 726 cases of oral cavity cancer, comprising cancers of the lip, buccal mucosa, gingiva, retromolar trigone, floor of mouth, palate and tongue (Table 5.1.7), were included in the study. The observed 5 yr survival of the cohort was found to be 52%. Sankaranarayanan R et al. (2010) in his study of 25 population-based cancer registries in 12 countries in sub-Saharan Africa, Central America and Asia, found India to have the lowest survival rate in Asian countries and this difference was attributed to lack of established screening and early detection programmes, which in turn results in majority of cases presenting with advanced stage disease and lower survival. (10) Survival rates similar to our study were reported by Rogers SN et al. (2009) who in their study of 541 patients with oral squamous cell carcinoma

found 5 yr overall survival of 56%. (177) However, more closer to home, Yeole et al. (35) in his study of 1808 oral cancer cases in Mumbai reported a 5-year observed and relative survival rates for oral cancer as 30.5 and 39.7%, respectively, 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 data from death certificates mentioning 'cancer' or 'tumour' obtained from the Bombay Municipal death registration office and many of these patients probably would have never received any significant medical care (35). In contrast, our study comprised of only those patients who were diagnosed and had received atleast one modality of cancer directed therapy at Tata Memorial Hospital (TMH). A multicentric study of 2003 patients who had received treatment for OCSCC from 2000 to 2011 in 7 cancer centers worldwide, including TMH, reported an observed 5yr survival of 70%. (178) The 5 yr survival rate of 52% found in our study is much lower than this multicenteric study which is due to, firstly, 5 out of the 7 collaborating centers were from developed countries, contributing to more than 70% of the data/cases. Secondly, in our study, almost 70% (stage IV 54%; and stage III 15.3%) of cases had advanced stage disease at diagnosis as compared to only 55% in multicentric international collaborative study. This is further substantiated by the fact that 5yr survival of patients with early stage disease (TNM I & II) was found to be same in both the studies i.e 77%. However in our study, 5yr survival of patients with advanced stage disease (TNM III & IV) was found to be much lower i.e 40% as compared to 63% found in multicentric international collaborative study. (178) Thus, higher percentage of advanced stage cases with lower survival rate can possibly explain the lower overall survival found in our study. The 5yr survival rate of 40% in advanced stage cases found in our study is comparable with similar rates reported from India by Sayed SI et al. (2013) in their study of 1,408 oral cavity cancer patients. (179) Furthermore, overall survival for

only tongue cancer cases (n=245) was found to be 50% (table 5.5.1) and for cheek mucosa and other sites of oral cavity cancer (n=481) was found to be 52% (table 5.5.1). Only a limited number of studies have examined large series of tongue cancer. Spiro and Strong evaluated 314 patients (1957-1963) with tongue cancer and found an overall 5-year survival rate of only 42%. (180) Pernot et al. found 5-year survival rate of 44% in his review the medical records of 448 patients with tongue cancer who were exclusively treated with radiation based therapy either as a combination of brachytherapy and external beam radiation or as a combination of brachytherapy and neck dissection. (181) A more recent study (Kokemueller H et al. @2011), of total 341 patients with squamous cell carcinoma of the tongue who were treated surgery alone or in combination with other modality found a 5 yr survival of 50.6%, (182) which is similar to survival rates found in our study.

6.2 Factors affecting survival:

6.2.1 Age: The median age of patients in our study was 51 Years (Range: 18-85 years), which is similar to median age and range reported in some of the oral cancer studies from Indian. (67,179) The correlation of prognosis with age seems controversial, and some authors show no relationship between them, (29,111,183) whereas others demonstrate worse prognosis in older patients. (23,60) This dichotomy on the role of age in prognosis is largely due lack of consensus for the age ranges which should be used to analyze effect the age on cancer survival. (28) In our study, we used multiple cut-offs of age to evaluate its influence on survival. When age was categorized based on decades of age or median age of series 51 yrs or taking old age 65 yrs as cut off, age was not found to influence survival. However, when 40 yrs was taken as a cut-off, age was found to influence overall survival (Table 5.2.2). Similar, 40 yr age cut-off has also been used by other studies from Indian subcontinent. (179). Thus in our study, age was found to

influence survival both in univariate and multifactorial in analysis of all cases combined and advanced stage disease subset (Table 5.2.18-19, 5.3.11). However, only tongue subset though the patients more than 40 yrs showed poorer 5yr survival rate, it failed to achieve statistical significance in multifactorial analysis (Table 5.4.14, 5.5.16 & 5.6.17) Many researchers have similarly found age as a factor to influence outcome in certain cancers. (184) Pulte and Brenner (185) analyzed the Surveillance, Epidemiology and End Results (SEER) database based on population based cancer registries during 1973–2006 in the US, and found improvement in survival among all age groups except in the elderly population (>75 years). They also noticed a lower survival rate of 52.7% for these patients and a better survival of 72% for patients younger than 44 years. It has been suggested that the affect of age may be because younger and older patients might have different etiological reasons for developing cancer that can influence its biological behavior and outcome. (186)

6.2.2 Gender: Majority of the patients in study were males 73% (table5.1.1) The lower number females as compared to males is indicative of gender differences in the lifestyle and behavioural patterns associated with incidence of oral cancer. In our study we did not find any survival/ prognostic differences between males and females. The role of gender in cancer survival remains ambiguous, some authors have reported lower survival rates in females, attributed to delay in seeking medical care and lower acceptance of treatment. (60) A few have also reported more favorable outcome for females. (67) Owing to biological superiority and higher awareness in women concerning their bodies. (132,133) However, majority of the studies have not found any correlation between gender and oral cancer survival. (177,187)

6.2.3 Level of education: Educational inequalities in mortality have been documented across a wide range of countries. Several investigators have examined the statistically significant

effect of income and education on cancer survival. This is true when treatment quality is expected to depend on income when health services must be brought in the open market. A difference in economic resources is not the only possible mechanism behind the relationship between education and health. Highly educated individuals may have better understanding of the relationship between health inputs and health outcomes, thus enabling them to choose treatment options better. A related hypothesis is that, more highly educated people may be better at finding their way through health bureaucracy, acquiring relevant information and communicating their symptoms (188). In our study, we did not find any statistically significant relationship between education status and oral cancer survival. The possible explanation is that though differences in lifestyle and health behaviors are the major factors driving the positive association between education and health, but the quality of treatment also plays a big role in survival. (188) As all the patients in our study were treated at a single institute, where singular aim is to provide high quality health care, regardless of caste, education or socioeconomic status, we could not find any difference in survival based on educational status. Similarly, some studies of oral cancer patients have also reported no association between education and overall survival. (31)

6.2.4 Marital Status: It is widely believed that, adhering to the vow, "'Till death do us part," may be health-promoting. Among individuals who are well and among patients who are suffering a wide array of illnesses, marriage is often associated with longer life and better quality of life. (189–191) It is well known that social support and environmental factors may influence overall mental state of well-being, so as to exerting a significant effect on the outcome, especially for cancer patients. Some studies have been shown that married persons have better mood and receive more social support, including practical support and financial resources, so that they can focus on treatment and may show a better recovery from malignancy. (192)

However, Studies assessing the impact of marital status on survival among patients with cancer have yielded inconsistent results, with some reporting protective effect, (39–43) and some failing to find any relationship. (46–48) In our cohort of patients 83.7% were married and 11.3 were either unmarried or widow/ widower at the time of registration in the hospital (table 5.1.3) and Marital status was not found to have any influence on oral cancer survival. There can be a number of reasons for not finding any association between marital status and oral cancer survival, firstly, only a very few number i.e 37 patients out of 726 were unmarried and therefore, it is very difficult to draw any logical conclusion from such a small number. Secondly, marital status was determined only at the time of diagnosis and patients' status may have changed over time. Thirdly, most of the studies showing improved survival in married individuals are from western developed world, where better social support and companionship have been cited as the main reasons for improved survival (47). India is culturally and socially very different from the western countries, and is socially very closely knit; particularly the concept of joint families may make up for the social and emotional support for the unmarried or widowed elders in the family.

6.2.5 Lifestyle Habits (Tobacco chewing, Smoking and Alcohol): There is convincing evidence that tobacco chewing and smoking, are both strong and independent risk factors for oral cancer especially in Indian subcontinent. (13) In addition, studies have also found habit of alcohol to be a risk factor as well as to have synergistic effect with tobacco in causation of oral cancer. (193) We tried to evaluate the association between survival and tobacco or alcohol use by retrieving details of a number of habits including Cigarette smoking, Biddi smoking, Tobacco chewing, Paan Masala, Gutkha, Betul nut chewing, alcohol consumption etc from the patients case sheets. Tobacco chewing was found to be the most common habit (54%), followed by betul chewing (19.3) in males and females combined (Table 5.1.5). This confirms the popularity of

tobacco / betul nut chewing in Indian subcontinent as reported by other studies. (187) However, the case sheets did not provide any information regarding the quantity, frequency and duration of use of tobacco/ alcohol product or any further detail regarding continuation or cessation of habits after diagnosis. Hence, for survival analysis we categorized the individuals into two categories as per the presence or absence of any habit. Presence of lifestyle habit was not found to have any prognostic impact on oral cancer survival overall or in any of the subset (early/ advanced stage, tongue, cheek mucosa). The effect of tobacco/ alcohol habit on prognosis of oral cancer patients has been controversial. Some studies have found poorer prognosis in tobacco/ alcohol users, especially in those who maintain tobacco and alcohol consumption following diagnosis of the malignancy. (194) Whereas, some researchers have reported no association between lifestyle habits and survival. (61,67)

6.2.6 Comorbidity: Comorbidity is common among cancer patients, in our study 34% patients had one or more comorbidities (Hypertension, Diabetes mellitus, Heart Disease, Asthma and Human Immunodeficiency Virus (HIV) (table 5.1.6). Although there is general agreement that comorbidity is common among cancer patients, it is difficult to state with any certainty how common it is. This is because the prevalence of measured comorbidity varies, sometimes dramatically, depending on the measure of comorbidity used, the study population, and the cancer type. In a review of the impact of comorbidity on chemotherapy use and outcomes among patients with solid tumors, Lee et al. reported a wide prevalence range for comorbidity of 0.4% to 90% among cancer patients. (195) Thus, though some studies have reported a prevalence of comobidity between 30-40% in different types of cancers. (196,197) In general, results from several studies (198–200) are consistent with there being a spectrum of comorbidity prevalence among cancer patients. In our study we found the presence of comorbidity to be independent

predictor of poor prognosis for patients with oral cancer (HR = 1.58, 95% CI = 1.23 - 2.03; p< 0.01) (table 5.2.18) as well as in subset analysis of advanced stage disease (HR = 1.44, 95% CI = 1.09 – 1.89; p< 0.05) (table 5.4.14) and tongue cancer (HR = 3.04, 95% CI = 1.94 - 4.78; p< 0.05) (table 5.5.16) patients. In early stage disease (table 5.3.5) and cheek mucosa (table 5.6.8) subset analysis patients with comorbidity were found to have considerably lower survival as compared to patients without co morbidity, however this difference failed to achieve statistical significance (p=0.06 & p=0.07, respectively). Comorbidity has consistently been found to have an adverse impact on cancer survival. (195,201,202) The magnitude of the association is variable, depending on how comorbidity is measured, the measure of survival used, the cancer studied, and the population included. It head and neck cancer, it has been shown to be an independent predictor of survival, with increased severity of comorbidity associated with as much as a 2- fold increase in cancer-associated mortality. (23) There are several reasons why comorbidity impacts survival. The most obvious is the direct, independent impact of concomitant disease on noncancer mortality. Cancer-specific survival is also sometimes found to be reduced among those with comorbidity. One possible explanation for this is that it is caused by artifact, where those with cancer who die of unrelated comorbid conditions are incorrectly categorized as dying from their cancer. (203) Secondly, there is consistent evidence that those with comorbidity receive less active treatment than those without, and this impacts their survival probabilities. Those with comorbidity may also suffer higher levels of toxicity from cancer treatments, which may also detrimentally impact their cancer-specific survival. (195) A third mechanism is through a direct impact of comorbidity on cancer progression. Researchers have found there is more rapid tumor progression as well a higher risk of recurrence in those with comorbidity. Consistent with this, Piccirillo et al. in their study of 17,712 cancer patients, found that the likelihood of

developing a recurrence of cancer increased with increasing level of comorbidity (hazard radio, 1.18 for mild, 1.37 for moderate, and 1.54 for severe. (204)

6.2.7 Blood group: In recent past, the associations between ABO blood group and survival have been evaluated in several malignancy, including pancreatic cancer (205) esophageal squamous cell carcinoma (206), colon cancer (207), lung (208) and breast cancer (209). However, to date, the impact of ABO blood group on the survival of patients with cancer remains uncertain. A few studies in Indian population, have shown that patients with blood group A have predisposition for oral cancer (210–212), but there is a dearth of evidence regarding role of blood group in oral cancer survival. In our study we did not find any association between ABO blood group and oral cancer survival (table 5.2.8).

6.2.8 Disease staging (TNM Staging): The TNM grading system has been the mainstay of cancer outcome prediction in patients with head and neck squamous cell carcinoma (HNSCC) for many years. It has served several important functions including therapeutic decision making, patient counseling, stratifying patients for clinical trials and interpreting results, and designing treatment strategies. (77) In our study, TNM staging was found to significantly affect survival in all cases (table 5.2.9) as well as in tongue (table 5.5.8) and cheek mucosa (table 5.6.9.) subset. The overall 5yr survival rates for stage I, II, III and IV were found to 84.7%, 69.9%, 52.8% and 35.9% respectively. Similar, 5 yr survival rates of 75%, 65.6%, 49%, and 30% for stage I, II, III and IV respectively, have been reported Lo WL et al. in his study of 378 Oral cavity squamous cell carcinoma patients (OSCC). (183) A large, international, multicenter, pooled study of 2738 patients who received treatment for OSCC from 1990 to 2011 in 7 cancer centers worldwide have also found a similar stage wise survival (stage I (81%), II (63%), III (55%) and IV (41%). (178) In multifactorial analysis also advanced stage (TNM stage III & IV) was found to be

independent predictor of poor survival (HR = 1.96, 95% CI = 1.37 - 2.80; p< 0.01) (table 5.2.18) in overall as well as in tongue (HR = 1.79, 95% CI = 1.09 - 2.95; p< 0.05) (table 5.5.18) and cheek mucosa subset analysis (HR = 2.38, 95% CI = 1.33 – 4.23; p< 0.05) (table 5.6.17).

6.2.9 Node metastases: In our study cervical node metastasis (both clinical node involvement and histologically positive nodes) was associated with poor survival. In multifactorial analysis also nodal metastasis was found to be independent predictor of poor survival overall (HR = 1.48, 95% CI = 1.11 - 1.97; p< 0.01) (table 5.2.19) as well as in each of the subset (early stage, advanced stage, tongue and cheek mucosa). Cervical node metastasis is widely accepted as one of the major prognostic factors in patients with OSCC. Its presence is associated with a decrease in survival as well as with higher recurrence rates. (89,97,213,214) In addition to clinical node involvement we also examined the role of histological nodal metatstasis, which was found to be independent predictor of poor survival. These findings are in line with many other studies who have reported histologically positive cervical lymph nodes for squamous cell carcinoma as one of the simplest, and perhaps most important, prognostic markers in oral cancer. (215–218)

6.2.10 Tumor Size: In this study, tumor size was taken as the pathologically measured maximum cross-sectional diameter of a resected tumor. (99) We found that tumor size significantly influenced oral cancer survival. Tumor size was observed to be independent predictor of poor survival overall (HR = 1.83, 95% CI = 1.23 – 2.74; p< 0.01) (table 5.2.19) as well as in early and advanced stage disease, tongue (HR = 2.77, 95% CI = 1.39 – 5.49; p< 0.05) (table 5.5.17) and cheek mucosa (HR = 1.73, 95% CI = 1.06 – 2.82; p< 0.05) (table 5.6.18) subset. Maximum tumor diameter has traditionally been considered an important risk factor for the presence of concomitant nodal metastases, local recurrence, and poor survival. For example,

in two studies conducted on a total of 603 patients with HNSCC, Magnano et al. found that T stage was a consistent, independent predictor of pathologically positive cervical lymph nodes.(219,220) In addition, pathologic maximal tumor diameter has been shown to predict local recurrence in tumors arising from the oral cavity. (221) Finally, numerous studies, (221–224) have shown a univariate association between either clinical or pathologic tumor diameter and survival. Furthermore, we also observed that in multifactorial analysis tumor size of 2-4 cms did not show significant increase the risk of outcome as compared to tumors < 2ms (reference category), while tumors of more than 4 cms continued to have significantly higher risk of outcome. Similar, limitation of using tumor size as a prognostic determinant was highlighted by Moore et al., who stratified 155 patients with oral SCC based on surface diameter of the primary tumor. (222) Eighty-four percent of patients with tumors ≤2 cm survived disease free for 3 years, compared with 52% of patients with tumors larger than 4 cm. However, no significant differences in survival existed between tumors with surface diameters in the following three groups: 2.1 to 3 cm and 3.1 to 4 cm. Thus, although a gross trend exists between surface diameter and survival, but this trend does not follow a simple dose–response relationship. (222)

6.2.11 Histological grade (Tumor differentiation): Pathologists have long recognized the potential prognostic significance of cellular morphology in squamous cell carcinoma. Over the years, it has become customary to grade OSCC according to the method originally described by Broders, (225) and adopted by the WHO which takes into account a subjective assessment of the degree of keratinisation, cellular and nuclear pleomorphism, and mitotic activity. However, in recent past tumor differentiation has come into criticism due subjective nature of the assessment; small biopsies from tumours showing histological heterogeneity and inadequate sampling; reliance on structural characteristics of the tumour cells rather than functional ones;

and evaluation of tumour cells in isolation from the supporting stroma and host tissues. In spite of these limitations, numerous authors have established significant correlations between lower histologic differentiation and poorer prognosis. (26,108,109,183,226) Similarly, in our study also poor tumor differentiation was found to be an independent predictor of poor survival overall as well as in all the subsets.

6.2.12 Skin involvement: Skin invasion is an established risk factor for head and neck cancer patients. It is regarded as a T4 category in the TNM classification of various types of head and neck cancers, i.e., oral and nasal/paranasal cancers. (227) Skin invasion is closely related to tumor volume, larger tumors tend to show skin invasion and, at the same time, may pose higher risk of poor prognosis. In our study skin infiltration was found to correlate with survival in univariate analysis (table 5.2.13) (table 5.6.13) but failed to predict survival in multifactorial modeling (table 5.6.17). Similarly, Kang et al in his study of 467 OSCC patients did not find skin infilteration to be an independent predictor survival. (228)

6.2.13 Bone Involvement: The extension of oral squamous cell carcinoma into bone classifies the tumor as stage IV and is considered an indicator of poor prognosis. In the present study, bone involvement was found to significantly influence survival on univaraite analysis. However, on multifactorial modeling it failed to emerge as an independent predictor of survival in overall (table 5.2.18/19) or in subset analysis. Evidences suggest that, mandible invasion may progress through the bone in an infiltrative, mixed or erosive histological fashion. (229) These distinct histological patterns exhibit a different behaviors and questions previous assumptions that bone invasion presents ominous sign. (230,231) Poor clinical outcome is highly correlated with the infiltrative histological pattern of invasion. (102) Woolgar et al. in his studies of mandibular resections from previously untreated patients, (103,105,232) found infiltrative, but not an

erosive, pattern of invasion was predictive for local recurrence and survival even after taking into account the prevailing soft tissue prognosticators. (105) Furthermore, it has been suggested that non-characterization of bone invasion may result in uncertainties on the prognostic significance of bone involvement. (99) Ours was a retrospective study and the details of histological pattern of bone invasion as erosive, mixed, or infiltrative pattern was not available, this could probably be the reason of bone invasion not emerging as an independent prognosticator of oral cancer survival in our cohort.

6.2.14 Perineural invasion (PNI): Almost 19% (18.9%) of patients in our study showed tumor cell infiltration into perineural spaces (PNI) (table 5.1.13). Another Indian study (Sayed et al) had also found 18% prevalence of PNI in their cohort of 1,408 OSCC patients. (179) Similarly, few others studies have also reported PNI prevalence between 20-25% (177,233). However, the percentage of mucosal HNSCCs positive for PNI varies widely in the literature, from 5% (234) to 52% (235), this discrepancy may result from a tendency of some researchers to identify PNI only when large, named nerves are involved. PNI may be mediated by the presence of nerve cell adhesion molecule (N-CAM) on the surface of squamous carcinoma cells, which engages in homophilic binding with N-CAM expressed in neural and perineural tissues. In two studies of 76 and 66 patients with HNSCC, expression of N-CAM on the surface of neoplastic cells was significantly associated with PNI detected on review of pathologic sections. (236,237) We found PNI to be an independent predictor of poor survival overall as well as in all the subsets. Numerous clinical studies of oral cavity, (235,238,239) have identified PNI as an important predictor of poor prognosis. The presence of PNI in the primary tumor is associated with poor local control (234,235,240), regional control (241), local-regional control (242–244), cause-specific survival (235,243) and overall survival (243,245). The

association between PNI and local recurrence may result from either centrifugal or centripetal propagation of malignant cells along perineural spaces and away from the primary tumor. Most primary tumors will only disseminate up to 2 cm along the perineural space, (246) although PNI 12 cm from the primary tumor has been also reported.(247) As a result, PNI may allow malignant cells to evade surgical excision or radiotherapy and result in local recurrence. In addition, the association between PNI and regional recurrence implies that these tumors may be more biologically aggressive. The association between perineural invasion and tumor aneuploidy, a known marker of poor prognosis, lends support to this hypothesis.(248)

6.2.15 Extracapsular spread (ECS): ECS was found in 76% of patients with positive nodes (table 5.1.14). ECS has been reported to occur in roughly 65-75% of patients with positive cervical nodes in many national and international publications.(67,179,249,250) In our study ECS was found to significantly influence survival and was an independent predictor of poor prognosis (HR = 2.33, 95% CI = 1.79 – 3.04; p< 0.01) (table 5.2.18). Woolgar et al. in their study of 173 positive neck dissections found ECS as the best prognosticator in the stepwise regression model of Cox. (89) The prognostic importance of ECS has also been emphasized by several recent studies. (97,213,251) Furthermore, extracapsular spread (ECS) is a also noticeably important prognostic factor, associated with higher locoregional recurrence rates, distant metastases, and lower survival rates. (88,89,97) Some authors report a decrease in survival rates between 29% and 60%, as well as an increase in nodal metastases rates, when ECS is observed (213); others have shown 5-year survival rates of 21% in patients with ECS vs 64% for those without ECS. (97) These 5 yr survival rates are similar to rates observed in our study i.e 65.7% and 27.3% in patients with and without ECS (table 5.2.17). A descriptive evaluation system of ECS extension subdivides it into macro- and microscopic. Macroscopic ECS is evident to the

naked eye, and microscopic ECS is only demonstrable during histologic analysis. By studying the cervical nodes of 173 patients diagnosed with OSCC and histologically confirmed presence of nodal metastases, Woolgar et al. (89) found that the 3-year survival probability was similar in those with macroscopic or microscopic ECS (33% and 36%, respectively) and much worse than those with strict intranodal metastases. In view of the recent convincing evidence on the importance of ECS, researchers have recommended to integrate ECS into pathologic staging systems. (89)

6.2.16 Treatment: Surgery is the frontline treatment for oral cancer. (252) In our study also 92% (671) of cases were treated with surgery either alone or in combination with radiotherapy (RT) or chemotherapy (CT) (table 5.1.11). In, unvariate analysis, we found that compared with surgery alone patients treated with RT alone or RT + CT to have consistently significant highest risks of death (table 5.2.18). Similarly, patients treated with surgery + RT or surgery + RT+CT showed significant improvement in survival as compared to RT/ RT+CT. Patients with surgery alone were found to have the best survival rates as compared to all the other modalities / combination of therapies (table 5.2.18). However, in multifactorial analysis treatment was not found to be an independent prognostic factor overall (table 5.2.19/20) as well as in all the subset analysis. Subjects who opt for early surgical intervention have been shown to have a survival advantage. (60,66,253,254) Leite et al. reported that subjects treated with surgery had the highest survival rate, followed by surgery plus radiotherapy, but subjects treated with chemotherapy or radiotherapy had the worst prognosis. (60) Other authors have also indicated that patients treated with radiotherapy alone had a higher risk of death than those receiving surgical treatment alone. (253,254) Selection of treatment modalities is not only according to primary carcinoma extension, but also might be decided by clinical indices (i.e. tumor size, clinical stage, distant

metastasis, histological differentiation, and lymph-node involvement). Subjects who accepted surgery alone were often at an earlier clinical stage (75% cases of stage I in our study were treated with surgery alone). On the other hand, treatment with CT alone or RT alone might indicate that they were diagnosed in advanced stages of the disease (In our study, 95% of patients treated with RT alone and all the patients treated with RT + CT had advanced stage disease). Therefore, the better survival rates seen in only surgically treated might have been due to differences in disease stage and presence of other tumor related factors, rather than differences in effectiveness of treatment methods.(60)

6.2.17 Laboratory parameters (Hematological Factors): 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 heamoglobin, total white blood cell count along with its individual cell components and neutrophil lymphocyte (NLR) ratio in oral cancer survival. However, the pretreatment counts/ levels of the mentioned parameters were available for only 458 patients; hence a subset analysis was carried out taking into consideration these 458 patients.

6.2.17.1 Hemoglobin: In our study, we did not find any association between pretreatment heamoglobin levels and oral cancer survival. Similarly, several other authors have also failed to find any association between pretreatment heamoglobin and overall survival or local recurrence in head and neck cancers (255,256). Thus, although several investigators in the past have documented the prognostic impact of heamoglobin levels on cancer survival. (128–132) The role of heamoglobin as an independent prognosticator has been largely inconclusive firstly, due to

variability in literature regarding optimal timepoint to assess anemia, which may include options such as pretreatment hemoglobin, midradiation hemoglobin, postoperative hemoglobin etc. Secondly, due to ambiguity regarding optimal hemoglobin cutpoint for defining anemia, hence, certain authors have suggested that a single cutpoint for defining anemia may be inadequate to assess influence of heamoglobin on oral cancer survival. (134,135)

6.2.17.2 Total white blood Cell and its components: The total and differential white blood cell (WBC) count has been historically used as a marker of infection and inflammation. Nonetheless, its role has gone beyond the assessment of infectious processes and it has become an important prognostic measurement of outcomes in cancer treatment. Thus, while a link between inflammation and cancer has been known for more than a century, compelling recent evidence have suggested a strong association between pretreatment peripheral inflammatory cells and prognosis in different kinds of cancers.(150,153,257–259) In the present study, total WBC count, neutrophil count, lymphocyte count, monocyte count and NLR were found to be significantly associated with survival in univariate analysis in all cases combined (n=458) as well as in cases of advanced stage disease (n=350) but not in early stage disease. There is substantial evidence that, in advanced cancer, the host systemic immune response is an important independent predictor of outcome, and that pretreatment measurements of the systemic inflammatory immune response can be used to independently predict cancer survival but the same has not been established in early disease. (153) However, in multifactorial analysis only monocyte count and NLR emerged as independent predicators of oral cancer survival (table 5.7.2.8) (table 5.7.4.9). These results are in consonance with other published studies that implicate role of monocyte count (Tsai et al, n = 213) (153) and NLR (Perisanidis et al, n = 97) (160) in prognostication of oral cavity cancer patients.

6.2.17.2.1 Monocyte count: We found that monocyte count was an independent prognostic factor for patients with oral cavity cancer (HR = 1.45, 95% CI = 1.08 – 1.96; p=0.01). Sasaki and colleagues (260,261) studied the pre-operative absolute monocyte count in patients who had liver resection due to hepatocellular carcinoma, as well as in patients who underwent hepatic surgery due to colorectal metastasis and found that pretreatment absolute monocyte count was an independent prognostic indicator of tumor recurrence and survival in patients with hepatocellular carcinoma. Similarly, absolute monocyte count has been reported to be independent prognostic indicator for breast cancer, (257) gastric cancer, (150) Colorectal cancer, (260,261) Ovarian cancer (262) and oral cancer (153). The exact underlying mechanism explaining the association between the elevated number of monocytes and unfavorable cancer prognosis is unclear. However, a possible explanation can be that monocytes secrete various proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-10, and TNF-α, which have been associated with shorter survival and worse prognosis in malignances.(263,264) 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 TGF-α, IL-1, and IL-6 to promote tumorigenesis, angiogenesis, and distant metastasis of malignant tumors.(264,265) 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 cancers.(264,266,267)

6.2.17.2.2 Neutrophil Lymphocyte ratio: In this study we also found that high pretreatment NLR was significantly associated with poor survival in oral cavity cancer patients. This result is

in accordance with previous observations on the association between NLR and a variety of cancers. (156) More specifically, in Head and Neck cancers, elevated pretreatment NLR has been shown to be significantly associated with worse survival in two studies of nasopharyngeal cancer patients (268,269) and only one study of oral cavity cancer patients.(160) In our study, we also assessed the prognostic value of the individual components of NLR, that is, neutrophil and lymphocyte count. However, individually in multifactorial analysis neither was significantly associated with survival of oral cavity cancer patients. Perisanidis et al also reported a significant relationship between NLR and oral cancer survival but not with its individual components.(160) It has been suggested that, in cancer patients, NLR is superior to other individual leukocyte parameters.(270) This superiority of NLR can be attributed to the stability of NLR compared with the absolute counts that could be altered by various physiological, pathological, and physical factors. Moreover, NLR may represent the two opposing inflammatory and immune pathways that exist together in cancer patients. (160) Therefore, NLR can be considered as the balance between pro-tumor inflammatory status and anti-tumor immune status. Patients with elevated NLR have a relative neutrophilic leukocytosis and lymphocytopenia, which denotes that the balance is inclined in favor of pro-tumor inflammatory and is associated with poor outcome. (268,270) The mechanisms underlying the association of high NLR and poor outcome of cancer patients are poorly understood. One potential mechanism underlying the prognostic impact of NLR may be an association of high NLR with inflammation. An elevated NLR has been associated with an increase in the peritumoral infiltration of macrophages and an increase in interleukin (IL-17).(271) Neutrophils and other cells such as macrophages have been reported to secrete tumor growth promoting factors, including vascular endothelial growth factor, (272) IL-6, (273) IL-8,(274) and elastases,(275) and, thus, likely contribute to a stimulating tumor

microenvironment. It is a consensus that the adaptive immune system carries out immune surveillance and can eliminate newborn tumors, but effective adaptive immune responses are always suppressed in established tumors through several pathways, including inhibition of dendritic cell differentiation and activation, infiltration of regulatory T cells. Lymphocytes are crucial components of adaptive immune system, and studies have reported infiltrating lymphocytes to indicate the generation of an effective antitumor cellular immune response. (276) A low peripheral lymphocyte level may indicate a poorer lymphocyte-mediated immune response to tumor and suggests poor prognosis.(276,277) NLR may be explained by the diverse effects of neutrophils and lymphocytes on tumor progression. In vitro studies have shown that the cytolytic activity of lymphocytes and natural killer cells was suppressed when cocultured with neutrophils, and the extent of suppression was proportionally enhanced to the addition of neutrophils,(157,158,277) implying that high NLR was associated with poor prognosis.(269)

6.2.17.2.3 NLR and monocyte counts were found to be independent predictors of overall survival for patients with oral cancer. Given the low cost, easy accessibility, and reproducibility of a full blood count, both NLR and monocyte counts seem promising candidates for use in clinical practice. However, the findings of the study are based on a retrospective design in a single center, thus, further studies in either multicenter or prospective manner should be undertaken to validate and determine the clinical usages of NLR and monocyte count as prognostic markers for oral cavity cancer patients.

6.2.17 Summary of Independent predictors of survival: Table 6.2.1 (given below) provides a summary of the identified independent predictors of overall survival in all cases as well as in various subset analysis. Age of more than 40 yrs was found to be an independent prognostic factor overall except tongue cancer cases, however in tongue cancer subset it was found to influence survival significantly in univariate analysis but failed to achieve statistical significance in multifactorial model, this may be because very few patients were of age less than 40 years in this subset (59 cases). Similarly, though patients with comorbidity were found to have lower survival it failed to attain statistical significance in early stage and cheek mucosa subsets. Heamatological parameters namely monocyte and neutophil-lymphocyte ratio were found to be independent predictors of poor survival both in overall and in advanced stage disease, but failed to influence survival of cases with early stage disease. This is because in contrast to early stage, advanced stage is known to be associated with higher inflammatory state of the body and heamatological parameters are known to be marker of infection and inflammation. This effect was also seen when all the cases was considered together as majority (70%) of cases in our cohort were of advanced stage disease. Apart from these few exceptions, age, comorbidity, poor differentiation, lymph node involment (clinical/ histopathological), advanced disease, tumor size, perinueral invasion and extracapsular spread were found to be independent predictors of survival overall, and also in all the subsets.

Table 6.2.1: Summary of independent predictors of survival

All Cases (n=726)	Advanced Disease (n=503)	Early Disease (n=223)	Tongue Cancer (n=245)	Cheek mucosa and others (n=481)
• Age • Comorbidity • Poor Differentiation • Tumor Size • Lymph node involvement • Advanced Stage • Perineural invasion • Extracapsualar Spread • Monocyte count • Neutrophil Lymphocyte ratio	• Age • Comorbidity • Poor Differentiaion • Tumor Size • Lymph node involvement (histological) • Perineural invasion • Extracapsualar spread • Monocyte count • Neutrophil Lymphocyte ratio	• Age • Poor Differentiation • Tumor Size (histological) • Perineural invasion	• Comorbidity • Poor Differentiation • Tumor Size • Lymph node involvement • Advanced Stage • Perineural invasion • Extracapsualar spread	• Age • Poor Differentiation • Tumor Size • Lymph node involvement • Advanced Stage • Perineural invasion • Extracapsualar spread

6.3 Timelines: Delay in cancer diagnosis and treatment may be detrimental in several ways: a more advanced stage at diagnosis, poorer survival, greater disease-related and treatment-related morbidity and adverse psychological adjustment. Conversely, harm may be caused to the patients by early detection of cancers without improving survival (lead-time), and detection of slow-growing tumors not needing treatment (over-diagnosis). (162) Hence in order to assess the influence of time on oral cancer survival we estimated four broad timelines in our study namely time between registration and diagnosis, time between diagnosis and commencement of treatment, time between treatment commencement and treatment completion and time between registration in this hospital (TMH) to treatment completion (OTT).

6.3.1 Time between registration and diagnosis: Extended period of delay in diagnosis following the onset of symptoms is hypothesized to provide an important explanation for diagnosis at an advanced stage and subsequent poor survival. Traditionally, diagnostic delay refers to the total period of time from onset of symptoms to diagnosis. Diagnostic delay is generally divided into two phases: the period from the onset of symptoms to seeking of care (patient delay) and the excess period elapsed between first contact with health care professional and specialist consult(s) for definitive diagnosis (provider delay). Porta et al. describes the set of influences that can affect the length of the period from onset of symptoms to diagnosis, which include ‘‘behavior of the patient and attending physician, tumor biology and host-tumor interactions, the functioning of the health care system and socio-cultural norms.’’ (278) In our study, we estimated the time period required to pathologically confirm the diagnosis of tumor from the time of registration of the patient in this institute. Majority, of the patients were diagnosed within 7 days and the median period of diagnosis was found to 3 days (table 5.8.1). On survival analysis time required for diagnosis was not found to be associated with survival

(table 5.8.3). Several studies for head and neck cancers have reported no association between time for diagnosis and survival. Seoane et al in his study of oral cancer cases found that when survival was adjusted for tumor stage at diagnosis, diagnostic delay did not influence survival, and hence suggested that survival from oral cancer is affected more by the biology of the cancer (rapid tumor growth) than by diagnostic delay. (279) Similarly, Teppo et al in his study of tongue cancer patients failed to find any association between time for diagnosis and survival. (280) 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.

6.3.2 Time between diagnosis and commencement of treatment: In the present study, the median time from diagnosis to initiation of treatment was found to be 30 days, and was not found to be associated with overall survival (p=0.76) (table 5.8.6). Jimmy J et al. in his study of locoregionally advanced head and neck cancer also reported a similar median time of 34 days and found that a longer diagnosis to treatment interval (DTI) was not significantly associated with locoregional control (P=0.11), distant metastases-free survival (P=0.32), or overall survival (P=0.07). (163) Similarly, several other studies of head and neck cancer with similar median DTI between 25 to 45 days have found no association between time of diagnosis to treatment initiation. (281,282) Most information supports the concept that timely initiation of therapy is a laudable approach. However, the results reported herein suggest that complex cases may require additional planning procedures, and these delays, which are aimed to improve the treatment, are unlikely to cause detrimental effects. (163)

6.3.2 Time between commencement of treatment to treatment completion and Overall treatment time (OTT): In addition to the time between commencement of treatment to treatment completion, we also calculated OTT which was the time taken from registration of the patient in this centre to treatment completion. The median time taken for treatment completion varied widely depending upon type of treatment given on the patient (table 5.8.7). Overall the median time required for treatment completion was 30 days (table 5.8.7) and OTT was 106 days. Both were not found to be associated with overall survival (table 5.8.9/ 11) ($p > 0.05$). However, when we categorized the patients as per stage, early stage disease patients who received treatment for less than 10 days had significantly ($p=0.02$) better than patients who received treatment for more than 10 days (table 5.8.12) All those patients who received treatment for less than 10 days underwent only surgical treatment and majority (87%) (table 5.8.13) of other patients with treatment of more than 10 days were given multimodality treatment, these patients though early stage at diagnosis were probably upstaged following surgical intervention and hence given multimodality treatment. On the other hand in advanced stage disease group patients with treatment of more than 80 days had better survival than who received treatment for less than 80 days (table 5.8.14). It is known that the complexity of multimodality treatment for patients with head and neck cancer can lead to delay in treatment completion. The same is evident in early stage disease as sizeable proportion (62.5%) of patients who received treatment for less than 80 days underwent only unimodality treatment. These patients represent the group of patients who probably did not complete treatment as planned and hence are likely to have a more ominous outcome. Thus, the stage wise survival analysis of treatment time indicates that other factors such as upstaging of disease due to tumor characteristics/ tumor biological behavior or treatment completion influence survival more rather than the treatment time. Nonetheless, it is

generally accepted that the overall treatment time for these patients should not exceed 100 days measured from the day of surgery to the end of adjuvant therapy. (283,284) Tribuis S et al analyzed survival in patients of head and neck cancer according to treatment duration >100 days vs ≤100 days and observed that disease free survival and recurrence free survival was not significantly different in these 2 groups, however overall survival was lower in patients with treatment time of more than 100 days. (166) In our study we tried to see the influence of treatment time on survival by taking multiple cut-offs (≤ 60 days, 61 – 90 days, 91 - 120 days and ≥ 121) as well as the traditional 100 days cut-off. In both the analysis we found that the patients treated for longer duration did have lower survival (36.6% for patient treated for ≥ 121 days (table 5.8.9); 45% for patient treated for > 100 days (table 5.8.10)), however this difference in survival as compared patients with lower treatment time failed to achieve statistical significance ($p > 0.05$) . One reason for this could be that majority (>80%) of our patients had completed treatment within 100 days. Nonetheless, as far as possible treatment delays should be avoided, especially delay in initiating radio(chemo)therapy after surgery should be minimized as much as possible under local circumstances and considering patient characteristics. However, some potential limitations of our study deserve consideration. This was a retrospective analysis of a patient's medical records and not a randomized clinical study and therefore is subject to the limitations of such analyses. There is a potential for selection bias, as duration of treatment may have been influenced by baseline characteristics that predispose the patient to either more rapid treatment or a greater delay in commencing adjuvant therapy, such as more advanced disease requiring more extensive dental work etc such details of the patients were not available for analysis. (166)

6.4.1 Loss-adjusted survival rate (LAR): The literature on survival analysis uses standard statistical methods such as actuarial (or life-table) method (285) and the product-limit method (21) for estimating survival rates. All these methods hold true only under certain assumptions. The main assumption of these methods is the independence of risk of death and withdrawal. Thus, survival estimates may be biased if the proportion of cases lost to follow-up is substantial (as in many developing countries, where health information systems are not well developed), and if the loss to follow-up is correlated with the probability of death (prognosis) of the patient after he or she was lost. Censoring in survival analysis should be "non-informative," i.e. participants who drop out of the study should do so due to reasons unrelated to the study. Informative censoring occurs when participants are lost to follow-up due to reasons related to the study. Several methods have been described to deal with the problem of informative censoring. These include imputation techniques for missing data, sensitivity analyses to mimic best and worst-case scenarios and use of the drop-out event as a study end-point. For unbiased analysis of survival curves, it is essential that censoring due to loss to follow-up should be minimal and truly "non-informative." In India, the withdrawals are most often non-technical withdrawals i.e. they are loss to follow-up. (174) Prognostic factors that may also predict loss to follow-up are related to the clinical characteristics of the disease, the patient and the social environment. For example, recurrence or relapse of the disease and serious comorbidity are prognostic factors that may cause the patient to move away (for treatment, or terminal care), making them impossible to trace. (286) Information on the association between prognostic factors and loss to follow-up can be used to reduce the bias in estimates of survival. (174,287) Furthermore, the bias in the estimation of 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 patients

lost 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 estimate is biased and too high. The 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 prognostic variables such as age, stage, etc. Computation of loss-adjusted survival (Ganesh, 1995) then takes into consideration such differential losses, by assuming that patients lost 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 patients lost to follow-up and with complete follow-up to be more similar within a prognostic group, than when all patients are considered together. The difference between the crude actuarial survival and the loss-adjusted value indicates the magnitude of the effect of differential loss to follow-up.

6.4.2 In our study overall 5 yr survival for all cases by actuarial method was found to be 52% and Loss adjusted survival rate was found to be 51.25%. Similarly, in subset analysis for early and advanced diseases the 5 yr survival by actuarial and LAR method was found to be 77% & 76.15%, and 40% & 39.40% respectively. Thus, adjustment for loss of follow-up gave an estimated 0.8% units less 5 years survival than the observed (actuarial) survival. The small difference between the absolute (actuarial) survival and the loss-adjusted survival observed in this study is much less than in other studies. (286,288). This can be because our study had only 18.1% loss to follow up as compared to much higher loss to follow-up reported by other quoted studies i.e Ganesh et al. (288) loss to follow-up of 35-43%; Sriamporn et al. (286) loss to follow-up- loss to follow-up of 26.7%. The low loss to follow-up observed in our study was because our study cohort comprised of only those cases who were residents of Mumbai and it has been seen that in patients treated at TMH, the proportion of loss to follow-up is much lower among

residents of Mumbai as compared to non-residents. (174) Furthermore, tracking of Mumbai cases is better because of integration of our data with Mumbai population based cancer registry and also due to sharing of mortality data by the local municipal vital registration system (Brihanmumbai Municipal Corporation). This method of calculating loss-adjusted survival rates has been shown to be useful where large numbers of patients are lost to follow-up (288). However, this observation of small difference between the absolute (actuarial) survival and the loss-adjusted survival is not confined to cancer of the oral cavity; differences for other sites like female breast (data from six registries from developing countries) and larynx (data from Chennai and Mumbai cancer registries) have also been reported to be of similar (small) size . (289) Thus, the small correction of survival by loss-adjustment seen in our study is probably due to low proportion of loss to follow-up and larger correction are more likely to occur in datasets with higher loss to follow-up, due to patients coming from a wide geographic area.

6.5 Strengths and Limitations: 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, pathological reports and OPD data, for a large cohort of patients treated at Tata Memorial Hospital between 2006 – 2008. Secondly, this study comprehensively covers the ambit of survival in oral cancer patients by providing patterns of survival overall as well as in different subsets. It 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 only five co-morbidities (diabetes, hypertension, ischaemic heart disease, HIV and asthama) were recorded in the medical case sheets, additionally, only information about the presence of comorbid disease was available but details regarding time of onset, duration of disease, whether on medication etc were not obtainable from the medical records. Similarly, in certain factors such as lifestyle habits in which there is possibility of change in patient's exposure status after diagnosis, such details were not available for analysis.

CHAPTER 7

SUMMARY AND CONCLUSION

7.1 Summary of findings: The summary of finding s is as follows

7.1.1 Overall Survival: The overall 5 year survival of oral cavity cancer (all cases) was found to be 52%. The 5 year overall survival for Early stage disease (TNM I &II), Advanced stage disease (TNM III & IV), Tongue and Cheek mucosa cancer was found to be 77%, 44%, 50% and 52% respectively.

7.1.2 In Oral cavity cancer (all cases) the independent predictors of prognosis were Age, Comorbidity, Poor differentiation, Tumor Size, Lymph node involvement, Advanced Stage, Perineural invasion, Extracapsualar Spread, pretreatment Monocyte count and Neutrophil-Lymphocyte ratio.

7.1.3 In Early stage cancer (TNM I & II) the independent predictors of prognosis were Age, Poor differentiation, Tumor size and Perineural invasion.

7.1.4 In Advanced stage cancer (TNM III & IV) the independent predictors of prognosis were Age, Comorbidity, Poor differentiation, Tumor Size, Lymph node involvement, Perineural invasion, Extracapsualar Spread, pretreatment Monocyte count and Neutrophil-Lymphocyte ratio.

7.1.5 In Tongue cancer the independent predictors of prognosis were Comorbidity, Poor differentiation, Advanced stage, Tumor Size, Lymph node involvement, Perineural invasion and Extracapsualar Spread.

7.1.6 In Cheek mucosa and other sites of oral cavity cancer (excluding tongue) the independent predictors of prognosis were Comorbidity, Poor differentiation, Advanced stage, Tumor Size, Lymph node involvement, Perineural invasion and Extracapsualar Spread.

7.1.7 Timelines: The median time period from registration to pathological confirmation of diagnosis was 3 days, from diagnosis to commencement of treatment was 30 days, from treatment commencement to treatment completion was 30 days and median overall treatment time was found to be 106 days. The time periods were not found to be associated with survival.

7.1.8 Overall 5 year survival rate and loss-adjusted survival rate were found to be 52% and 51.25% respectively.

7.2 Conclusion The current study is one of the few Indian studies to comprehensively analyze and present a holistic picture of oral cancer survival in patients treated at a premier cancer hospital of India. Our study shows that oral cancer mortality may be reduced if lesions are detected, diagnosed, and treated at an earlier stage. The survival rates of 5-year were better in patients with the early stages of OSCC than in those with the advanced stages. Therefore, we are tempted to conclude that the periodic screening of high risk populations for OSCC and early treatment may appreciably reduce oral cancer mortality in India. Thus, promotive and preventive public health approach holds the key to reduce the OSCC burden in India. Contrary to what is generally accepted socio-demographic factors such as education and marital status were not found to affect oral cancer survival in our study. Similarly, various time periods involved in evolution of

cancer treatment in the hospital namely, time for diagnosis, treatment initiation, treatment completion and overall treatment time were not found to influence overall survival. Furthermore, cancer as a disease bears such an intense burden that role other chronic co-morbities is often undermined, but our study shows that presence of co-morbidity has a significant influence on outcome of oral cancer patients. In addition, ours is the only study in India to report prognostic role of heamatological parameters such as neutrophil-lymphocyte ratio (NLR) and monocyte counts in oral cancer patients. Given the low cost, easy accessibility, and reproducibility of a full blood count, both NLR and monocyte counts seem promising candidates for use in clinical practice. Finally, our study demonstrates that, in addition to TNM classification other clinical and pathological factors also have a significant role in predicting survival. Therefore, although the TNM classification harbors very important clinical information the role of other factors viz tumor differentiation, extracapsular spread and perineural invasion cannot be ignored and hence, there is a need to develop a more powerful and precise modular prognostic system that will not only be reliable and reproducible but also flexible and easy to use.

CHAPTER 8

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