PROGNOSTIC FACTORS IN HEAD & NECK CANCER PATIENTS TREATED WITH RADIOTHERAPY: A RETROSPECTIVE ANALYSIS

THESIS

Submitted to

All India Institute of Medical Sciences, Jodhpur

In partial fulfillment of the requirement for the degree of

Doctorate of Medicine (DM)

Radiotherapy & Oncology

July 2020

AIIMS, Jodhpur

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DECLARATION

I hereby declare that the thesis titled "**PROGNOSTIC FACTORS IN HEAD & NECK CANCER PATIENTS TREATED WITH RADIOTHERAPY: A RETROSPECTIVE ANALYSIS**" embodies the original work carried out by the undersigned at All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled "**PROGNOSTIC FACTORS IN HEAD & NECK CANCER PATIENTS TREATED WITH RADIOTHERAPY: A RETROSPECTIVE ANALYSIS**" is a record of the bonafide research work of **Dr. Atul Kumar Gupta** carried out under our guidance and supervision in the Department of Radiation Oncology, Department of Surgical Oncology and Department of Pathology, All India Institute of Medical Sciences, Jodhpur, Rajasthan. Dr. Atul Kumar Gupta has learned and performed all the clinical and analytical procedures involved in the study under guidance and supervision.

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TO

SERVE HUMANITY

ACKNOWLEDGEMENT

First and foremost, I bow in reverence to The Almighty for allowing me to undertake this task and strength and ability to complete it. I fell elated to stoop low at the feet of my God and express my thanks for blessing me with everything I prayed for.

Words are inadequate to express my gratitude and appreciation to my dearest parents, Mr. Rajesh Kumar and Mrs. Sunita Devi, and my Grandparents Mr. Jagdish Prasad and Mrs. Santosh Devi for their love, care, blessings and constant encouragement. I pray to God to give me enough strength and capability to fulfill their dreams.

I gratefully acknowledge and thank my elder sister Mrs. Priyanka Gupta, younger sister Miss Shweta Gupta, My brother in law Mr. Kuldeep Garg and my niece Pihu for supporting me throughout this course.

No words of gratitude are sufficient to express my sincere regards to my revered teachers and my Guide, Dr. Puneet Pareek, Prof R. K. Vyas, Dr. Akanksha Solanki, Dr. Bharti Devnani, Dr. Sandeep Bairwa, Dr. Parmod Kumar, Dr. Akanksha Garg. Their keen interest, competent guidance and constant help in solving my day-to-day problems was instrumental in nurturing this project to its present shape.

It was a matter of great honor to work under the guidance and blessings of my co-guides Prof. Poonam Elhence, Department of Pathology, Dr. Jeevan Ram Vishnoi, Department of Surgical Oncology, AIIMS Jodhpur.

It was great support from Dr. Harsha, Dr. Sweta, Dr. Shekhar, Dr. Harika, Dr. Ramakant, Dr. Vaibhav, Dr. Avni, Dr. Prateek Senior Residents, Department of Radiation Oncology.

I'm thankful to especially Dr. Amith Mohan, Dr. Sujoy Fernandez, Dr. Sanjay Santhyavu, Dr. Mukul Choubisa, Dr. Samiran Chavan, Dr. Kalyani Nair for their fruitful discussions and genuine feedback that have made this whole experience a pleasurable one.

I am highly blessed to have such a cooperative co-PG, Dr. Rishi P Nair, who helped me in completing my thesis with his valuable input.

It was enlightening to work with Mrs. Sonal Varshney, Mr. Irfad, Miss Monika, and Mr. Mohsin, who were partners as Medical Physicist planning and assuring all patients' quality of treatment.

I am indebted to the wonderful team of Radiation Technologists of our Department Mr. Pankaj, Mr. Jitendra, Ms. Sakshi, Mr. Upendra, Mr. Sujeet, Mr. Deepak, Mr. Nayan, Ms. Anjali, Mr. Harsh

I thank for the care and compassion for our study patients provided by the Nursing Staff of our Department and ward for the coordination and so many big and small works, Mr. Gajendra Ji, Mr. Laxmikant, Mr. Najir, Mr. Raj from the Administrative Staff of our Department.

Our office staff Mr. Mangi Lal, Mr. Rajesh, Mr. Dileep, Mrs. Aarti, Mrs. Rinku and Mrs. Sangeeta all took care of patients and made them and me feel at home.

I am thankful and pray for forgiveness to all who have helped the patients and the study and by mistake I have forgotten to mention their names.

My gratitude should extend to my dearest friends Dr. Ankit Singh, Dr. Megha Bhargava, Ms. Richa Arora, Mr. Rahul Sharma and Mr. Jaikumar Gupta for their immense support and the willingness to cheer me up in my bad times.

Last but not least, I thank all the patients who participated in this study for sharing their experiences and feelings, even when they were going through so much in their own lives.

DR ATUL KUMAR GUPTA

LIST OF ABBREVIATIONS

HNC	HEAD AND NECK CANCER
HPV	HUMAN PAPPILOMA VIRUS
HNSCC	HEAD AND NECK SQUAMOUS CELL CANCER
QOL	QUALITY OF LIFE
RT	RADIATION THERAPY
EXTREME	ERBITUX IN FIRST-LINE TREATMENT OF RECURRENT OR METASTATIC HEAD AND NECK CANCER
EGFR	EPIDERMAL GROWTH FACTOR RECEPTOR
NACT	NEO ADJUVANT CHEMOTHERAPY
EORTC	EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENTOF CANCER
NCCN	NATIONAL COMPREHENSIVE CANCER NETWORK
5FU	5 FLUORO-URACIL
GY	GRAY
IV	INTRAVENOUS
RCT	RANDOMISED CONTROLLED TRIAL
TP	TAXANE AND PLATINUM
OAR	ORGAN AT RISK

BMI	BODY MASS INDEX
BSA	BODY SURFACE AREA
BSC	BEST SUPPORTIVE CARE
PFS	PROGRESSION FREE SURVIVAL
OS	OVERALL SURVIVAL
DFS	DISEASE FREE SURVIVAL
GLOBOCAN	GLOBAL CANCER OBSERVATORY
ESMO	EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY.
WHO	WORLD HEALTH ORGANISATION
PF	PLATINUM AND 5 FLUORO-URACIL
TPF	TAXANE, PLATINUM AND 5 FLUORO-URACIL
RTOG	RADIATION THERAPY ONCOLOGY GROUP
LA	LOCALLY ADVANCED
LRC	LOCOREGIONAL CONTROL
LVSI	LYMPHOVASCULAR SPACE INVASION
PNI	PERINEURAL INVASION
ENE	EXTRANODAL EXTENSION

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INTRODUCTION

BACKGROUND-

Head and neck cancers (HNCs) are malignant tumors of the upper aerodigestive tract including the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx. Squamous cell carcinoma (SCC) constitutes >90% of HNCs.

1. PROBLEM STATEMENT-

Head and neck cancers are common in multiple regions worldwide. The primary risk factors associated with head and neck cancer include tobacco use, alcohol consumption, human papillomavirus (HPV) infection (mainly for oropharyngeal cancer), and Epstein-Barr virus (EBV) infection (for nasopharyngeal cancer). Chronic exposure of the upper aerodigestive tract to these carcinogenic factors can result in dysplastic or premalignant lesions in the oropharyngeal mucosa and ultimately result in the development of cancer. The relative prevalence of these risk factors contributes to the variations in the observed distribution of head and neck cancer in different areas of the world.

Worldwide, head and neck cancer account for approximately 900,000 cases and over 400,000 deaths annually. In the United States, head and neck cancer accounts for 3 percent of malignancies, with approximately 66,000 cases annually and 15,000 deaths(1).In India, it constitutes 25-30% of all cancers as opposed to 3-4% in the Western World(2). This gross variation in the incidence is predominantly attributed to the rampant use of tobacco and areca nuts in India. While epidemiological data suggest a steady decline of tobacco-related cancers in the West with a concomitant rise in human papilloma virus (HPV) related oropharyngeal malignancies this trend has not been observed in India; HPV-related head and neck cancers being a relative rarity.

2. RISK FACTORS IMPLICATED IN HNC CARCINOGENESIS-

The risk factors most frequently associated with head and neck cancer include alcohol consumption, smoking, tobacco chewing, HPV infection (especially for oropharyngeal carcinoma) and EBV infection (especially for nasopharyngeal carcinoma in Asia).

2.1 TOBACCO CONSUMPTION-

Tobacco has widespread social acceptance in the Indian community. According to the Global Adult Tobacco Survey, the consumption rate of tobacco among adults in India is 34.6%. It is

higher in males (47.9%) compared to females (20.7%). It is more prevalent in rural areas (38.4%) where two-thirds of the nation's population resides. Of tobacco users, 60% consumed smokeless tobacco, 25% used the smoked tobacco form alone and 15% consumed both the forms. The relative risk (RR) of oral cancer is much higher in smokeless tobacco users compared to the never users (RR 5.5 with 95% confidence interval (CI) 3.3-9.0 for those currently using smokeless tobacco against RR 1 in never users)(3).

2.2 ALCOHOL CONSUMPTION-

Alcohol drinking is considered to be an established risk factor for HNC, and this association may be stronger among cancers of the oropharynx and hypopharynx than the oral cavity or larynx. In addition, higher alcohol consumption over a shorter period was more harmful than less alcohol consumption over a longer period (4).

2.3 ASSOCIATION WITH HPV INFECTION-

It has been demonstrated that human papillomavirus (HPV) infection is involved in up to 25% of HNCs, particularly in the oropharyngeal carcinoma subtype where it can account for up to 30 to 60% of such cases(5).

2.4 ASSOCIATION WITH EBV INFECTION-

The Epstein-Barr virus (EBV), a human B lympho-trophic herpes virus, is strongly associated with undifferentiated carcinoma of the nasopharynx and African-type Burkitt's lymphoma(6).

3. CLINICAL PRESENTATION OF PATIENTS WITH HNC-

Patients with HNCs present with a variety of symptoms, depending on the site where they originate. Laryngeal cancers commonly present with hoarseness, whereas pharyngeal cancers often present late with dysphagia or sore throat. Many often present with a painless neck node. Patients with head and neck cancer can present with non-specific symptoms or symptoms commonly associated with benign conditions, however, such as sore throat or ear pain(7). Mostly symptoms in patients with HNCs are attributable to local disease itself or due to its regional spread.

3.1 Oral cavity tumors – Patients may present with mouth pain or nonhealing mouth ulcers, loosening of teeth, ill-fitting dentures, dysphagia, odynophagia, weight loss, bleeding, or referred otalgia. Up to 66 percent of patients with primary tongue lesions have cervical lymph

node involvement, depending on T stage and depth of invasion, while the incidence is substantially lower in patients with hard palate cancers.

• Lip cancer usually presents as an exophytic or ulcerative lesion of the lower lip, occasionally associated with bleeding or pain. Some patients complain of numbness of the skin of the chin due to the involvement of the mental nerve.

3.2 Nasopharyngeal carcinoma – The most frequent presenting complaint is a neck mass due to regional lymph node metastasis, which occurs in nearly 90 percent of patients. Symptoms due to the primary tumor may include hearing loss (associated with serous otitis media), tinnitus, nasal obstruction and pain, and its associated growth into adjacent anatomical structures, which can lead to muscle involvement and impaired function of cranial nerves II to VI. Adults with unilateral effusion should have an examination of the nasopharynx.

3.3 Oropharyngeal tumors – Presenting complaints can include dysphagia, pain (odynophagia, otalgia), obstructive sleep apnea or snoring, bleeding, or a neck mass.

3.4 Hypopharyngeal tumors – Patients with these tumors often remain asymptomatic for a longer period and are therefore more likely to be seen in the later stages of the disease. Dysphagia, odynophagia, otalgia, weight loss, hemoptysis, dyspnea, and neck mass are common presenting symptoms.

3.5 Laryngeal cancer – The symptoms associated with cancer of the larynx depend upon location. Persistent hoarseness may be the initial complaint in glottic cancers; later symptoms may include dysphagia, referred otalgia, chronic cough, hemoptysis, and stridor. Supraglottic cancers are often discovered later and may present with airway obstruction or palpable metastatic lymph nodes. Primary subglottic tumors are rare. Affected patients typically present with stridor or complaints of dyspnea on exertion.

4. MANAGEMENT STRATEGY-

HNCs have a lower incidence of systemic dissemination as compared to other cancers as breast cancer. They mainly grow and erode locally, causing suffering. The site of head, neck and face is the location of airway and digestive tract both and special senses of smell, taste, vision and hearing. Overall, HNCs affect the quality of life of a patient so management should be aimed at improving the quality of life along with reducing treatment complications.

For early-stage head and neck cancer (HNC), definitive surgery or definitive radiotherapy (RT) is a standard treatment(8).

For locally advanced Head & Neck cancers, Surgery followed by radiotherapy (RT) /Concurrent chemoradiotherapy (CTRT) or definitive RT/CTRT are potentially curative approaches. While chemotherapy itself is not curative, it can improve cure rates when given as an adjunct to RT(9).

For metastatic HNCs, the prognosis is dismal and management depends on multiple factors as age, financial condition, performance status, expression of multiple biomarkers etc. along with improving quality of life that includes wholesome approach with proper nutritional support, good oral hygiene, spiritual support etc. While metronomic chemotherapy can offer some inexpensive palliation, for patients with metastatic HNCs with PD-L1 expression, first-line systemic therapy is pembrolizumab or pembrolizumab with chemotherapy. Inclusion of chemotherapy is associated with a higher objective response proportion in all biomarker subgroups and may have a greater impact on survival in HPV-associated cancers(10).

In summary, the complexity of HNCs is due to heterogeneity in anatomic and physiological functions of the organs and thereby demanding a multimodality approach. In addition, the patient population (elderly /patients with poor performance status/comorbidity status etc.) requires individually tailored treatment plan. Furthermore, treatment goals which include cure, organ and function preservation, quality of life and palliation- must also be considered. Current research directions in this disease focus on treatment de-intensification to minimize long-term toxicity while maintaining disease control among patients with favorable risks of cure and on the optimization of multi-modality regimens among patients with worse prognostic risks.

The present study attempted to find out the various patient and tumor profiles of head and neck cancer patients treated in the Department of Radiation Oncology and calculate their outcomes retrospectively.

AIMS & OBJECTIVES

Aims & Objectives-

Aim of study-

To study the survival and prognostic factors of different sites of head and neck cancers.

Objectives-

Primary Objective-

To assess the treatment outcomes as Overall Survival, Disease-free survival, Progression-free survival.

Secondary Objective-

To assess the host, disease, and treatment-related prognostic factors. Assessing the demographic profile of the patients suffering from the disease.

1. Describe treatment-related factors such as Radiation Dose, Technique, Dose to Targets.

2. Inference relationship between tumor characteristics and treatment factors.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

- **Hyuna Sung et al** published his data on global cancer statistics in 2020 which provides an update on the global cancer burden using the GLOBOCAN 2020 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer. Worldwide, an estimated 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) and almost 10.0 million cancer deaths (9.9 million excluding nonmelanoma skin cancers) occurred in 2020. Female breast cancer surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases (11.7%), followed by lung (11.4%), colorectal (10.0 %), prostate (7.3%), and stomach (5.6%) cancers. Lung cancer remained the leading cause of cancer death, with an estimated 1.8 million deaths (18%), followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers. Overall incidence was from 2-fold to 3-fold higher in transitioned versus transitioning countries for both sexes, whereas mortality varied. (11)
- **Mathur et al** published in 2020, the systematic collection of data on cancer by various population-based cancer registries (PBCRs) and hospital-based cancer registries (HBCRs) across India under the National Cancer Registry Program–National Centre for Disease Informatics and Research of Indian Council of Medical Research since 1982. This study examined the cancer incidence, patterns, trends, projections, and mortality from 28 PBCRs and also the stage at presentation and type of treatment of patients with cancer from 58 HBCRs (N = 667,666) from the pooled analysis for the composite period 2012-2016. Time trends in cancer incidence rate were generated as annual percent change from 16 PBCRs (those with a minimum of 10 years of continuous good data available) using Join point regression. The projected number of patients with cancer in India is 1,392,179 for the year 2020, and the common 5 leading sites are breast, lung, mouth, cervix uteri, and tongue. Trends in cancer incidence rate showed an increase in all sites of cancer in both sexes. The majority of the patients with cancer were diagnosed at the locally advanced stage for breast (57.0%), cervix uteri (60.0%), head and neck (66.6%), and stomach (50.8%) cancer, whereas in lung cancer, distant metastasis was predominant among males (44.0%) and females (47.6%). (78)

Epidemiology of Head & Neck cancer-

- **Mark Gormley et al** published in 2022, concluded that tobacco smoking and tobacco used in combination with alcohol consumption are the major risk factors associated with pathogenesis of head and neck carcinogenesis. Betel chewing has been established as a risk factor in Southeast Asian countries and in people from Southeast Asian minority ethnic groups. Oropharyngeal cancers have been found to be associated with Human Papilloma virus (HPV) infection. Head and neck cancers represent a socioeconomical pattern, with those from the poorest socioeconomic background having the greatest burden, but this socioeconomic risk is not entirely explained by smoking and alcohol behavior. Moreover, HNCs are considered to male predominant entity (although the trends are diverging) and its incidence increases with increase in age, although oropharyngeal cancer incidence peaks around ten years younger, at around 60-65 years. (12)
- **Richa Chauhan et al** published in 2022, concluded that there is high prevalence of tobacco use in Head and neck cancer patients whether in form of chewing or smoking or smokeless. This is strongly correlated with high incidence of occurrence of head and neck cancer in male as compared to females. Some lifestyle modifications and good oral hygiene should be recommended for prevention of head and neck cancers. (13)
- **Halmos et al** published in 2018, concluded that among head and neck cancer subsites, oral cavity is the most common site to be involved followed by larynx followed by pharynx. He also concluded that multimodality and intense management is applied more for younger population that could help in improving survival of the these patients. (15)
- **V Aggarwal et al** published in 2015 to find out the prevalence of Head and neck and oral cavity cancer in Western Rajasthan population. He found out that almost 34% cases out of all cancer patients were having head and neck involved out of which almost 57% were having oral cavity involved. (17)
- **Leoncini et al** published in 2014, to find out the association of height with incidence of head and neck cancer and concluded a positive association between the both. He found the inverse association between height and incidence of head and neck cancer (adjusted OR per 10 cm height = 0.91, 95% CI 0.86-0.95 for men; adjusted OR = 0.86, 95% CI 0.79-0.93 for women). In Men, various other factors as smoking,

educational status, geographical area also influence incidence of head and neck cancers. There was no difference between different subsites detected. (18)

- **Lu Wang et al** published in 2020, to find out the causal association between obesity and incidence of head and neck cancer. Increased body mass index (BMI) was associated with pathogenesis of multiple malignancies as endometrial cancer, breast cancer, colorectal cancer and cervical cancer etc. But increased BMI has no causal association with occurrence of head and neck cancers. (20)
- **Edgar P. Simard et al** published in 2014, concluded that there is variation in incidence of head and neck cancers in different countries. It is strongly associated with tobacco consumption; especially oral cavity cancers. Oropharyngeal cancer is associated with human papilloma virus infection and is more prevalent in developed world. (22)
- **H Maier et al** published in 1995 concluded that tobacco consumption is having positive correlation with occurrence of head and neck cancer in dose-effect manner. Alcohol consumption is also associated with occurrence of head and neck cancer and is solely dependent on daily alcohol consumption, not on the quality of beverage. Alcohol and tobacco consumption altogether do have synergistic effect on occurrence of head and neck cancer. (26)
- **Vinidh Paleri** et al published in 2010 found that comorbidity, presence of additional illness unrelated to tumor, do affect the prognosis of the patient with head and neck cancers. Comorbidities are associated with increased treatment cost as well as worse prognosis. So collecting co-morbidity data and their management is also a crucial step in management of head and neck cancers.(27)
- **Pandey KC et al** published in 2015, concluded that In Indian subcontinent, due to more tobacco consumption and unawareness, most of the patients with non-metastatic head and neck cancer usually present in locally advanced stage while few present in early stage. Due to late and advanced stage presentation, most patients need multimodality treatment with Chemotherapy, Surgery +/- radiation therapy and also carries a dismal prognosis. So awareness regarding cancer and tobacco cessation program will be a milestone in improving therapeutic look. (28)
- **Vernham et al** published his data in 1994 and concluded that among head and neck cancer patients, majority were having primary site as larynx followed by oral cavity followed by pharynx and others. Most of the patients presented in locally advanced stage. No association between disease stage and symptoms duration could be

established. Earlier diagnosis will not make a significant impact on the overall prognosis in head and neck cancer. (29)

- **Teofil Lung et al** published his data in 2007 after analyzing head and neck cancer patients for almost a decade and concluded that most of the de novo cases were carcinomas (93%) followed by sarcoma (4%). Almost half of the patients presented with positive lymph node at initial presentation. (31)

MANAGEMENT OF HEAD AND NECK CANCER-

ROLE OF INDUCTION CHEMOTHERAPY-

- **Haddad et al** published in 2006, concluded that in locally advanced head and neck cancer patients, induction chemotherapy with 3 drug regimen (Cisplatin + Docetaxel + 5-FU) resulted in better pathological complete response rate (89%) as compared to 2 drug regimen (Cisplatin+5-FU) which was reported as 25-50% in previous studies. (36)
- **Posner et al** published in 2000, emphasized on the role of induction chemotherapy in locally advanced head and neck cancer patients. He concluded that Induction chemotherapy with 2 drug regimen (Cisplatin + 5-FU) resulted in more organ preservation without compromising survival and improved survival in unresectable disease. (37)
- **Rapidis et al** conducted a phase 2 trial in 2006 on role of induction chemotherapy followed by definitive concurrent chemoradiation in advanced head and neck SCCs. He concluded that patients who were treated with induction chemotherapy followed by definitive concurrent chemoradiotherapy were having better disease control and also improved overall survival. (38)
- **Ferrari et al** published in 2020, emphasized on judicious use on induction chemotherapy in advanced head and neck cancer patients. He demonstrated non-inferiority of induction chemotherapy followed by concurrent CTRT vs Definitive CTRT, except its use in preventing metastatic spread. He concluded that induction chemotherapy can be a strong option for selected high risk population if used judiciously. (39)

- **Lorch et al** published long term follow-up result of TAX 324 trial in 2011 and concluded that patients with locally advanced head and neck cancers who were treated with Induction chemotherapy (TPF) followed by Definitive CTRT were having better outcome and survival that those treated with dual agent induction chemotherapy. So wherever possible, three drug regimen (TPF) should be used as induction chemotherapy in eligible patients. (40)

LYMPH NODE DISSECTION IN HEAD & NECK CANCER-

- **Vasu Divi et al** published in 2016, found the association of adequate vs inadequate lymph node dissection with survival. Adequate lymph node dissection was defined as >=18 LN dissection and vice versa. He concluded that adequate lymph node dissection in clinically node negative or positive patients was associated with significant improvement in overall survival .(41)
- **Mark Hamoir et al** published in 2014, put an emphasis on the role of lymph node dissection in head and neck cancer patients. Lymph node metastasis is considered to be an important prognostic factor in patients with head and neck cancers. Inadequate lymph node dissection can result in locoregional failure and furthermore hamper the survival. (42)

Prognostic Factors-

1. Body Mass Index-

- **Pastorino et al** published in 2022, investigated the role of baseline BMI in predicting overall survival and found that high BMI was statistically significantly associated with better improved outcome while underweight patients were associated with poor outcome in ever smokers. In never smokers, overall BMI status was not associated with HNC specific survival. (45)
- **Eric L et al** published in 2021, concluded that increased BMI is a protective factor in head and neck cancer patients and results in better outcome while mostly locoregional recurrences do occur in underweight or normal weight patients due to lack of nutrition reserve.(44)

- **Gama et al** published in 2017, resulted that being underweight at the time of diagnosis is considered to be an independent worse prognostic factor for patients with Head & Neck Squamous cell carcinoma. In early adulthood, it was not found to be as a factor affecting outcome. (43)

2. DEPTH OF INVASION(DOI)-

- **Pentenero et al** published in 2005, done review of literature and found that DOI can be considered as a reliable predictor of outcome and cervical nodal metastasis. (46)

3. SITEWISE SURVIVAL ANALYSIS-

- **Eugenie et al** published in 2019, conducted a prospective cohort study for finding the impact of various factors as site, stage, HPV status on overall survival and concluded that p16+ oropharyngeal cancer was having better prognosis followed by oral cavity, larynx, p16- oropharyngeal cancer, hypopharynx. Site, stage, smoking, and p16 status are significant prognostic factors. These data provide important prognostic information for HNSCC. (50)
- **Yeole et al** published in 2000, conducted 5-year survival analysis from head and neck cancer patients in Mumbai and concluded that lip, mouth, larynx and pharynx are subsites with better prognosis than other sites of head and neck cancers. Other factors as age, religion, marital status, stage of the disease are also independent predictors of prognosis. (48)
- **Pruegsanusak et al** published in 2012, conducted a study in Thailand to find out the survival analysis and prognostic factors of different subsites of head and neck cancer patients. He concluded that stage and treatment type were strong predictors of prognosis. Furthermore larynx and oral cavity were proved to be subsites with favorable prognosis. (47)

4. STAGEWISE SURVIVAL ANALYSIS-

- **National Cancer institute physician's data query system** published in 2003 the 5-year overall survival results for different subsites of head and neck cancers and

concluded that in all subsites, advanced stage patients are having dismal prognosis as compared to early-stage disease. Furthermore, subsites like hypopharynx, larynx stage IV disease was having worse prognosis as compared to stage IV disease of other subsites. (51)

- **Ambakumar Nandakumar et al** published in 2016, conducted a multi-institutional study to analyze the survival outcomes in head and neck cancer patients. He concluded that early-stage ca tongue patients were having three-year cumulative survival percentage ranging from 62.6% to 91.6% depending on treatment modality they received while for locally advanced ca tongue patients, three-year cumulative survival percentage ranges from 13% to 68.9%. Likewise for other subsites also as oral cavity, hypopharynx, oropharynx and larynx, there was statistically significant difference in patients with early-stage vs locally advanced stage. (49)

6. <u>EFFECT OF SURGICAL MARGIN STATUS ON OUTCOME</u>-

- **Harry Michael et al** published in 2016**,** studied the different aspects of surgical margin status and their clinical implications and concluded that margin positivity (R1 resection) was associated with increased risk of locoregional recurrence. He also put an emphasis on the utility of frozen section analysis. How-ever he did not emphasize on the difference between various treatment modalities used for managing margin positive cases. (55)
- **Reina Haque et al** published in 2006, studied the effect of margin positivity on overall survival in head and neck cancer patients and concluded that margin positivity was associated with poor outcome as compared to margin negativity (54% vs 29% with p value of 0.005). (57)
- **Hany Eldeeb et al** published in 2012, conducted a single institution study to find the effect of margin status on overall survival as well as recurrence rate and concluded that margin distance between 1-5mm was associated with recurrence rate of 59%, 5-10mm was associated with RR of 50% while margin positivity was associated with RR of 90%. 5-year overall survival rates were 39%,54% and 10% respectively for the groups. (56)

7. <u>EFFECT OF LYMPHOVASCULAR INVASION(LVSI) ON OUTCOME-</u>

- **Cassie Fives et al** published in 2016, conducted a retrospective analysis of floor of mouth cancer patients to find the association between LVSI and outcome. He concluded that presence of LVSI was an adverse prognostic factor in floor of mouth cancer patients and these patients require further adjuvant radiotherapy. (60)
- **Barbara et al** published in 2019, conducted systemic review and meta-analysis to find out the association between LVSI and its prognostic significance in adenoid cystic carcinoma patients and found it to be a predictor of increased incidence of lymph nodal metastasis and consequently poor prognosis. (61)

8. <u>EFFECT OF PERINEURAL INVASION (PNI) ON OUTCOME</u>-

- **Hughes et al** published in 2021, conducted a retrospective study to find the impact of isolated presence of PNI in resected head and neck cancer patients with otherwise no pathological high-risk factor. He concluded that post operative radiotherapy remains the standard of care in resected head and neck cancer patients with isolated PNI to reduce the risk of locoregional recurrence. (64)
- **Richard L Bakst et al** published in 2019 concluded that PNI is an important pathologic finding associated with poor clinical outcomes and morbidity. Appropriately targeted radiation therapy can improve local control and reduce the risk of unresectable failures in cases of PNI/PNTS (perineural tumor spread). (63)
- **Schmitd et al** published in 2018 found the mechanism of perineural spread in head and neck cancer patients and associated proteins involved in the mechanism. PNI presence was associated with poor overall and disease specific survival. Presence of PNI was associated with increased incidence of lymph nodal metastasis. (66)

9. <u>Effect of Extra-nodal Extension (ENE) on outcome</u>-

- **G. Tirelli** et al published in 2021, investigated the role of stratification of extra-nodal extension (ENE) on the basis of extension of tumor outside the lymph-node capsule. He stratified into ENEmi (<2mm) and ENEma(>2mm) and found the association with outcome and found that ENEmi was associated with better outcome in terms of 3-year overall survival, DFS, disease specific survival as compared to ENEma. (70)

- **Fumihiko Matsumoto et al** published in 2017, investigated the prognostic significance of surgical extra-nodal extension in different subsites of head and neck cancer. He found that Surgical ENE was important prognostic factor in head and neck cancer patients. He found that 3-year DFS in pN0, ENE negative, non-surgical extra-nodal extension and surgical extra-nodal extension was 90.9%, 79.6%, 63.8% and 48.3%, respectively. Further-more he concluded that surgical ENE was more clinically significant in patients with laryngeal/hypopharyngeal cancer as compared to oral cancer. (69)
- **Minsu Kwon et al** published in 2015, found the prognostic significance of ENE and thickness of metastatic lymph-node as a marker for recurrence and survival in head and neck cancer patients. He concluded that ENE-positive patients had a higher risk of recurrence and a lower overall survival rate; however, multivariate analysis failed to identify a significant difference in disease specific survival (DSS) between those with and those without ENE. On the contrary, ENET $\geq$ 2 mm was significantly associated with a poor DSS, even in multivariate analysis. (68)

10. EFFECT OF CONCURRENT CHEMOTHERAPY ON OUTCOME-

- **EORTC 22931 trial** published in 1999, randomized the surgically resectable head and neck cancer patients with high risk features into post op either Radiotherapy alone or concurrent radiotherapy and concluded that 5-year overall survival (53% vs 40%) and locoregional control rate(82% vs 69%) favored combined modality treatment with a significant p-value. (76)
- **Ryan J Burri et al** published in 2009, investigated the role of concurrent chemotherapy in locally advanced head and neck cancer and concluded that addition of concurrent chemotherapy added an absolute difference of 6.5% in overall survival in locally advanced head and neck cancers as compared to radiotherapy alone. Cisplatin was approved to be a good agent as monotherapy agent. (72)
- **Brockstein et al** published in 2004, concluded that concurrent chemoradiotherapy is superior to radiotherapy alone for unresectable head and neck tumors and equivalent or sometimes superior to surgery plus radiotherapy in resectable tumors also. CTRT was associated with more acute toxicities as compared to RT alone while long term data on toxicities is debatable. (71)

- **Iqbal et al** published in 2017, analyzed the effect of weekly concurrent cisplatin (40mg/m^2) in patients who received definitive chemoradiation and concluded that weekly cisplatin is an acceptable alternative to 3 weekly cisplatin (100mg/m^2) without compromising outcome and acceptable toxicity profile. (73)
- **Xiang et al** published in 2019, investigated the value of carboplatin as a radiosensitizer in patients with locally advanced head and neck cancer patients. He concluded that definitive chemoradiation with carboplatin was equivalent to cisplatin-based therapy and superior to RT alone or RT with cetuximab. (75)
- **RTOG 1016** trial published in 2019, emphasized on the role of concurrent cisplatin vs cetuximab in HPV positive oropharyngeal tumors and found that Radiotherapy with cetuximab was inferior to cisplatin in terms of 5-year Overall survival (77.9% vs 84.6%) and progression free survival (67.3% vs 78.4%). Further concluded cisplatin as standard of care in eligible patients with HPV positive oropharyngeal cancers. (79)
- **De-ESCALate**, a phase 3 Randomized trial published in 2019, concluded that in patients with low risk HPV positive oropharyngeal cancers, concurrent cetuximab was associated with poor tumor control as compared to cisplatin and was not associated with any benefit in toxicity profile. (80)

MATERIALS & METHODS

Materials and Methods-

Study Setting- The study will be conducted in the Department of Radiation Oncology, AIIMS Jodhpur

Study design: Single-arm retrospective study

Study participants: All patients of biopsy-proven head and neck cancers who received radiation therapy in the Department of Radiation Oncology, AIIMS Jodhpur from the year 2018 to 2020.

Study Period: 2 years

Eligibility Criteria-

Inclusion criteria-

1. All head and neck cancer patients treated with radiotherapy in the Department of Radiation Oncology, AIIMS, Jodhpur.

Exclusion Criteria-

1. Patients with thyroid malignancy.
2. Patients with incomplete/wrong contact details.
3. Patients with grossly incomplete records.
4. Patients with a second primary cancer other than in the head and neck.

Sample size-

All patients of biopsy-proven head and neck cancers who received radiation therapy in the Department of Radiation Oncology AIIMS Jodhpur from the year 2018 to 2020. The records were accessed from the registration records of CPMS and records in the Department of Radiation Oncology**.**

Study Procedure-

Creation of Database:

A database was created using software such as Microsoft Excel Spreadsheet and Google Sheets. The study database was used for the entry of data obtained from various sources such as the Computerized Patient Management System (CPMS) of the Institute and records of the Department of Radiation Oncology and Pathology**.**

Entry of Data:

Data was captured as per the study form attached to the Database. Data will be collected using: Manual search and entry from CPMS and Records from Radiation Oncology and Pathology, Automated Entry using software and scripts with/ without AI (Python /Julia and various other modules)

All the records of patients with head and neck cancer who have been treated with a radical/adjuvant intent using radiotherapy in AIIMS, Jodhpur was compiled. After fitting the available records to inclusion and exclusion criteria, screening of all records was made for the complete availability of treatment details and contact details. Various variables were collected related to the patient profile (age, sex, education, occupation, socioeconomic status, religion, geographic residence, symptoms at presentation, duration of symptoms, addiction history, comorbidities, performance status, history of head and neck radiotherapy, etc.), disease status (T stage, N stage, AJCC 8^{th} edition prognostic stage group, histology, gross tumor, and nodal volume, level of nodal involvement, presence of extra-nodal extension, presence of necrosis within the gross tumor or nodes etc.), and treatment factors (receipt of surgery, adequacy of surgery, nodal dissection, technique of radiotherapy, dose received by 95% of the planning target volume, receipt of chemotherapy and agent used, cumulative dose of chemotherapy, significant gaps in radiation treatment etc.).

The response to treatment was based on either Clinical Examination (CR, PR, SD, PD) based on WHO criteria or if the imaging of the patients after at least three months of completion of definitive treatment is available, same were considered while assessing the response to treatment. The response assessment was done according to the RECIST criteria. The present status of the patient was enquired from the contact details available through whichever means feasible. Telemedicine was used wherever necessary to examine the patient if the patient was unable to visit the hospital. If the disease relapses or progresses after treatment, the date of

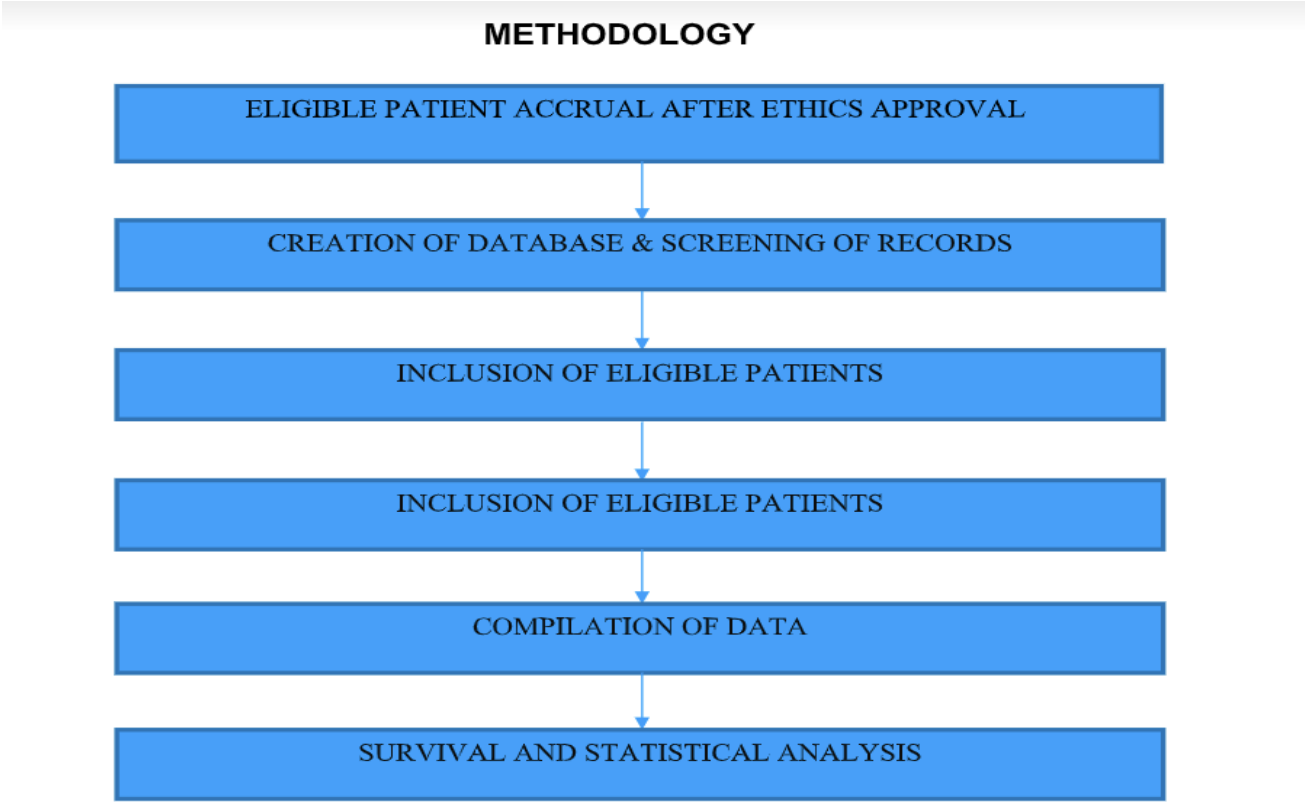
biopsy if available or imaging if a biopsy is not available, was regarded as the date of progression. In patients who relapse/progress, the type of relapse, time to relapse/progression and the treatment offered was also recorded. If the patient was not contactable, the last documented visit in CPMS was taken as the last follow-up and will be censored in the further time points.

Based on this data, various outcome variables were studied like overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS).

1. **Overall survival**- Defined as the time from diagnosis to death from any cause.

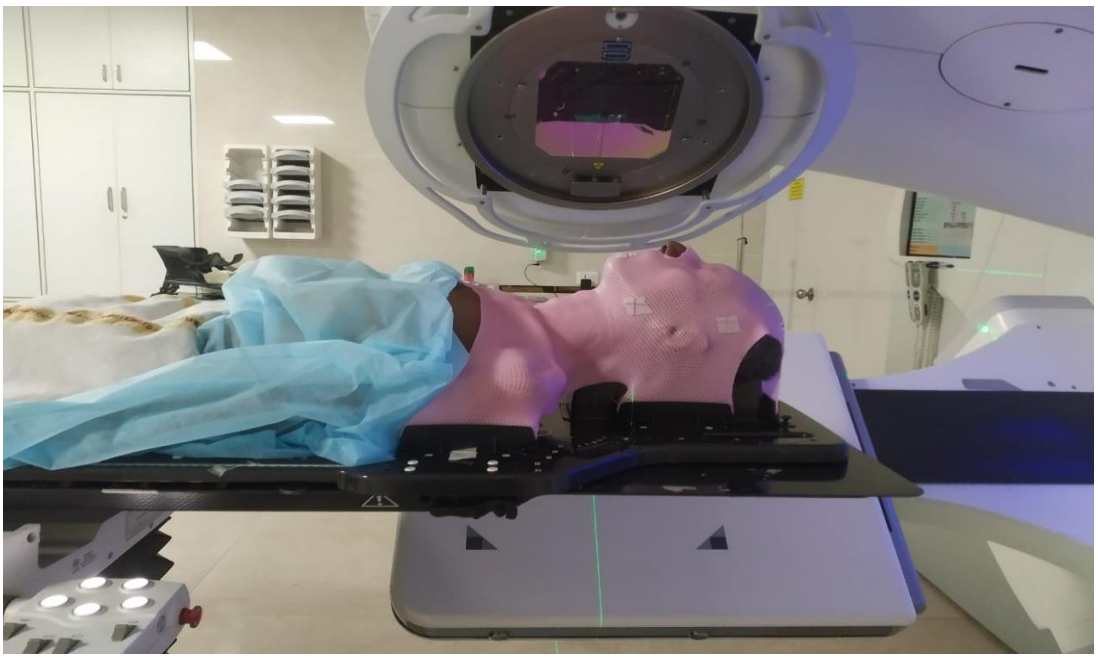
2. **Disease-free survival**- The period after successful treatment during which there are no signs and symptoms of the disease that was treated.

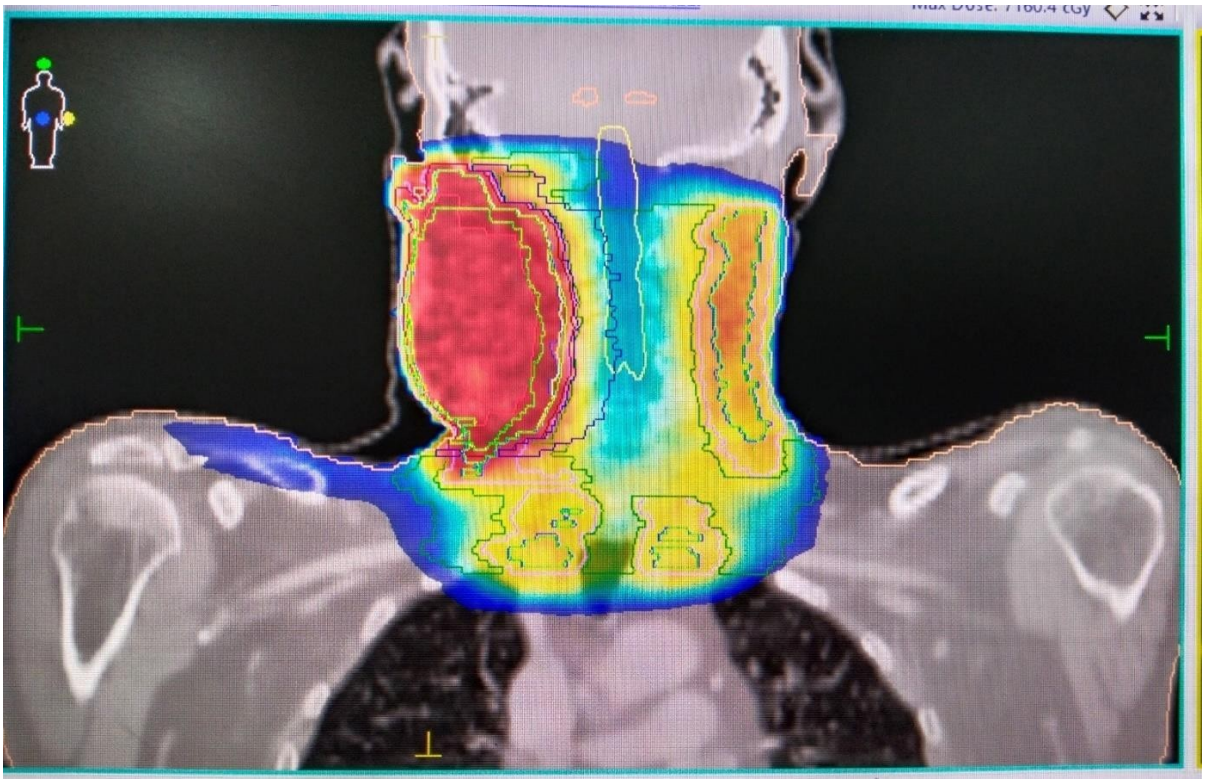
3. **Progression-free survival**- The period during and after the treatment of the disease for which the patient lives with the disease but doesn't progress.



Details about Radiation Therapy- The patients with Head and neck cancers of different subsites received Radiation Therapy in the Department of Radiation Oncology, AIIMS Jodhpur by LINAC (VERSA HD/ELEKTA) using 6MV photon and most of the dose

prescriptions were 60Gy/30#/6weeks, 66Gy/33#/6weeks, 70Gy/35#/7weeks via IMRT/VMAT Technique.





Statistics | Display

Structure	Volume (cm³)	Min. Dose (cGy)	Max. Dose (cGy)	Mean Dose (cGy)	Cold Ref. (cGy)	Volume < (cm³)	Volume < (%)	Hot Ref. (cGy)	Volume > (cm³)	Volume > (%)	% in Volume	Is in SS	Heterogeneity Index	Conformity Index
BRAIN STEM	23.621	90.5	1245.5	261.9							100.00	yes	4.77	
CTV 54	625.651	1816.3	7160.4	6395.7							100.00	yes	1.24	
CTV 66	388.968	1816.3	7160.4	6641.9							100.00	yes	1.05	
CTV N+	263.912	3295.7	7160.4	6643.3							100.00	yes	1.05	
CTV NODE	413.515	4830.9	7160.4	6297.3							100.00	yes	1.25	
CTV P	148.102	6144.0	7129.6	6634.5							100.00	yes	1.04	
Carbon Fiber	5756.016	0.0	0.0	0.0							99.60	no		
EYE LT	7.250	99.1	328.8	174.2							100.00	yes	2.12	
EYE RT	7.649	93.7	358.8	165.6							100.00	yes	2.19	
Foam Core	4330.659	0.0	0.0	0.0							99.56	no		
GTV	5.866	6327.2	6906.0	6623.2							100.00	yes	1.04	
GTV-N	135.991	4436.0	7160.4	6634.9							100.00	yes	1.06	
LENS LT	0.200	134.2	234.4	167.2							100.00	yes	1.54	
LENS RT	0.222	112.9	202.1	152.3							100.00	yes	1.47	
MANDIBLE	85.613	732.3	6926.3	5551.0							100.00	yes	3.19	
Metal	259.273	0.0	0.0	0.0							100.00	yes		
OPTIC CHIASM	1.342	171.9	258.7	211.5							100.00	yes	1.30	
OPTIC N LT	1.048	153.5	260.1	199.9							100.00	yes	1.46	
OPTIC N RT	0.947	157.1	285.6	210.2							100.00	yes	1.49	
PAROTID LT	33.059	439.1	5954.9	2683.8							100.00	yes	8.95	
PAROTID RT	30.270	3122.5	7020.7	6075.9							100.00	yes	1.60	
PTV 54	977.999	3435.0	7160.4	6254.7							100.00	yes	1.25	
PTV 66	523.456	4171.6	7160.4	6601.1							100.00	yes	1.07	
SPINAL CORD	42.957	27.6	4426.0	2148.6							100.00	yes	85.98	
body(Unsp.Tiss.)	17772.736	3.2	6729.8	508.0							99.56	no	150.47	
spare	832.167	1014.0	6941.6	4800.0							100.00	yes	1.84	
spare2	355.334	2640.4	6899.7	5681.6							100.00	yes	1.48	

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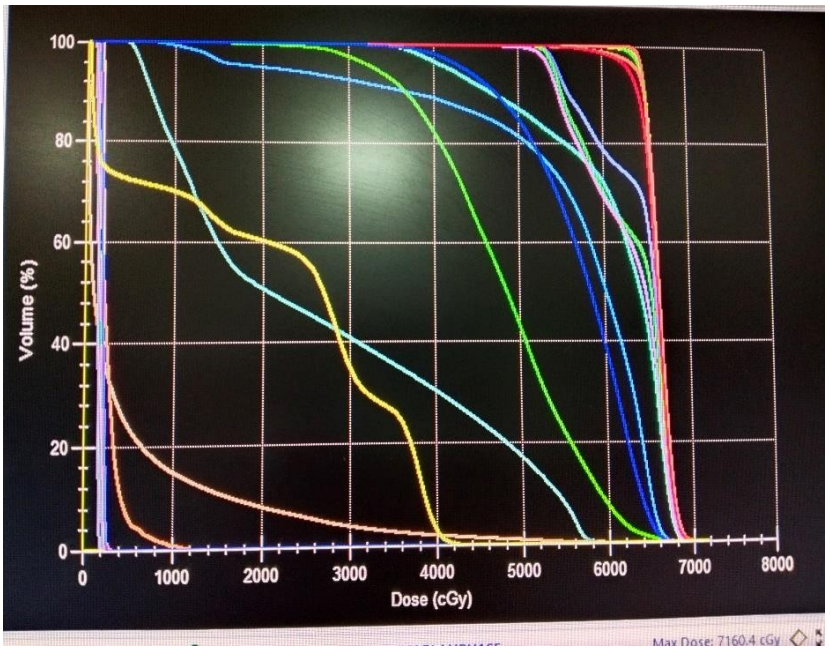

100
80
60
40
20
0
Volume (%)
0
1000
2000
3000
4000
5000
6000
7000
8000
Dose (cGy)
Max Dose: 7160.4 cGy


Structure
body
BRAIN STEM
Carbon Fiber
CTV 54
CTV 66
CTV N+
CTV NODE
CTV P
EYE LT
EYE RT
Foam Core
GTV
GTV-N
LENS LT
LENS RT
MANDIBLE
Metal
OPTIC CHIASM
OPTIC N LT
OPTIC N RT
PAROTID LT
PAROTID RT
PTV 54
PTV 66
spare
spare2
SPINAL CORD

Response Evaluation-

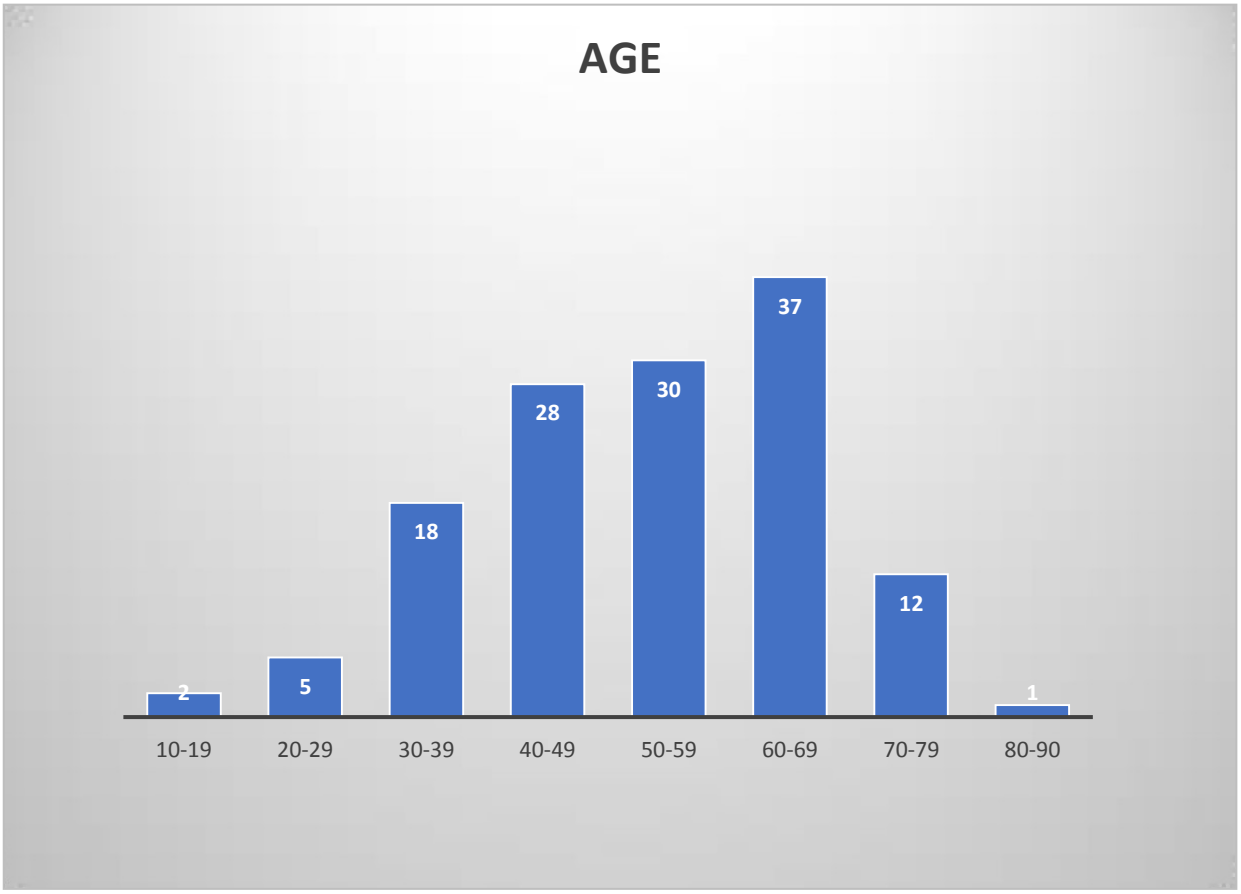
Response evaluation was done on the basis of WHO clinical criteria of Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD). Wherever response assessment scans were available, iRECIST Criteria 1.1. was used.

Statistical Analysis-

All the qualitative data was expressed as frequencies and quantitative data will be expressed as mean, median with range. Survival outcomes of OS, DFS, PFS were depicted using Kaplan-Meier Curve. The prognostic factors associated with the disease were assessed using univariate and the significantly associated factors in the univariate analysis were tested using multivariate analysis. A p-value of less than equal to 0.05 was taken as statistically significant.

RESULTS

1. Age-wise Distribution-



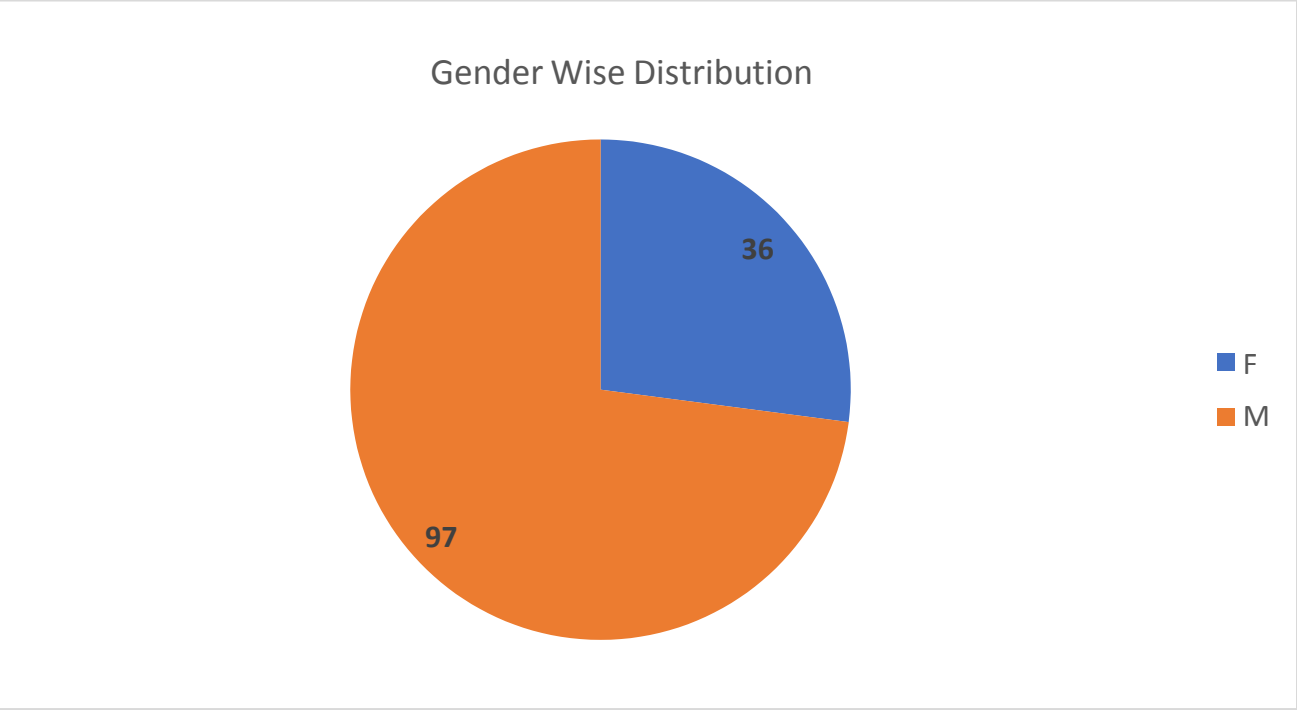
Age Groups	Frequency
10-19	2
20-29	5
30-39	18
40-49	28
50-59	30
60-69	37
70-79	12
80-90	1
Grand Total	133

Variable	AGE

Sample size	133
Lowest value	14.0000
Highest value	83.0000
Arithmetic mean	52.4737
95% CI for the Arithmetic mean	50.0720 to 54.8753
Median	55.0000
95% CI for the median	50.7184 to 58.0000
Variance	196.0542
Standard deviation	14.0019

- Analysis was done of 133 patients with age ranging from 14 to 83 years , with a mean of 52 years (95% C.I. ranging from 50.07 to 54.87 years) , median of 55 years (95% C.I. ranging from 50.71 to 58 years).

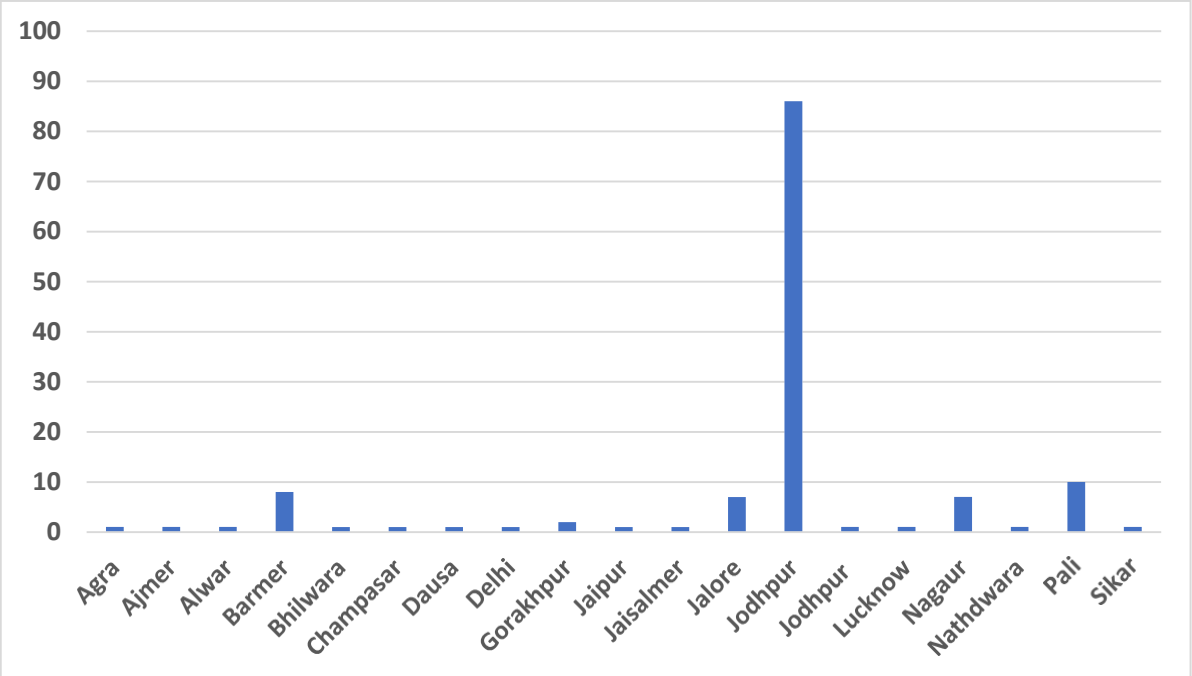
2. Gender-wise Distribution-



Gender	Frequency
F	36
M	97
Grand Total	**133**

- Out of 133 patients, 36 j(27%) were female and 97 (73%) were male.

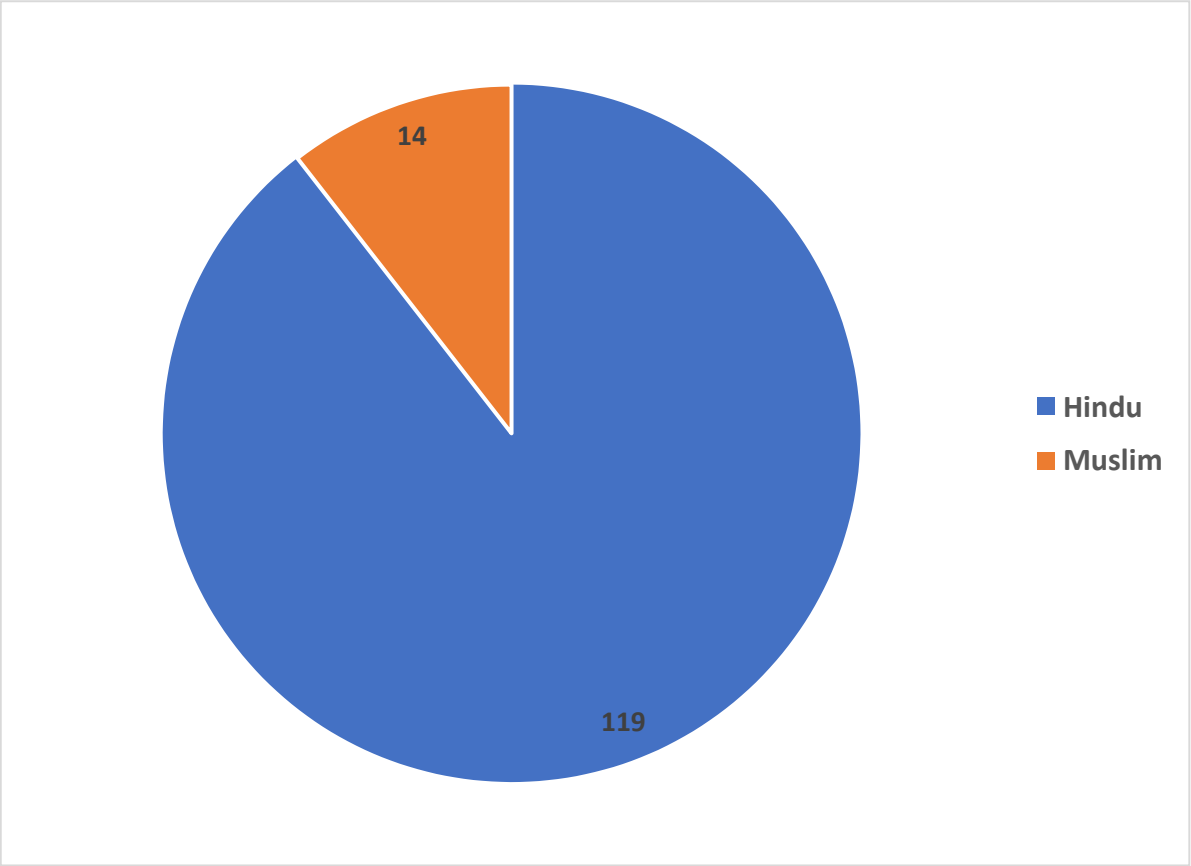
3. District Wise Distribution-



District	Frequency
Agra	1
Ajmer	1
Alwar	1
Barmer	8
Bhilwara	1
Champasar	1
Dausa	1
Delhi	1
Gorakhpur	2
Jaipur	1
Jaisalmer	1
Jalore	7
Jodhpur	86
Jodhpur	1
Lucknow	1
Nagaur	7
Nathdwara	1
Pali	10
Sikar	1
Grand Total	133

- Out of 133 patients, 120 (90%) were from Western Rajasthan, 6 (7%) from Eastern Rajasthan, 3(2.5j%) from Uttar Pradesh, 1(1%) from New Delhi.

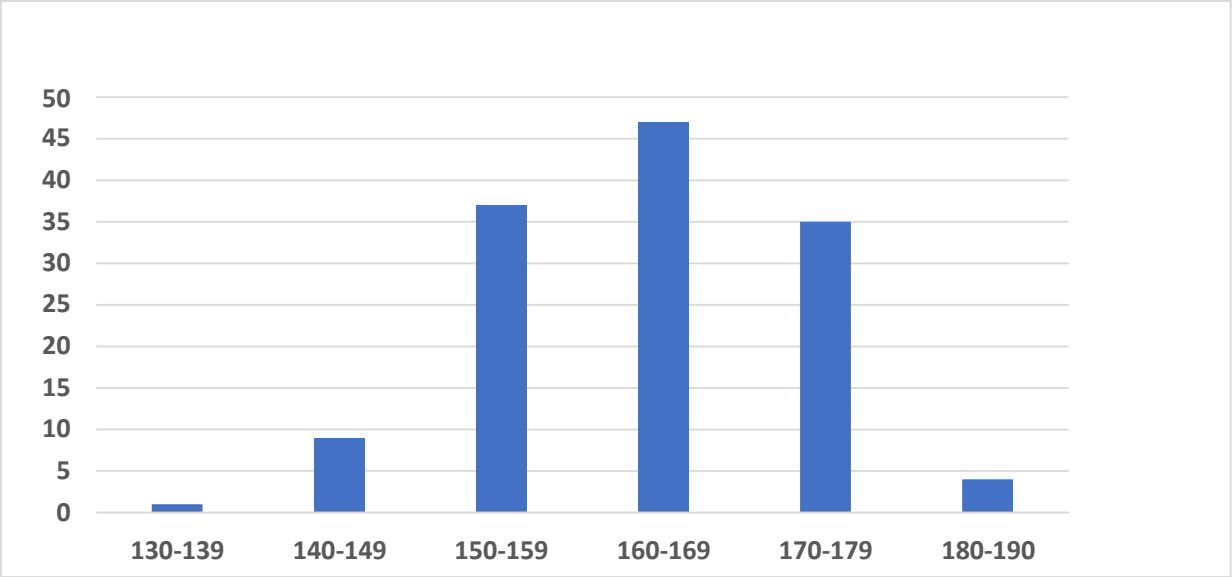
4. <u>Religion Wise Distribution</u>-



Religion	Frequency
Hindu	**119**
Muslim	**14**
Grand Total	**133**

- Out of 133 patients, 119(90%) were Hindu and 14 (10%) were Muslim.

5. Height Wise Distribution-

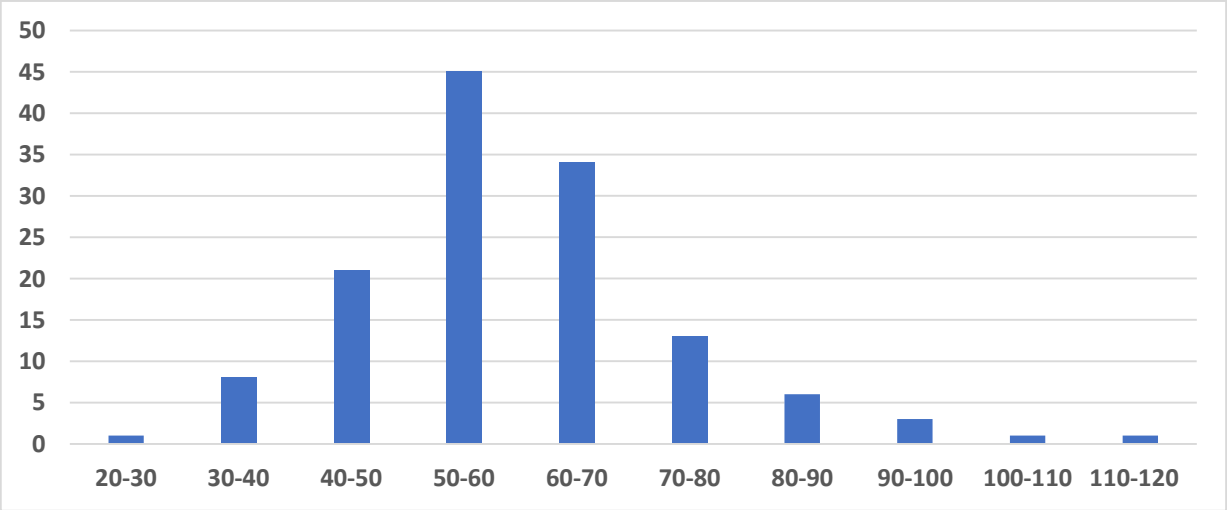


Height Groups (cm)	Frequency
130-139	1
140-149	9
150-159	37
160-169	47
170-179	35
180-190	4
Grand Total	133

Sample size	133
Lowest value	135.0000
Highest value	190.0000
Arithmetic mean	163.5414
95% CI for the Arithmetic mean	161.9707 to 165.1120
Median	164.0000
95% CI for the median	162.0000 to 167.0000
Variance	83.8562
Standard deviation	9.1573

- Out of 133 patients, Height ranging from 135 to 190 with a mean of 163cm (95% C.I. ranging from 162 to 165cm) and median of 164cm (95% C.I. ranging from 162 to 167cm).

6. Weight Wise Distribution-

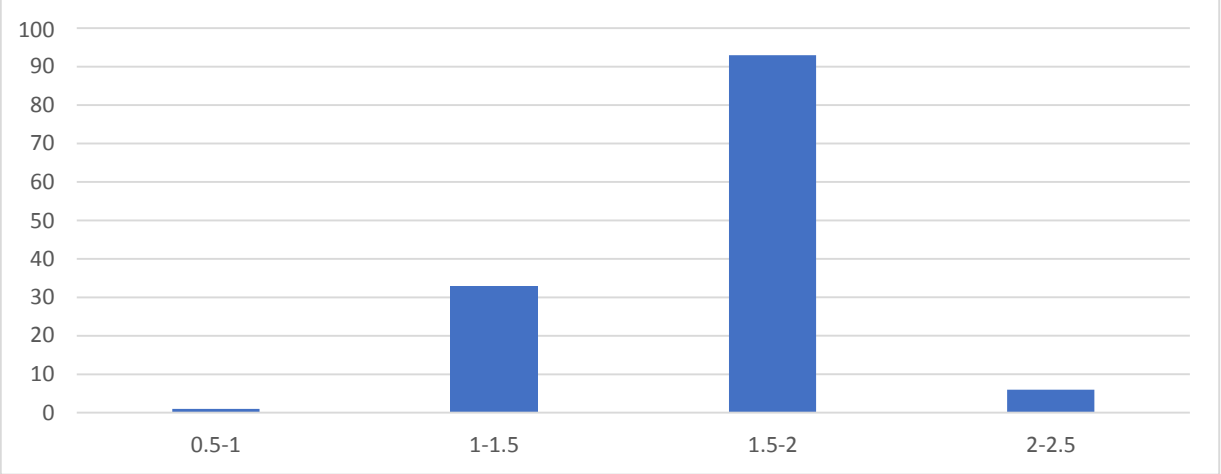


Weight Groups (kg)	Frequency
20-30	1
30-40	8
40-50	21
50-60	45
60-70	34
70-80	13
80-90	6
90-100	3
100-110	1
110-120	1
Grand Total	133

Sample size	133
Lowest value	24.8000
Highest value	115.0000
Arithmetic mean	59.7015
95% CI for the Arithmetic mean	57.1928 to 62.2103
Median	58.6000
95% CI for the median	55.5437 to 60.5563
Variance	213.9298
Standard deviation	14.6263

- Out of 133 patients, weight ranging from 24.8 kg to 115kg with a mean of 59.7 kg (95% C.I ranging from 57.19 to 62.21kg) and median of 58.6 kg (95% C.I. ranging from 55.54 to 60.55kg).

7. Body Surface Area (BSA) wise distribution-

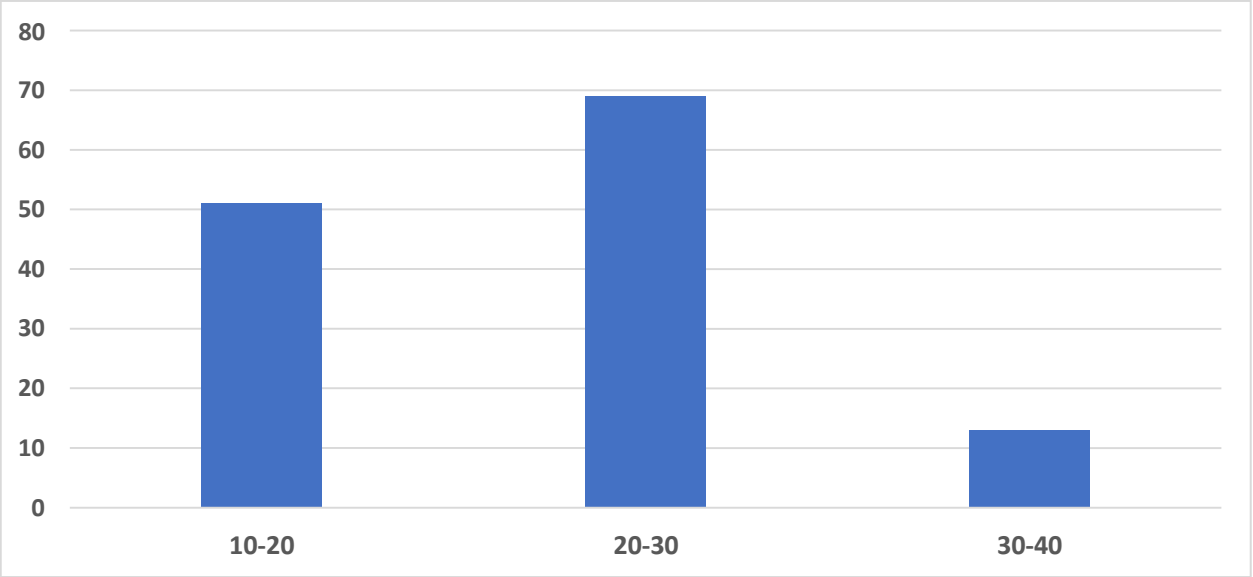


BSA wise groups	Frequency
0.5-1	**1**
1-1.5	**33**
1.5-2	**93**
2-2.5	**6**
Grand Total	**133**

Sample size	133
Lowest value	0.9600
Highest value	2.4600
Arithmetic mean	1.6357
95% CI for the Arithmetic mean	1.5976 to 1.6738
Median	1.6200
95% CI for the median	1.5972 to 1.6600
Variance	0.04935
Standard deviation	0.2221

- Out of 133 patients, BSA ranging from 0.96 m^2 to 2.46 m^2 with a mean of 1.63 m^2 (95% C.I. ranging from 1.59 to 1.67 m^2) and median of 1.62 m^2 (95% C.I. ranging from 1.59 to 1.66 m^2).

8. <u>Body Mass Index (BMI) wise distribution</u>-

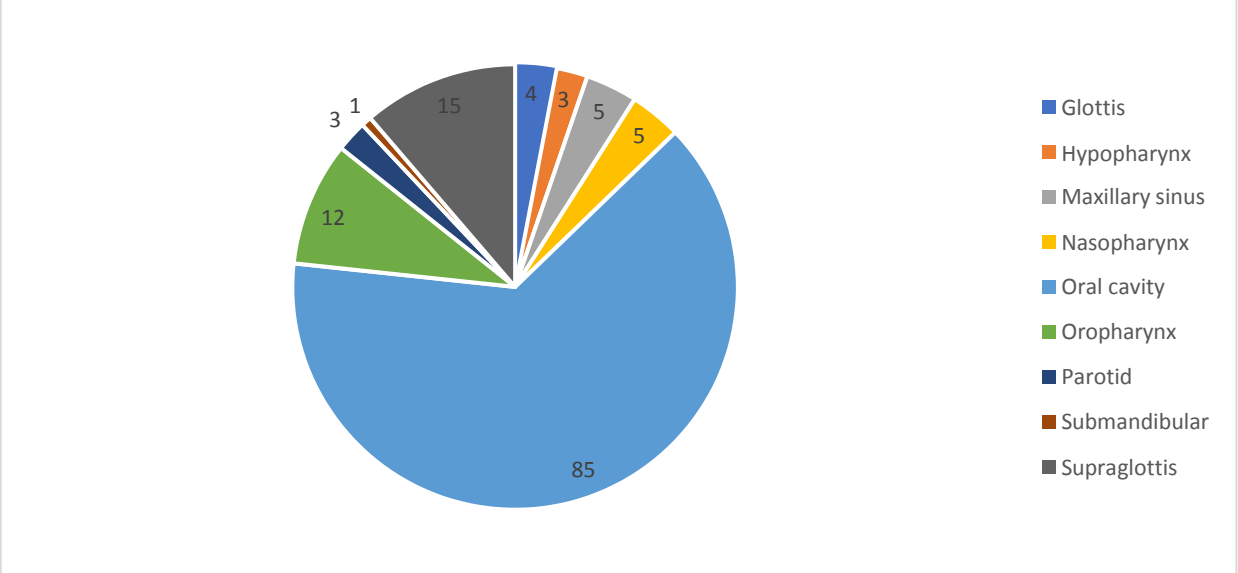


BMI groups	Frequency
10-20	**51**
20-30	**69**
30-40	**13**
Grand Total	**133**

Sample size	133
Lowest value	13.6200
Highest value	37.7000
Arithmetic mean	22.2982
95% CI for the Arithmetic mean	21.4424 to 23.1540
Median	21.7100
95% CI for the median	20.3544 to 22.3184
Variance	24.8949
Standard deviation	4.9895

- Out of 133 patients, BMI ranging from 13.62 to 37.7 kg/m^2 with a mean of 22.29 kg/m^2 (95% C.I. ranging from 21.44 to 23.15 kg/m^2) and median of 21.71 kg/m^2 (95% C.I. ranging from 20.35 to 22.31 kg/m^2).

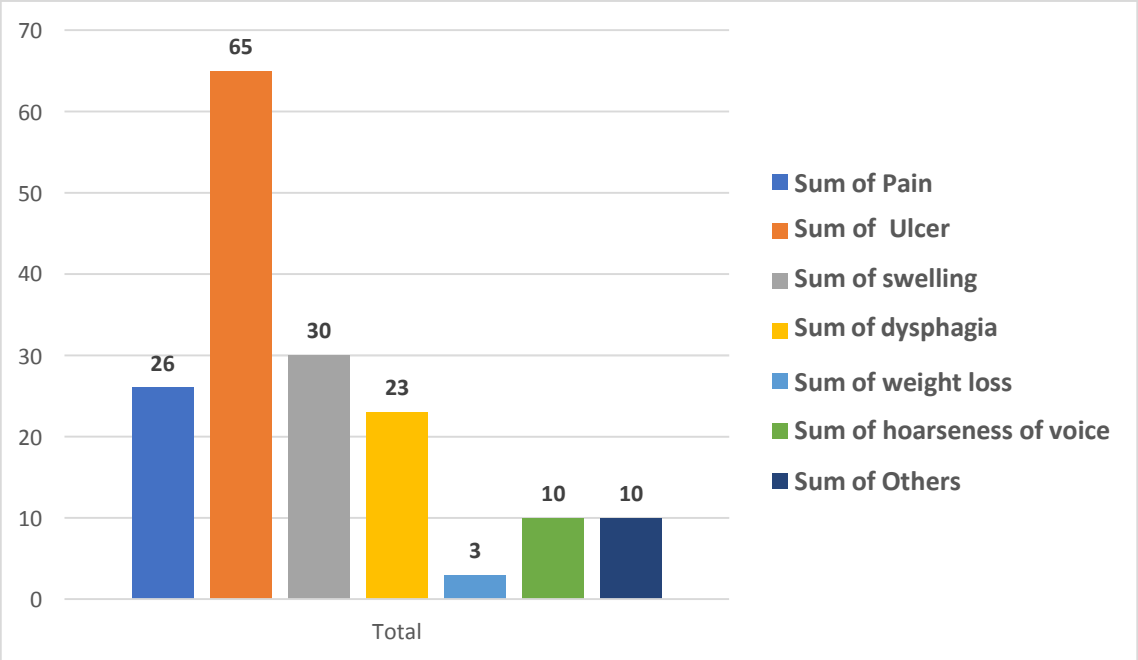
9. <u>Site Wise Distribution-</u>



Subsites	Frequency
Glottis	4
Hypopharynx	3
Maxillary sinus	5
Nasopharynx	5
Oral cavity	85
Oropharynx	12
Parotid	3
Submandibular	1
Supra-glottis	15
Grand Total	**133**

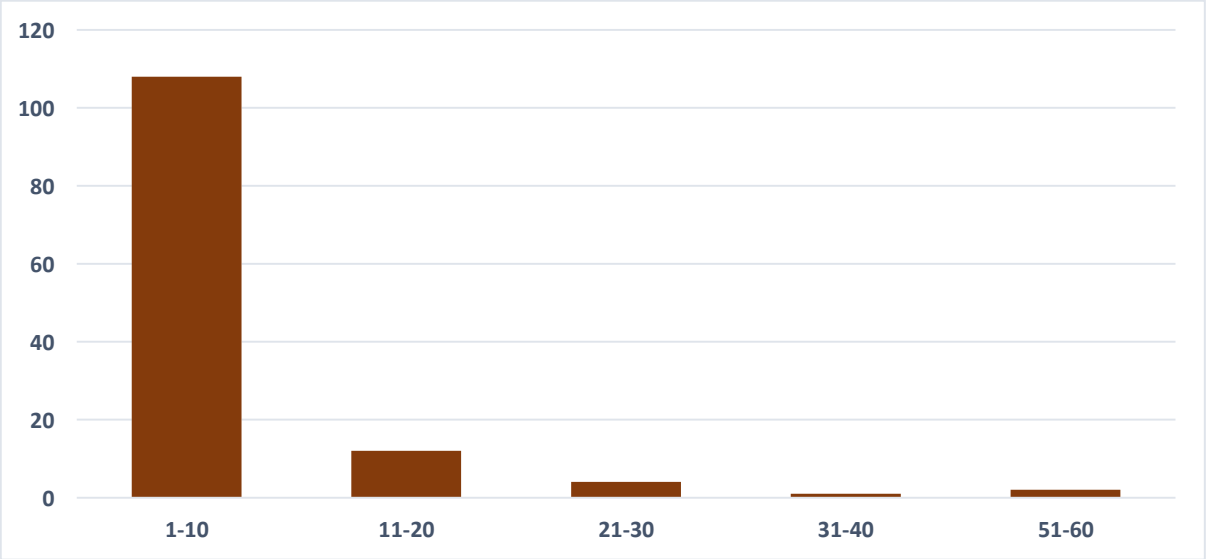
- Out of 133 patients, involved sites were 85(63%) were oral cavity, 15(11%) were Supra-glottis ,12 (8%) Oropharynx, 5(3%) Maxillary sinus and Nasopharynx each, 4(3%) Glottis, 3 (2%) Hypopharynx and Parotid gland each, 1(1%) submandibular gland.

10. Initial Presenting symptoms-



- Out of 133 patients, data of initial presenting symptoms was available for 127 patients. Out of 127 patients, 65 (51%) patients presented with ulcer, 26(20%) presented with pain, 30(23%) presented with swelling and mass, 23(18%) presented with dysphagia, 3 (2%) presented with weight loss, 10(8%) presented with hoarseness of voice and 10 (8%) presented with other symptoms as nasal discharge, regurgitation of food and dryness of mouth.

11. Duration of initial symptoms-

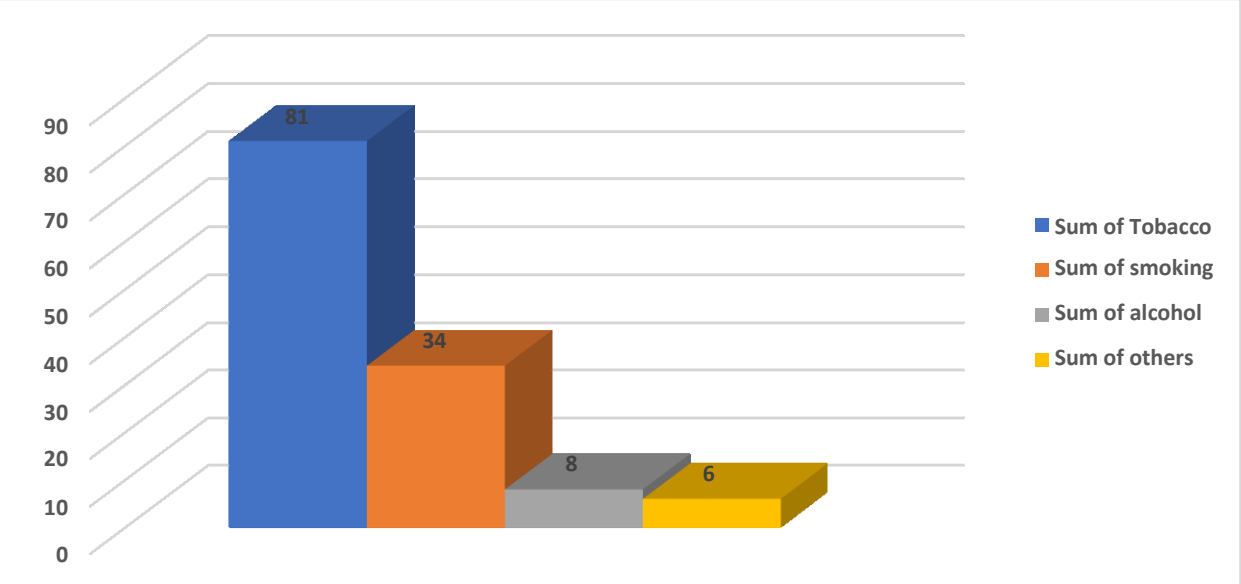


Duration of months	Frequency
1-10	108
11-20	12
21-30	4
31-40	1
51-60	2
Grand Total	127

Sample size	127
Lowest value	1.0000
Highest value	60.0000
Arithmetic mean	6.0472
95% CI for the Arithmetic mean	4.5098 to 7.5847
Median	4.0000
95% CI for the median	3.0000 to 4.0000
Variance	76.6485
Standard deviation	8.7549

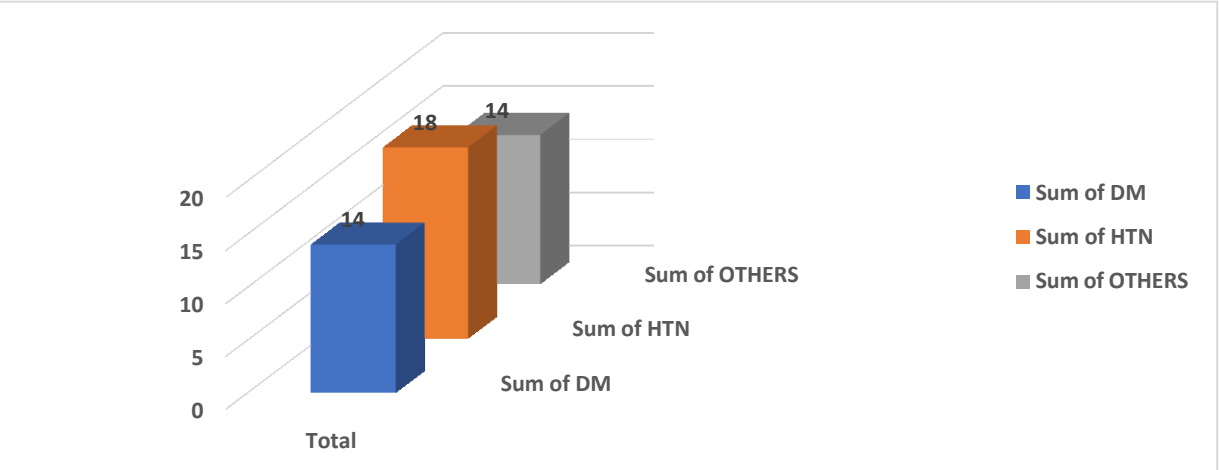
- Out of 133 patients, duration of initial symptoms was available for 127 patients. Out of 127 patients, presented with duration of initial symptoms ranging from 1 to 60 months with a mean of 6.04 months (95% C.I. ranging from 4.50 to 7.58 months) and median of 4 months (95% C.I. ranging from 3 to 4 months).

12. Addictions –



- Out of 133 patients, addiction history was available for 127 patients out of which 81 (64%) presented with history of oral tobacco addiction, 34(27%) presented with smoking addiction, 8 (6%) presented with alcohol addiction and 6 (5%) presented with other addiction as pan, betel nuts and opium addiction.

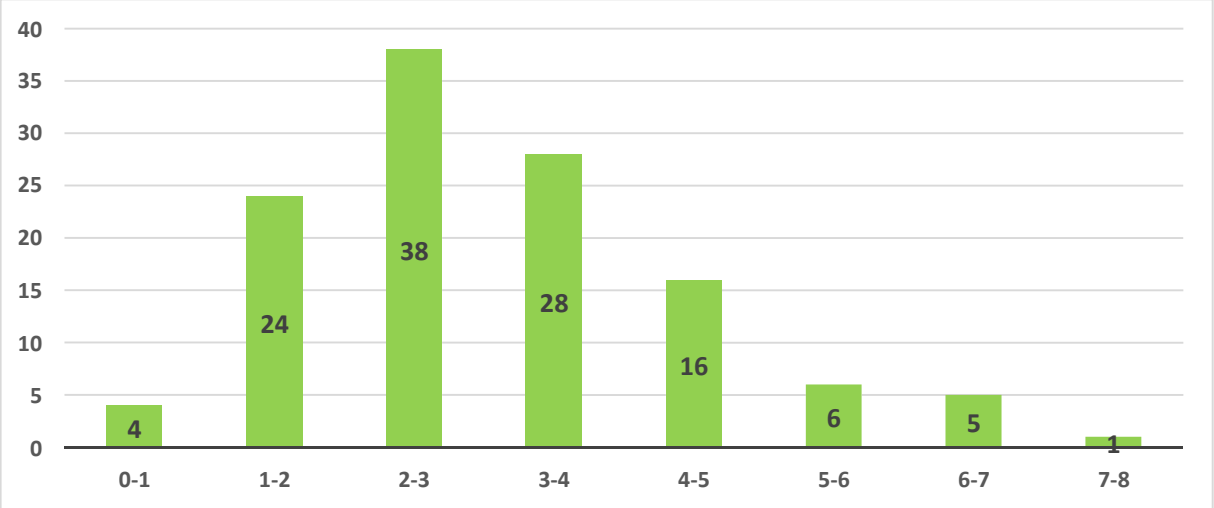
13. <u>Co-morbidities</u>-



- Out of 133 patients, data of co-morbidities was available for 131 patients out of which 14 (11%) were diabetic, 18(14%) were hypertensive and 14(11%) were having other co-morbidities as Chronic Kidney disease (CKD), hypothyroidism, cardiac disease etc.

14. <u>Largest dimension of primary site at presentation on imaging</u>-

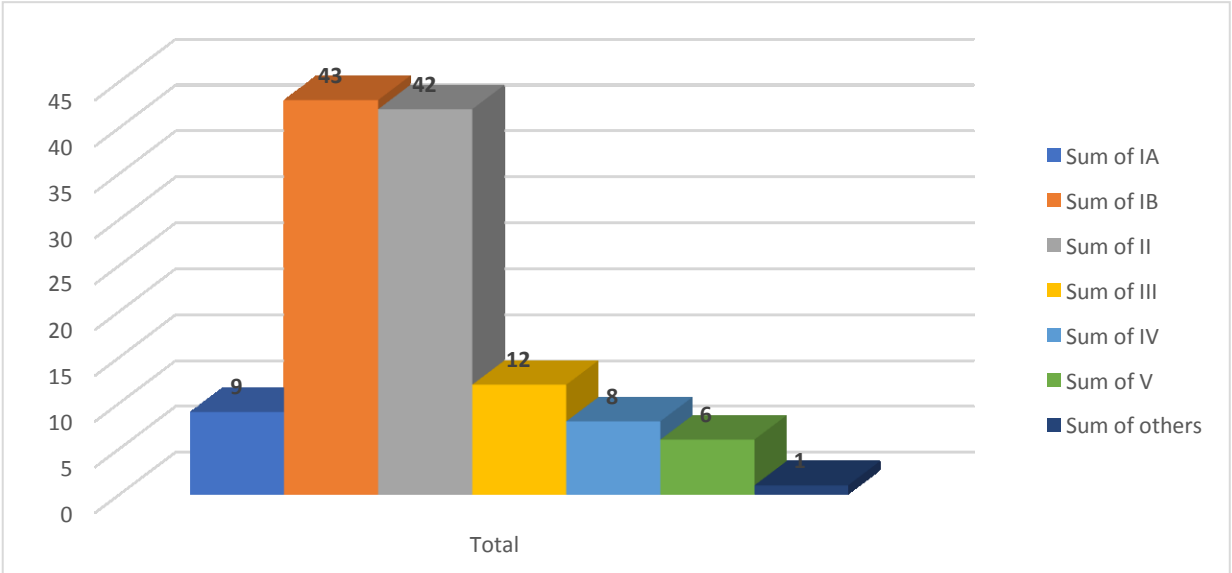
Largest dimension of primary	Frequency
0-1	4
1-2	24
2-3	38
3-4	28
4-5	16
5-6	6
6-7	5
7-8	1
Grand Total	**122**

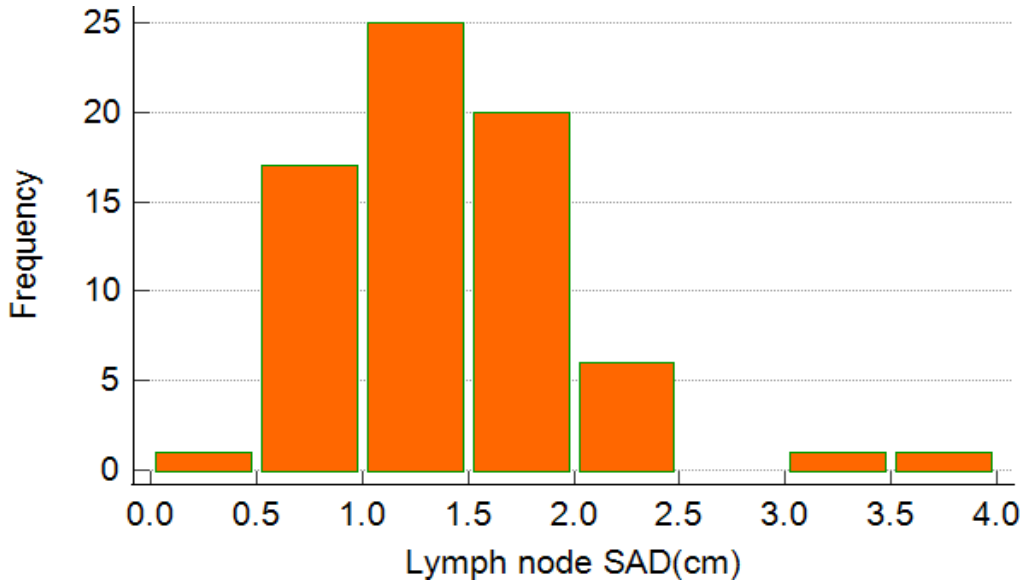


Sample size	122
Lowest value	0.1400
Highest value	7.3000
Arithmetic mean	2.9645
95% CI for the Arithmetic mean	2.7176 to 3.2114
Median	2.8000
95% CI for the median	2.4000 to 3.1000
Variance	1.8979
Standard deviation	1.3776

- Out of 133 patients, data of largest dimension of primary site was available for 122 patients. Largest dimension of primary on imaging was ranging from 0.14 to 7.3 cm with a mean value of 2.96cm (95% C.I. ranging from 2.71 to 3.21cm) and median value of 2.8cm (95% C.I. ranging from 2.4 to 3.1 cm).

15. Status of Lymph nodes at baseline imaging-

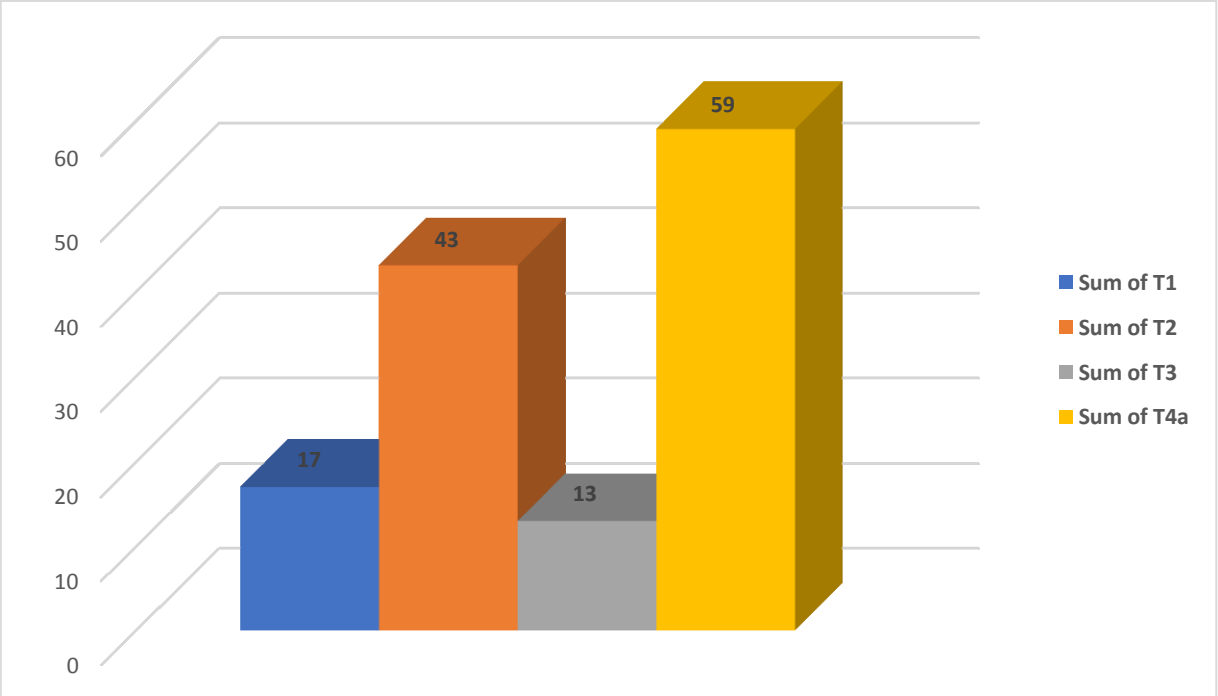


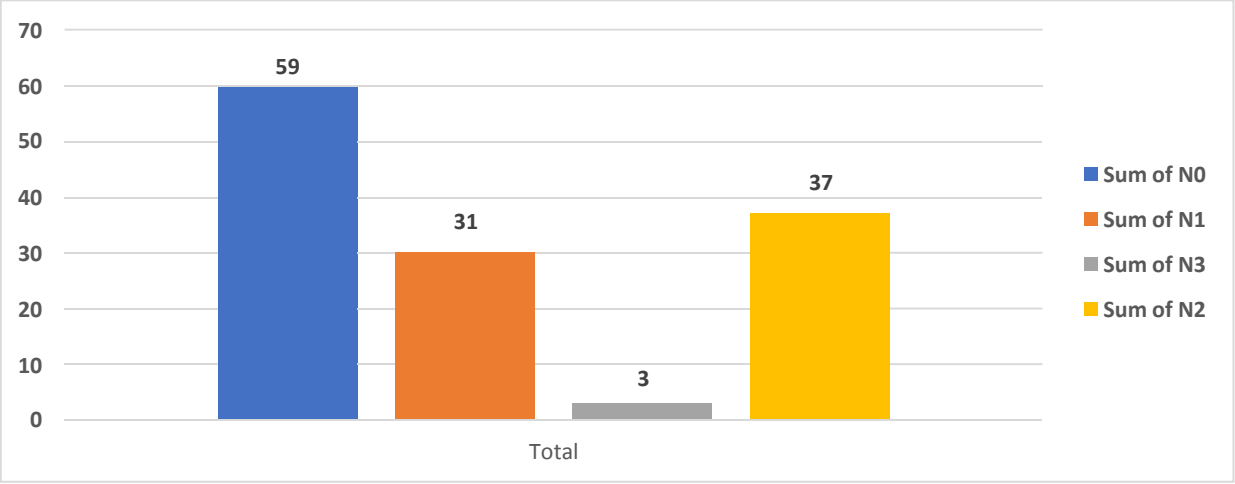


Sample size	71
Lowest value	0.4000
Highest value	3.8000
Arithmetic mean	1.3392
95% CI for the Arithmetic mean	1.2005 to 1.4778
Median	1.2200
95% CI for the median	1.1000 to 1.5000
Variance	0.3433
Standard deviation	0.5859

- Out of 133 patients, data of initial lymph node status on imaging was available for 125 patients out of which 68(54%) presented with lymphadenopathy. Out of 68 patients, 9(13%) presented with level IA enlargement, 43 (63%) presented with level IB enlargement ,42(62%) presented with level II enlargement, 12(18%) presented with level III enlargement, 8(12%) presented with level IV enlargement, 6(9%) presented with level V enlargement, 1 (1%) presented with other as paratracheal/paraoesophageal lymph node enlargement.
- Short axis diameter (SAD) ranging from 0.4 to 3.8cm with a mean value of 1.33cm (95% C.I. ranging from 1.25 to 1.47cm) and median value of 1.22cm (95% C.I. ranging from 1.1. to 1.5 cm).

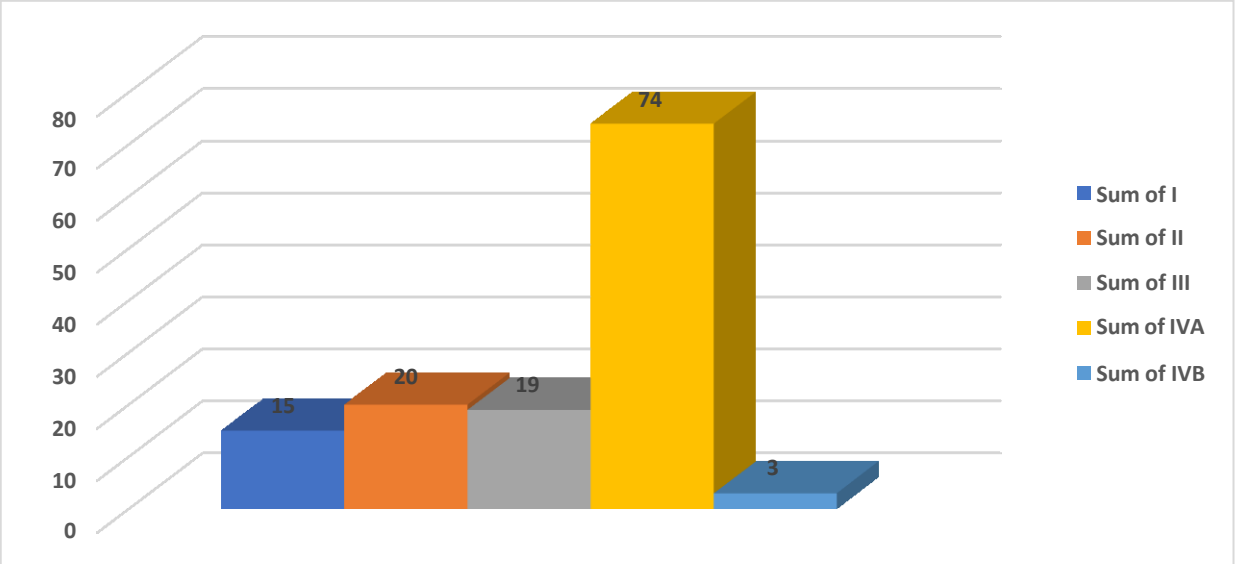
16. <u>Clinical Stage (TNM) at initial presentation-</u> (AJCC 8th edition)





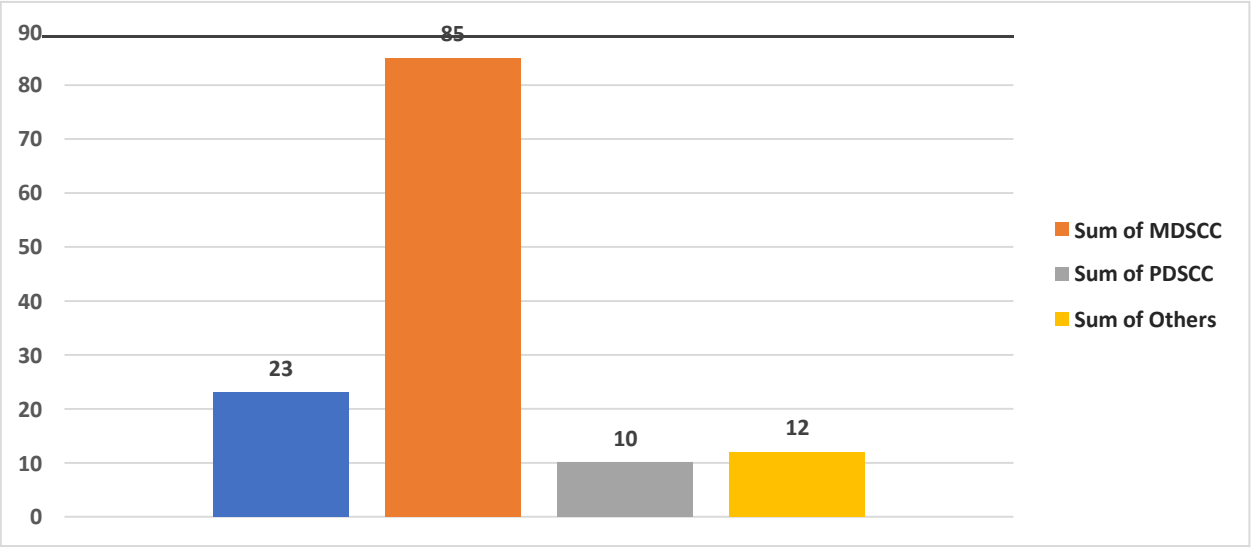
- Out of 133 patients, data of initial TNM staging was available for 131 patients. All were non-metastatic (M0), out of which 17 (13%) presented with T1 stage, 43(33%) presented with T2 stage, 13(10%) presented with T3 stage and majority of patients (45%) presented with T4a stage.
- In nodal staging, 59 (45%) presented with N0 stage, 31 (24%) presented with N1 stage, 3 (2%) presented with N2 stage and 37(28%) presented with N3 stage.

17. Prognostic group at presentation- (AJCC 8th edition)-



- Out of 133 patients, data regarding initial stage at presentation was available for 131 patients. Out of these patients, 15 (11%) presented with Stage I, 20 (15%) presented with stage II, 19 (14%) presented with stage III, 74 (56%) presented with stage IVA, 3 (2%) presented with stage IVB.

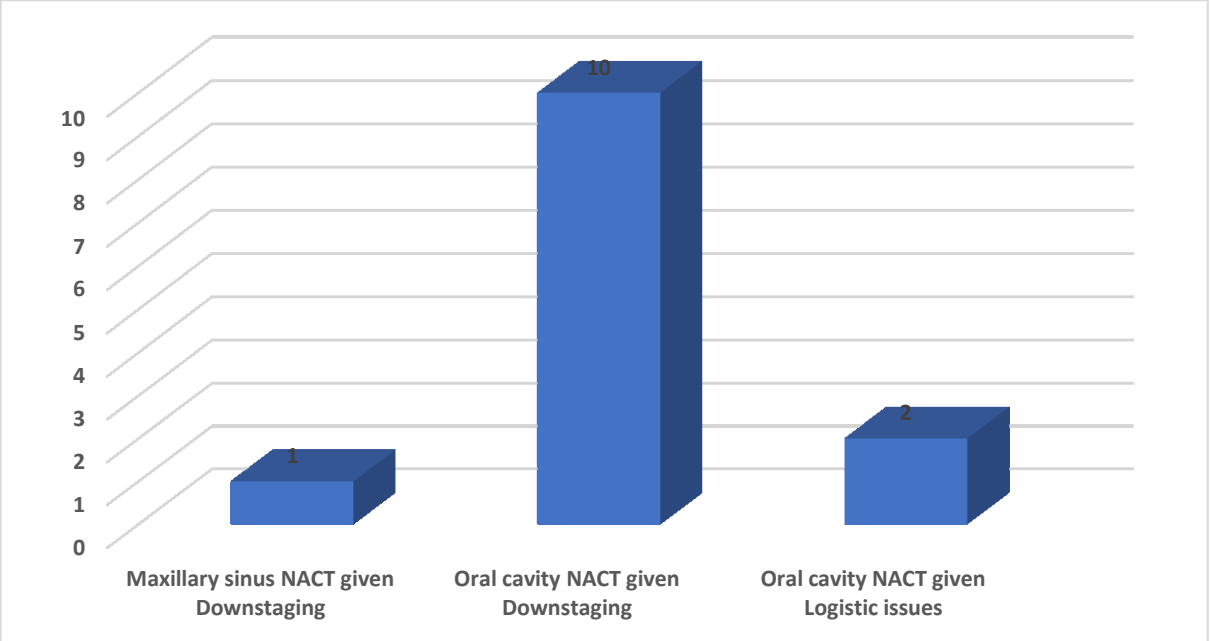
18. Pre-treatment tumor histology at presentation-

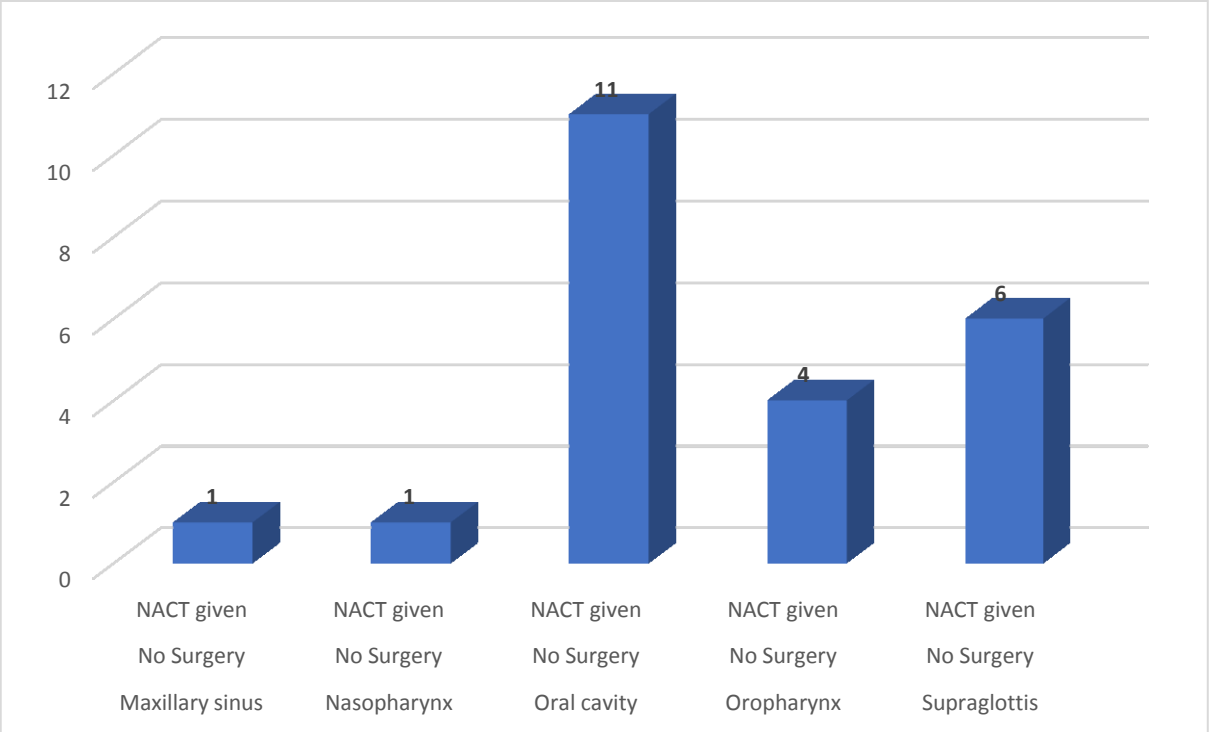


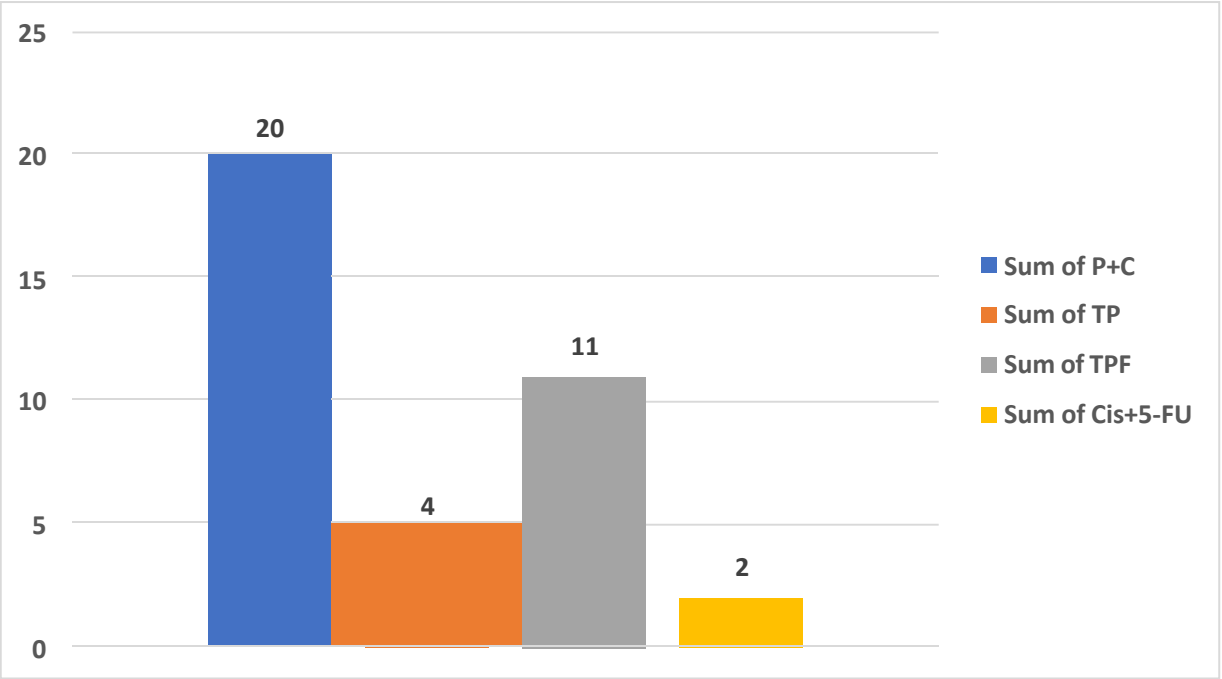
- Out of 133 patients, data of pre-treatment histology was available for 130 patients out of which 23(18%) presented with Well Differentiated Squamous cell carcinoma (WDSCC), 85(65%) presented with Moderately differentiated Squamous cell carcinoma (MDSCC) , 10(7%) presented with poorly differentiated squamous cell

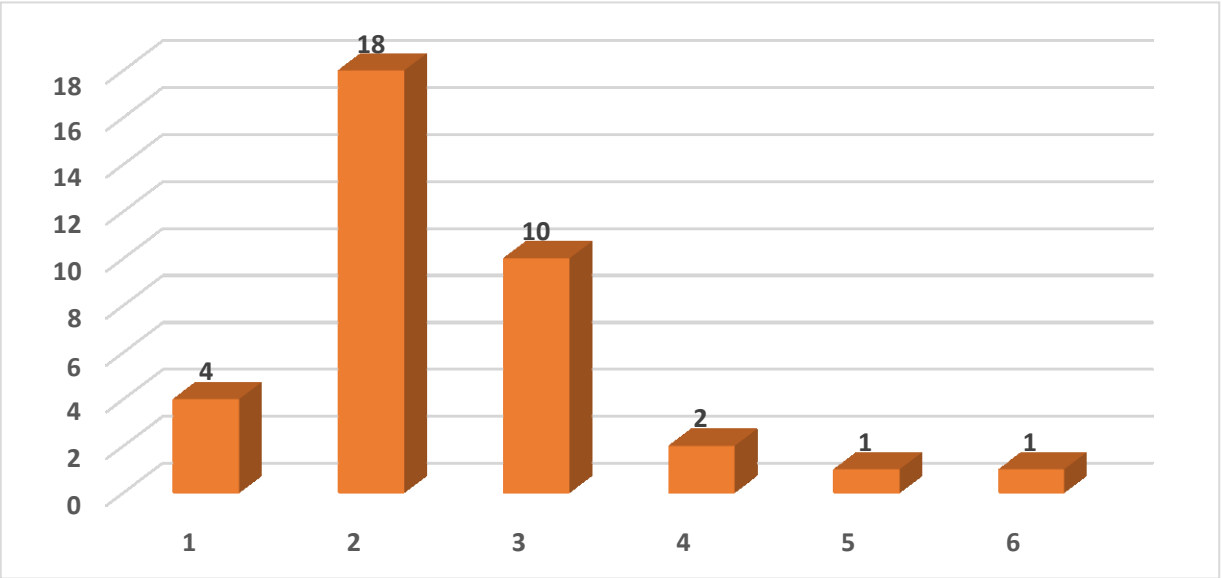
carcinoma(PDSCC) and 12(9%) presented with other tumor histology as 2 with adenoid cystic carcinoma, 1 with porokeratosis, 1 with paraganglioma, 1 with spindle cell variant of SCC, 1 with basaloid variant of SCC, 1 with malignant melanoma, 1 with high grade dysplasia, 2 with myoepithelial carcinoma and 1 with pleomorphic adenoma.

19. History of Neoadjuvant chemo & Regimens–









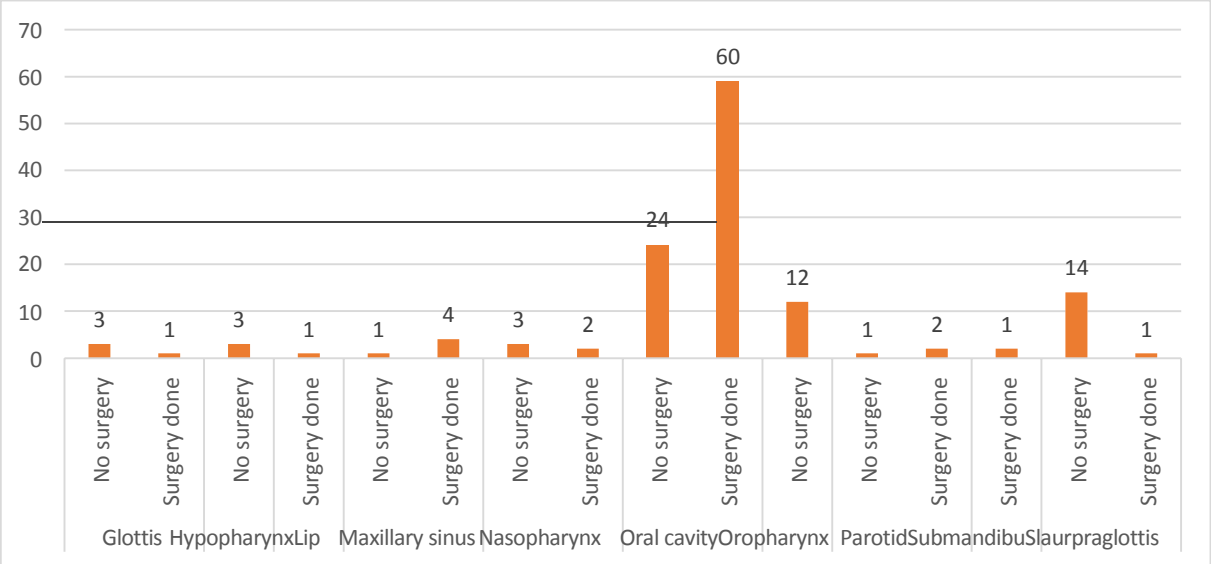
- Out of 133 patients, data of neoadjuvant chemotherapy was available for 129 patients out of which 36(28%) patients received neoadjuvant chemotherapy. Out of which 20 (55%) received neoadjuvant chemotherapy with Paclitaxel + Carboplatin, 11 (31%) received triplet regimen with Cisplatin+Docetaxel+5-FU (TPF), 4(11%) received doublet regimen with Cisplatin + Docetaxel (TP) and 2 (5%) received Cisplatin + 5-FU.
- Out of 36 patients who received neoadjuvant chemotherapy, number of cycles was different. 4 patients (11%) received 1 cycle of NACT, 18 (50%) patients received 2

cycles of NACT, 10(28%) received 3 cycles of NACT, 2 (5%) patients received 4 cycles, 1(3%) patient received 5 cycles and 7 cycles each.

- In surgically resectable Oral cavity tumors, 12 patients received neo-adjuvant chemotherapy out of which 10(83%) patients received for downstaging while 2 (17%) received due to logistic issues.

20. DETAILS ABOUT SURGICAL INTERVENTION-

20.1 Surgical Intervention Done or Not-



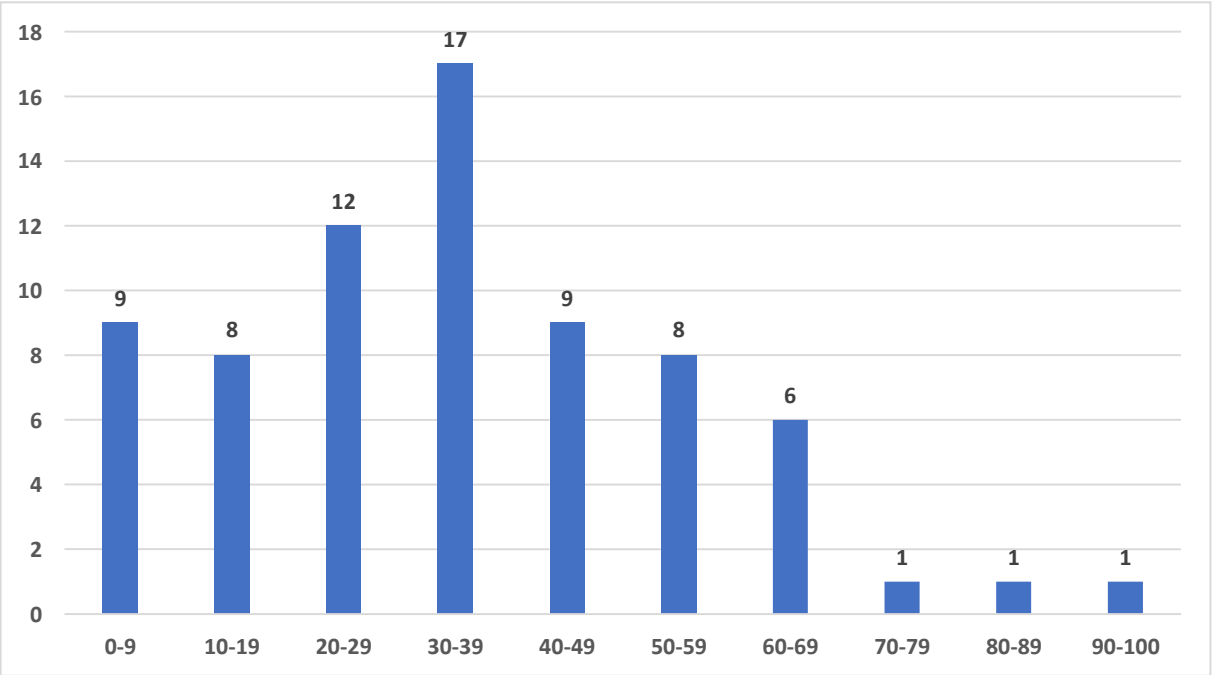
Subsites	Frequency of Surgical intervention
Glottis	**4**
No surgery	3
Surgery done	1
Hypopharynx	**3**
No surgery	3
Lip	**1**
Surgery done	1
Maxillary sinus	**5**
No surgery	1
Surgery done	4
Nasopharynx	**5**
No surgery	3

Surgery done	2
Oral cavity	**84**
No surgery	24
Surgery done	60
Oropharynx	**12**
No surgery	12
Parotid	**3**
No surgery	1
Surgery done	2
Submandibular	**1**
Surgery done	1
Supra-glottis	**15**
No surgery	14
Surgery done	1

- Out of 133 patients, 72 (54%) underwent surgical intervention while 61 (46%) were treated with definitive Radiotherapy without surgical intervention.
- Out of 83 oral cavity tumors, 59(71%) underwent surgical intervention while remaining 24 (29%) underwent definitive radiotherapy or concurrent chemoradiotherapy.

20.2 NUMBERS OF LYMPH NODE DISSECTED-

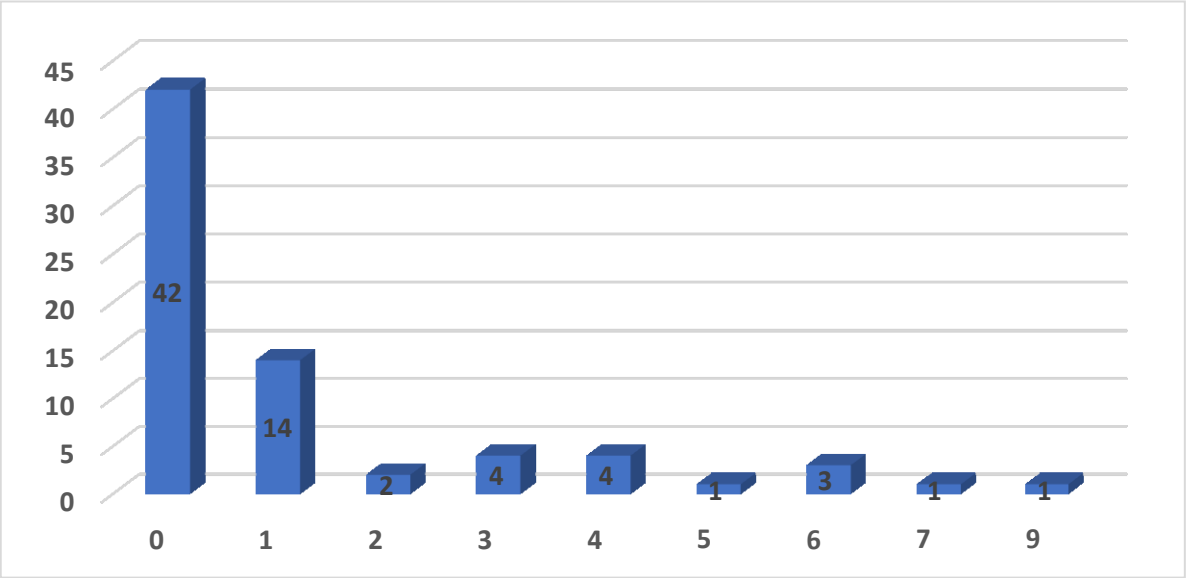
Number of LN dissected	Frequency
0-9	**9**
10-19	**8**
20-29	**12**
30-39	**17**
40-49	**9**
50-59	**8**
60-69	**6**
70-79	**1**
80-89	**1**
90-100	**1**
Grand Total	**72**



Sample size	72
Lowest value	0.0000
Highest value	92.0000
Arithmetic mean	34.5694
95% CI for the Arithmetic mean	29.6685 to 39.4704
Median	33.5000
95% CI for the median	28.2120 to 37.7880
Variance	434.9810
Standard deviation	20.8562

- Out of 133 patients, 72 underwent surgical intervention. Number of lymph node dissected ranges from 0 to 92 with a mean value of 34 (95% C.I ranging from 29 to 39 LNs) and median value of 33 (95% C.I. ranging from 28 to 37).

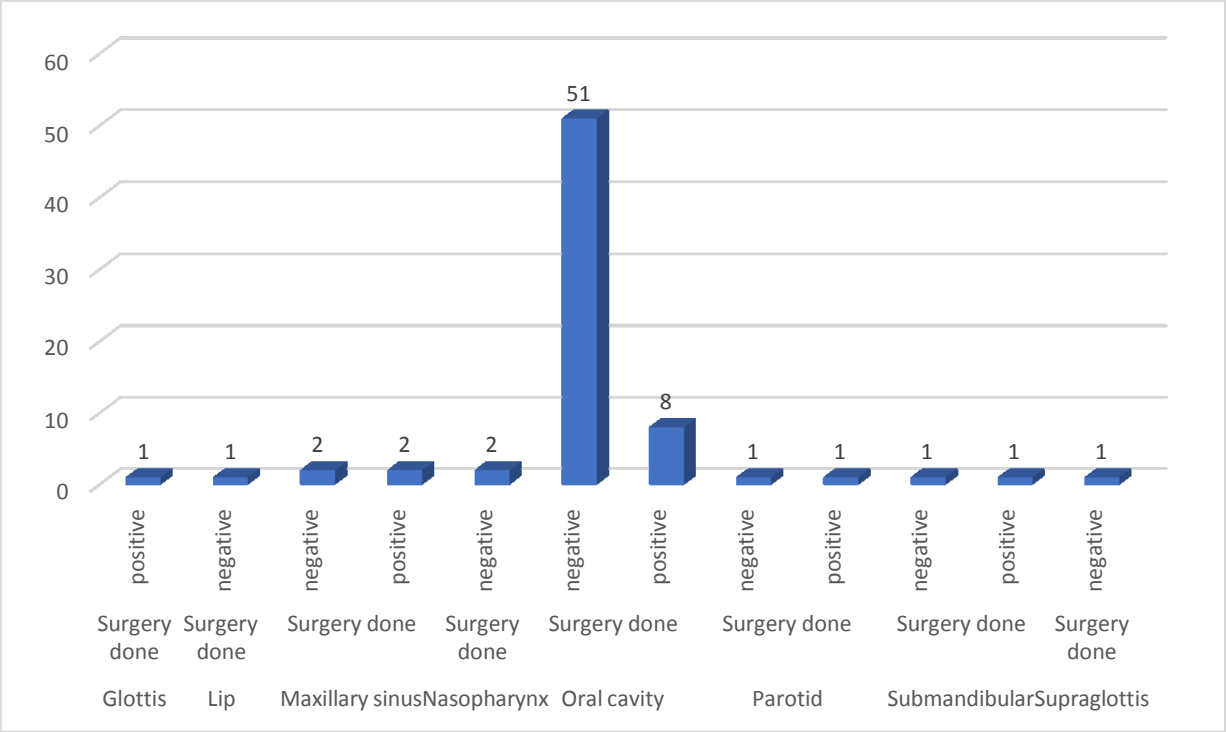
20.3 Lymph Node positivity-

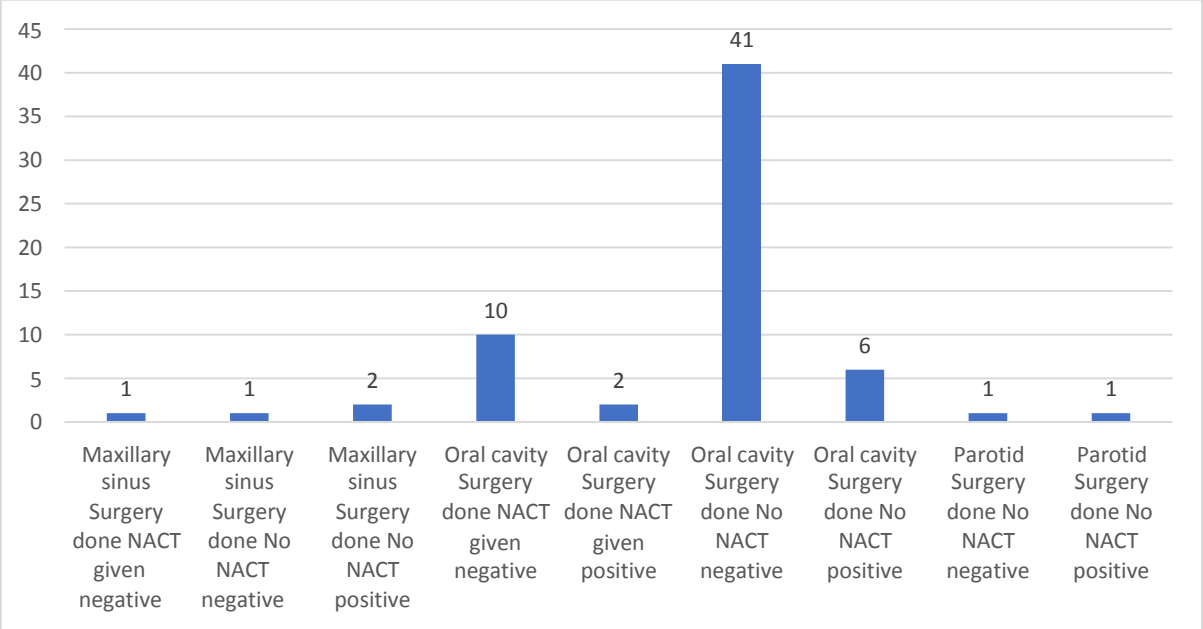


Sample size	72
Lowest value	0.0000
Highest value	9.0000
Arithmetic mean	1.1806
95% CI for the Arithmetic mean	0.7100 to 1.6511
Median	0.0000
95% CI for the median	0.0000 to 1.0000
Variance	4.0092
Standard deviation	2.0023

- Out of 133 patients, 72 underwent surgical intervention. Number of histopathological positive lymph node ranges from 0 to 9 with a mean value of 1.18 (95 C.I. ranging from 0.71 to 1.65).

20.4 Margin Positivity-

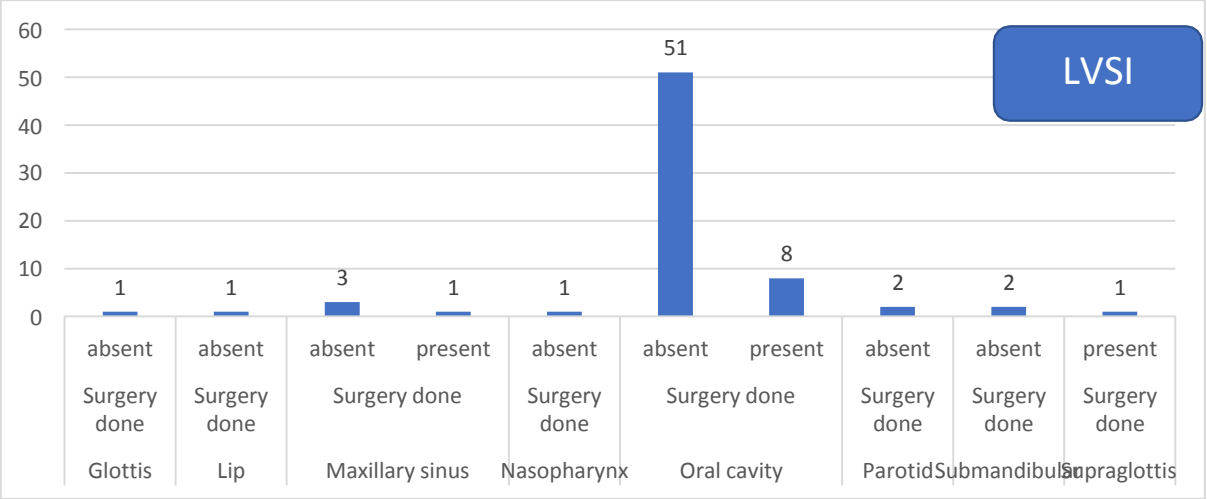


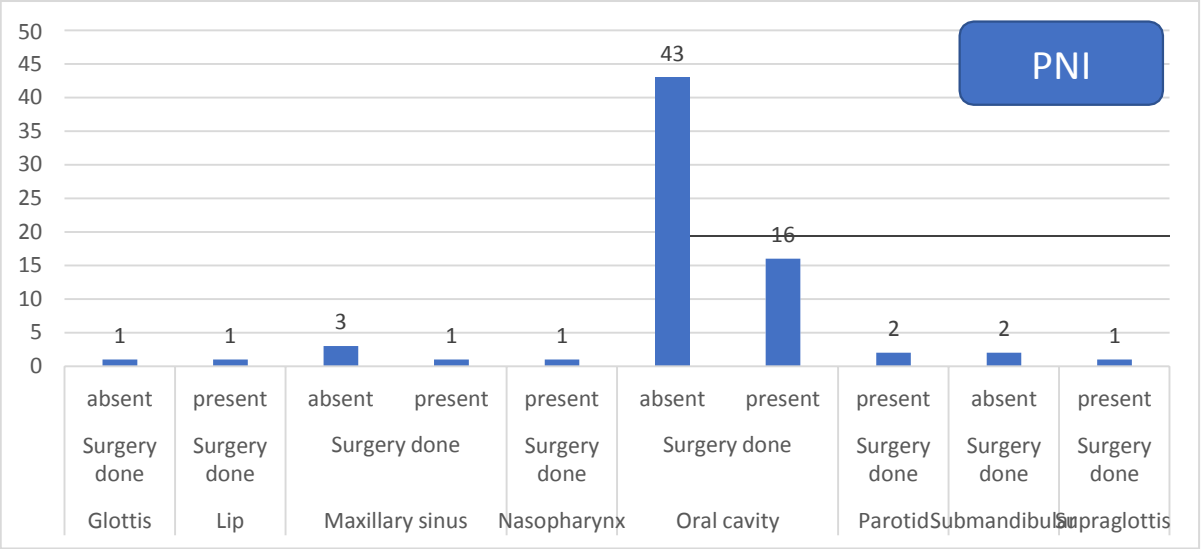


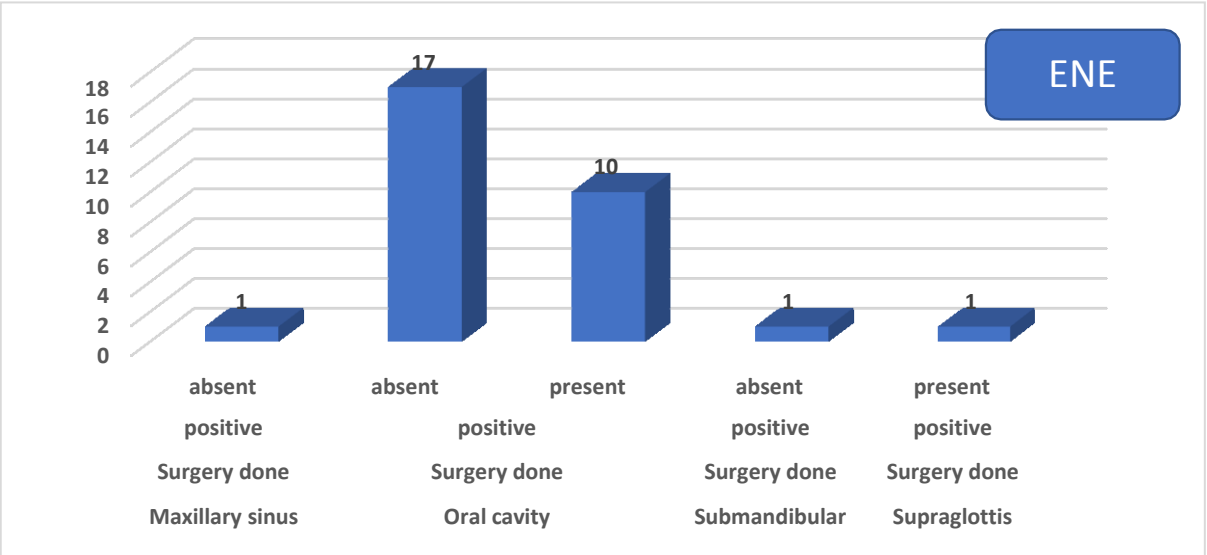
Subsites	Count of MARGIN STATUS
Maxillary sinus	**4**
Surgery done	**4**
NACT given	1
negative	1
No NACT	3
negative	1
positive	2
Oral cavity	**59**
Surgery done	**59**
NACT given	12
negative	10
positive	2
No NACT	47
negative	41
positive	6
Parotid	**2**
Surgery done	**2**
No NACT	2
negative	1
positive	1
Grand Total	**65**

- Out of 133 patients, 72 underwent surgical intervention. Out of 72 patients, 13 (18%) were margin positive while 59 (82%) were margin negative.
- Maximum margin positivity rate was in oral cavity tumors (13.5%).

20.5 Presence of Lympho-vascular invasion (LVSI) / Perineural invasion (PNI)/Extra nodal extension (ENE)-

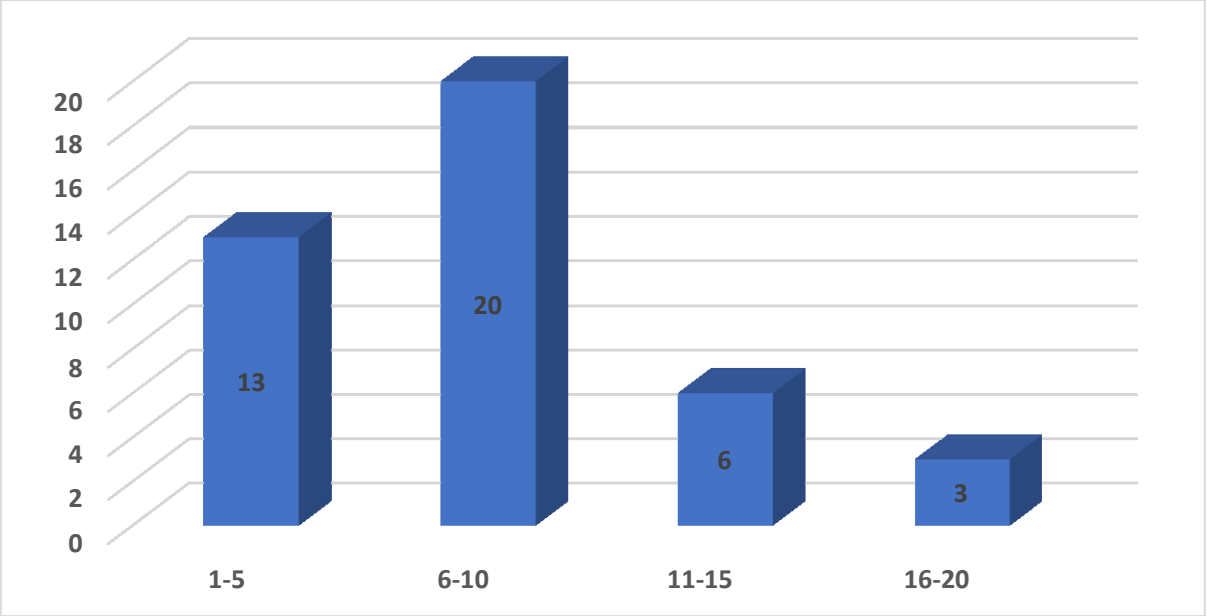






- Out of 133 patients, 72 underwent surgical intervention. Out of which LVSI details were available for 71 patients. 61 (86%) were LVSI negative while 10 (14%) were LVSI positive.
- PNI details were available for 70 patients, out of which 49 (70%) were PNI negative while 21 (30%) were PNI positive.
- ENE details were available for 68 patients out of which 11 (16%) were ENE positive and 57 (84%) were ENE negative.

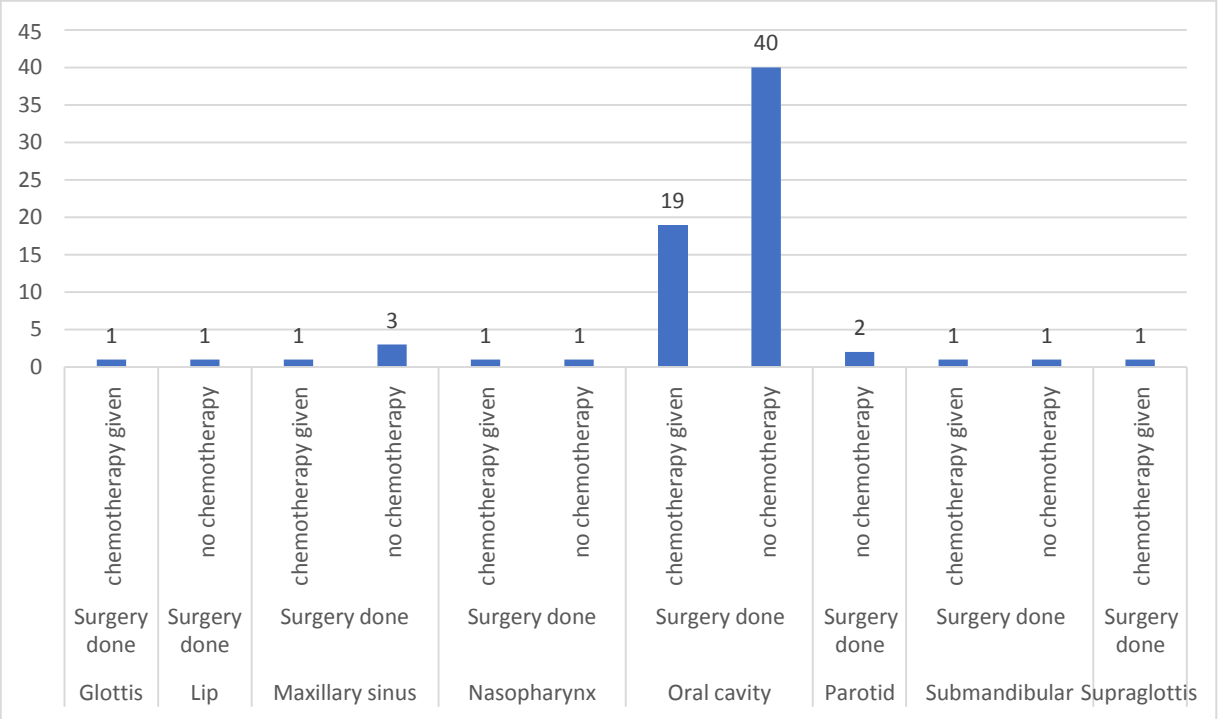
20.6 Depth of invasion (DOI) in mm-

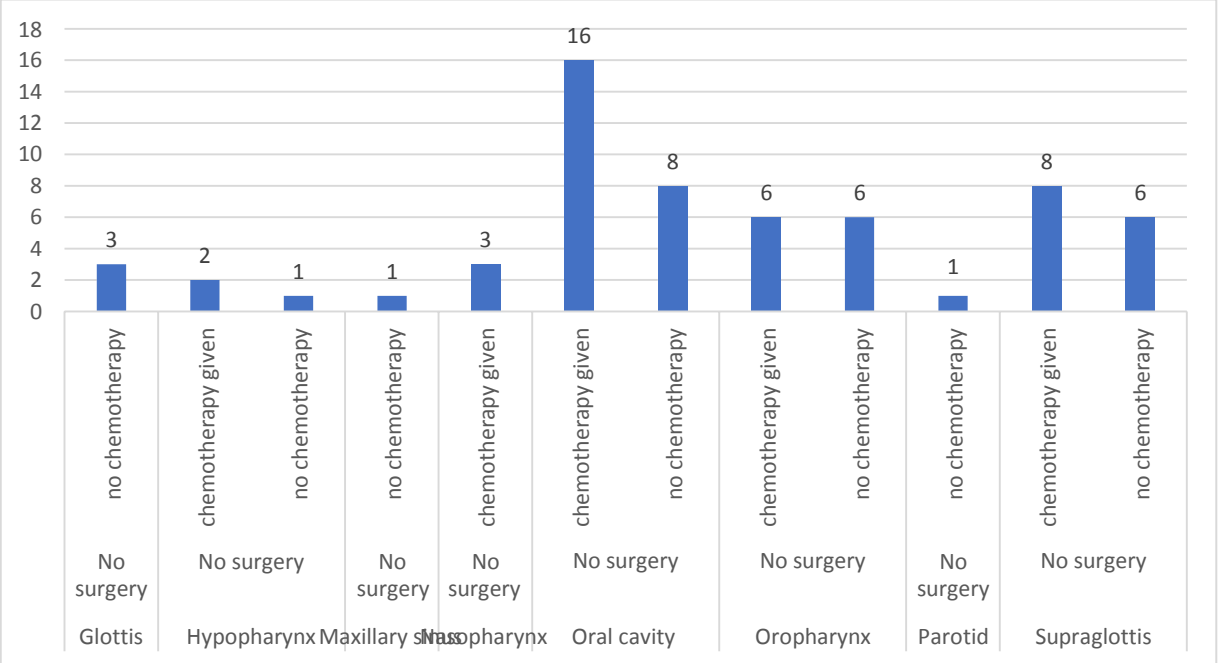


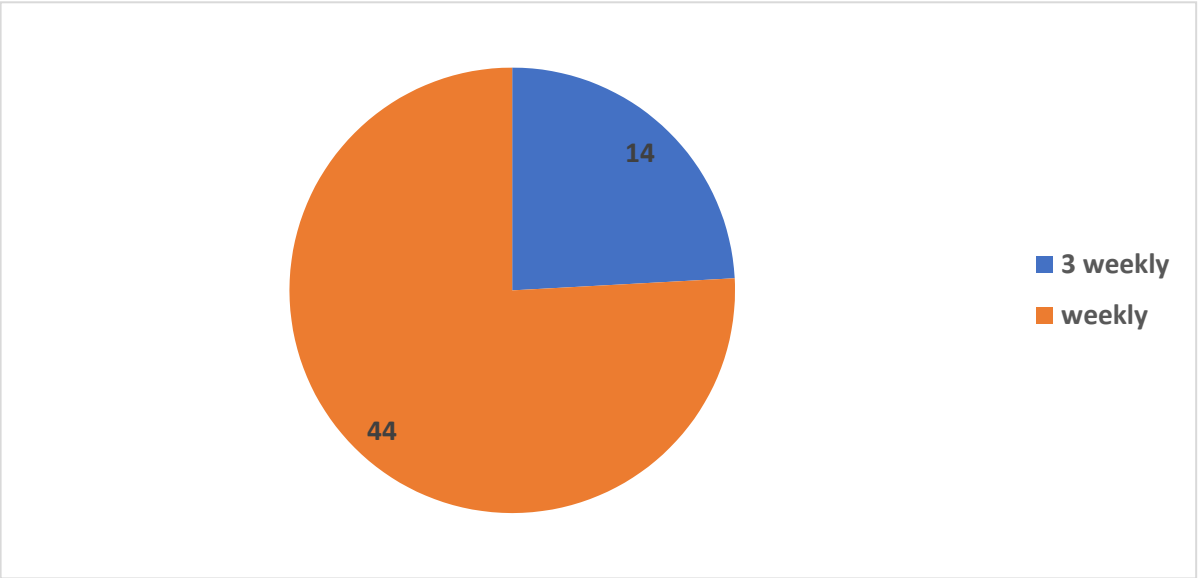
Sample size	42
Lowest value	4.0000
Highest value	20.0000
Arithmetic mean	8.5952
95% CI for the Arithmetic mean	7.3038 to 9.8866
Median	8.0000
95% CI for the median	7.0000 to 10.0000
Variance	17.1736
Standard deviation	4.1441

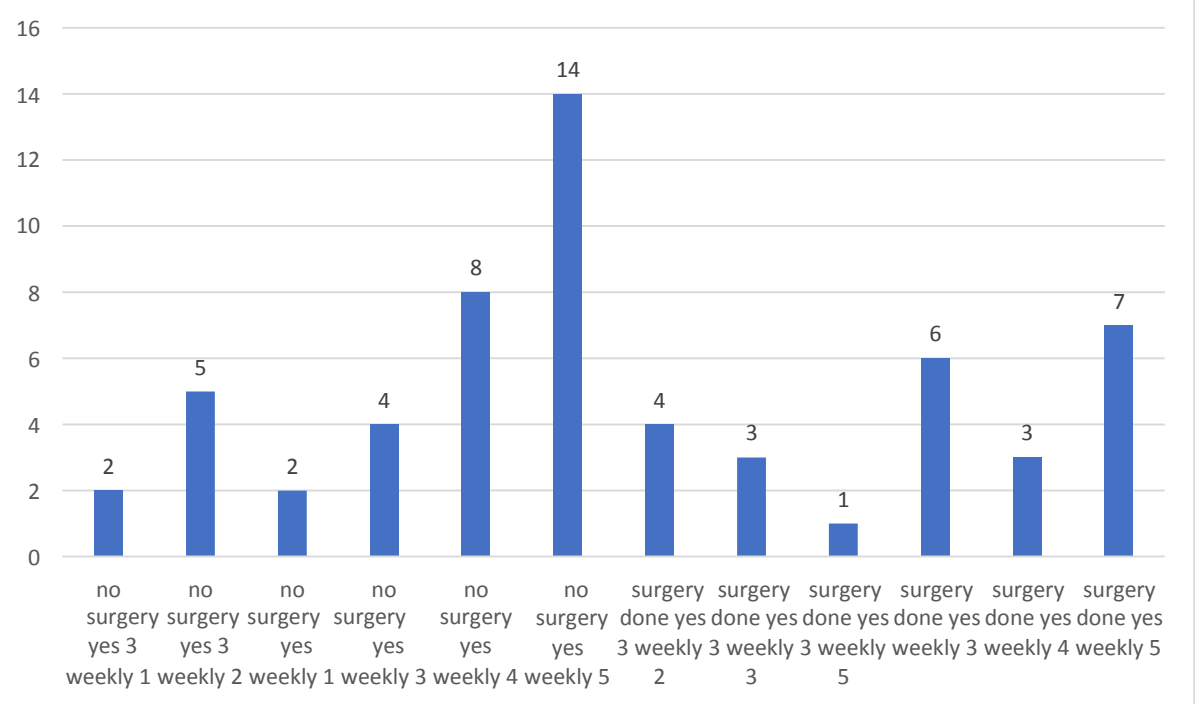
- Data regarding Depth of invasion was available for 42 patients. DOI ranges from 4 to 20 mm with a mean of 8.6mm (95% C.I. ranging from 7.3 to 9.88mm) and median of 8 (95% C.I. ranging from 7 to 10mm).

21. Details about concurrent chemotherapy-



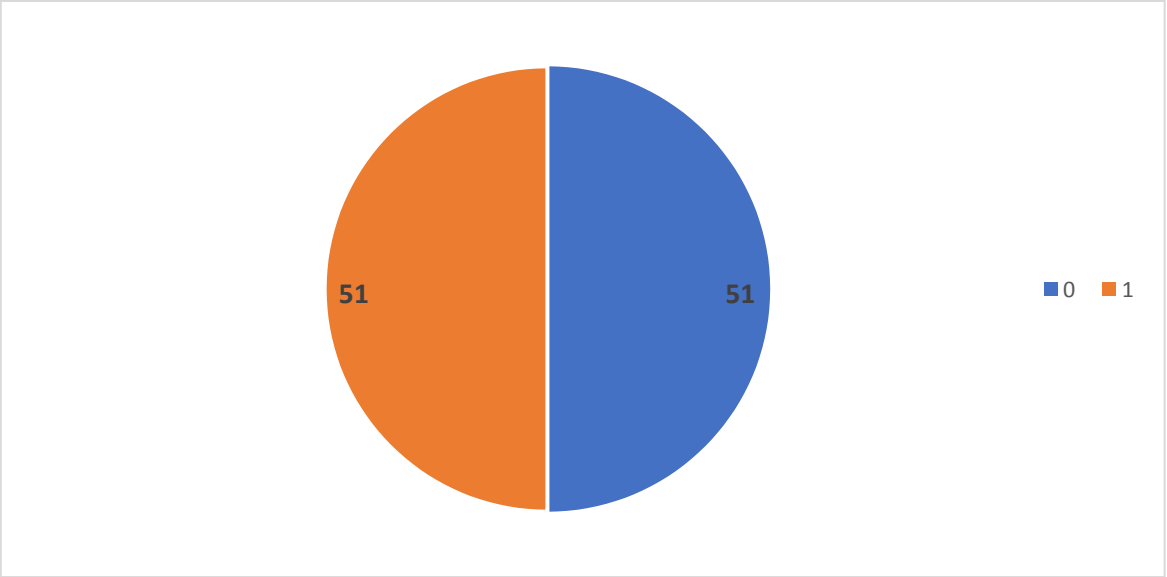






- Out of 133 patients,59 (44%) patients received concurrent chemotherapy.
- Out of 59 patients, 58 received Injection Cisplatin as concurrent chemotherapy while 1 patient received VAC (Vincristine, Adriamycin, Cyclophosphamide) Chemotherapy as concurrent chemotherapy.
- Out of 58 patients, 44 (76%) received weekly regimen while 14 (24%) patients received 3 weekly regimen of cisplatin.
- Out of 58 patients, 4 (7%) received 1 cycle of concurrent chemotherapy, 9 (16%) received 2 cycles, 13(22%) received 3 cycles, 11(19%) received 4 cycles and 21 (36%) received 5 cycles of concurrent chemotherapy.

22. <u>Final Outcome (Dead or Alive)-</u>



- Out of 133 patients, contact could be made with only 102 patients due to wrong contact details. Out of 102 patients, 51 (50%) are dead and 51 (50%) are alive.

23. <u>Median Follow up time</u>- Median follow-up time was calculated using Reverse Kaplan Meier curve.

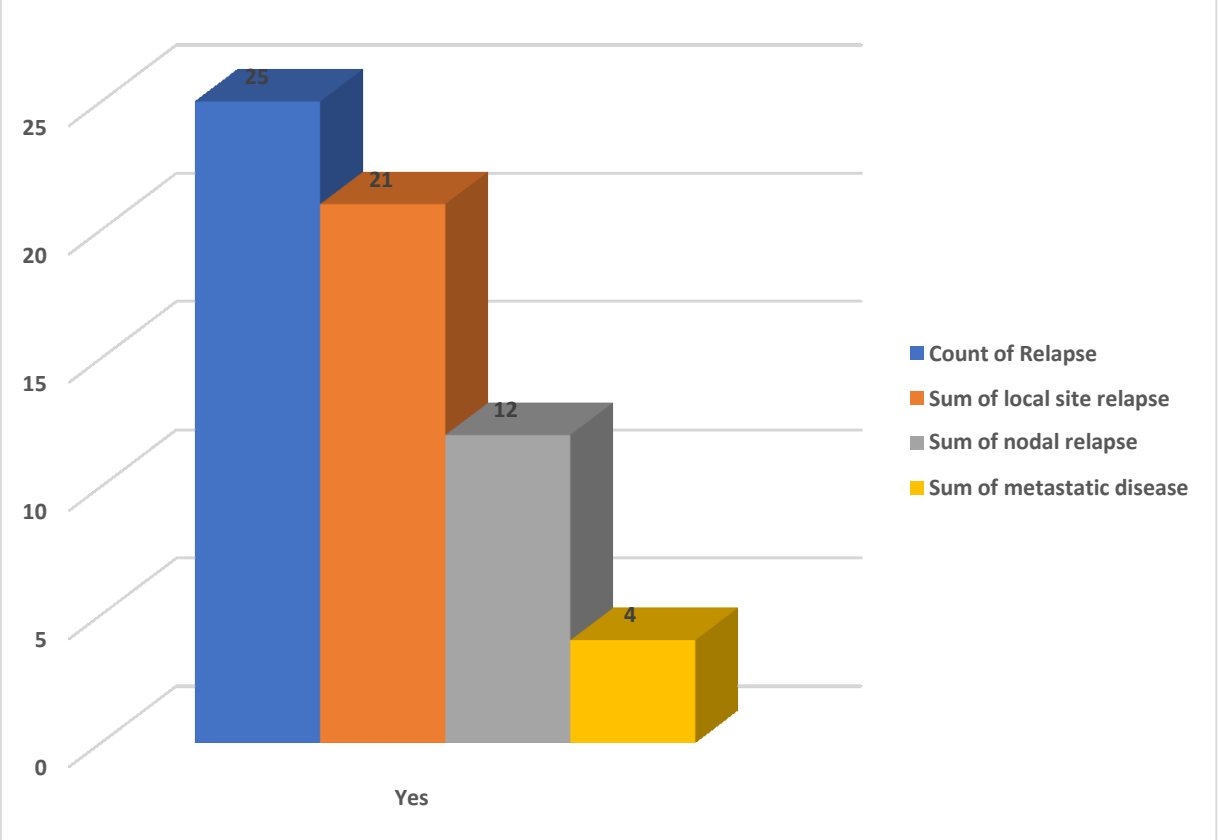
- Median follow-up time was found to be 29.733 months (95% C.I. ranging from 22.063 to 37.403 months).

Means and Medians for Survival Time

Mean[a]				Median			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
32.925	2.162	28.687	37.162	29.733	3.913	22.063	37.403

a. Estimation is limited to the largest survival time if it is censored.

24. <u>Presence/Absence of relapse-</u>



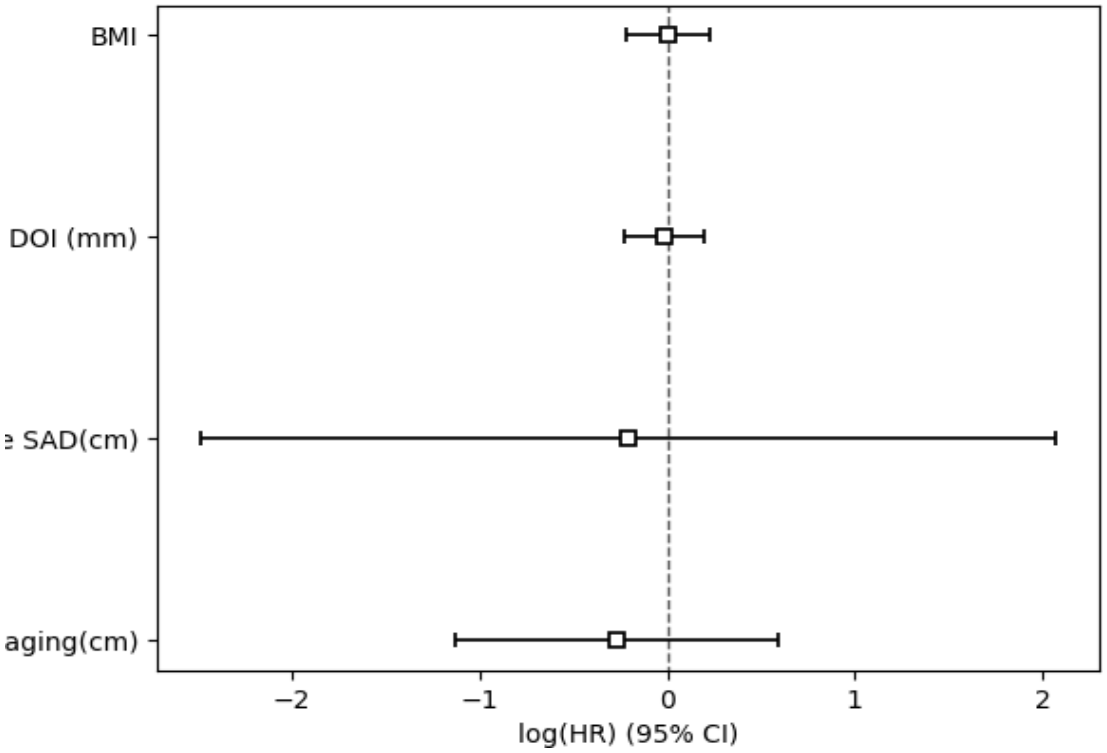
- Out of 133 patients, data regarding presence or absence of relapse was available for 96 patients out of which 25 (28%) developed relapse post treatment completion and 71 (72%) were relapse free.
- Out of 25 patients, 21(80%) patients developed local site relapse, 12 (48%) developed nodal relapse while 4 (16%) developed distant failure.

25. <u>Effect of various variables on overall survival</u> –

- Correlation between BMI and overall survival was analyzed using Cox Regression Test. It was found to be statistically insignificant with p value of 0.99 and Hazard ratio of 1.00 (95% C.I. ranging from 0.80 to 1.25).
- Correlation between largest dimension of primary on imaging and overall survival was done using Cox Regression test. It was found to be statistically insignificant with p value of 0.54 with Hazard Ratio of 0.77 (95% C.I. ranging from 0.32 to 1.81).
- Correlation between lymph node short axis diameter (SAD) on presentation, (irrespective of the treatment protocol of Surgery followed by Post Operative RT or

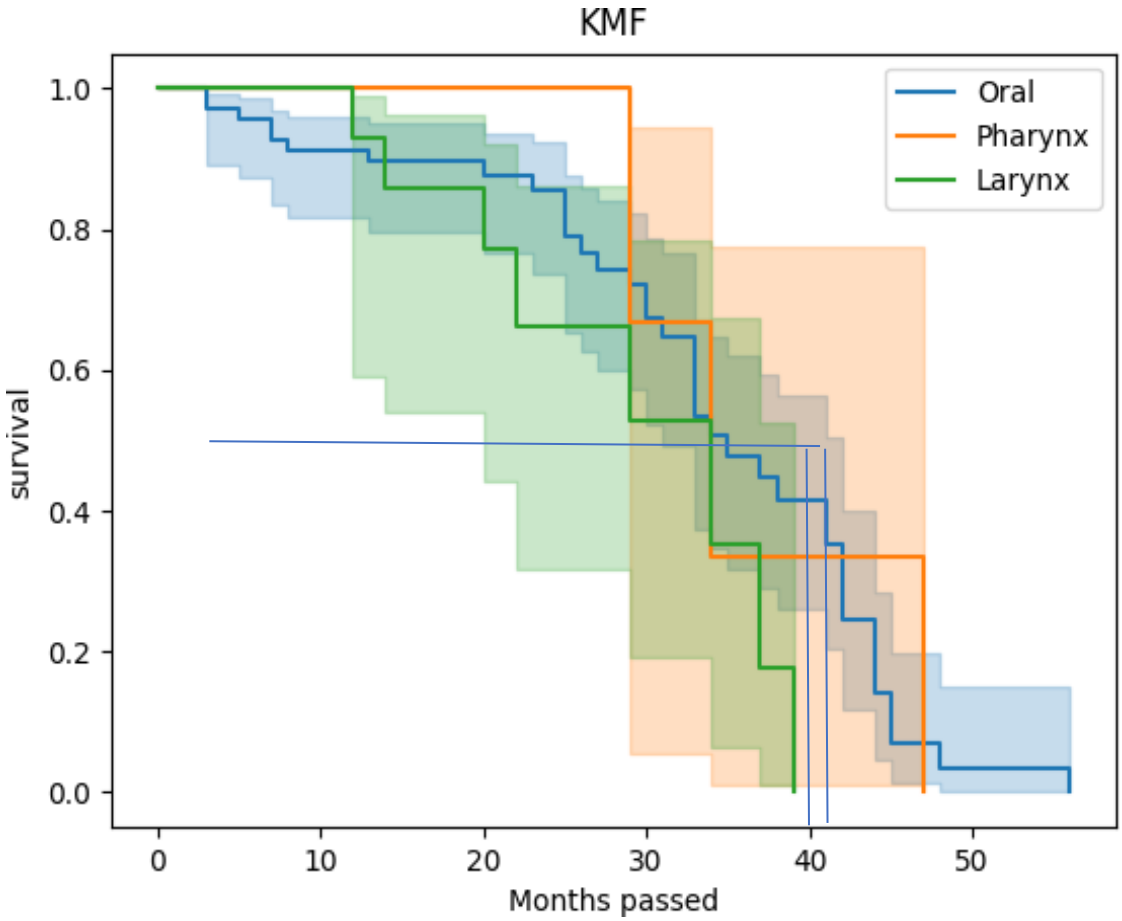
Radical Chemoradiation), and overall survival was done using Cox regression test. It was found to be statistically insignificant with p value of 0.86 with Hazard ratio of 0.81 (95% C.I. ranging from 0.08 to 7.98).

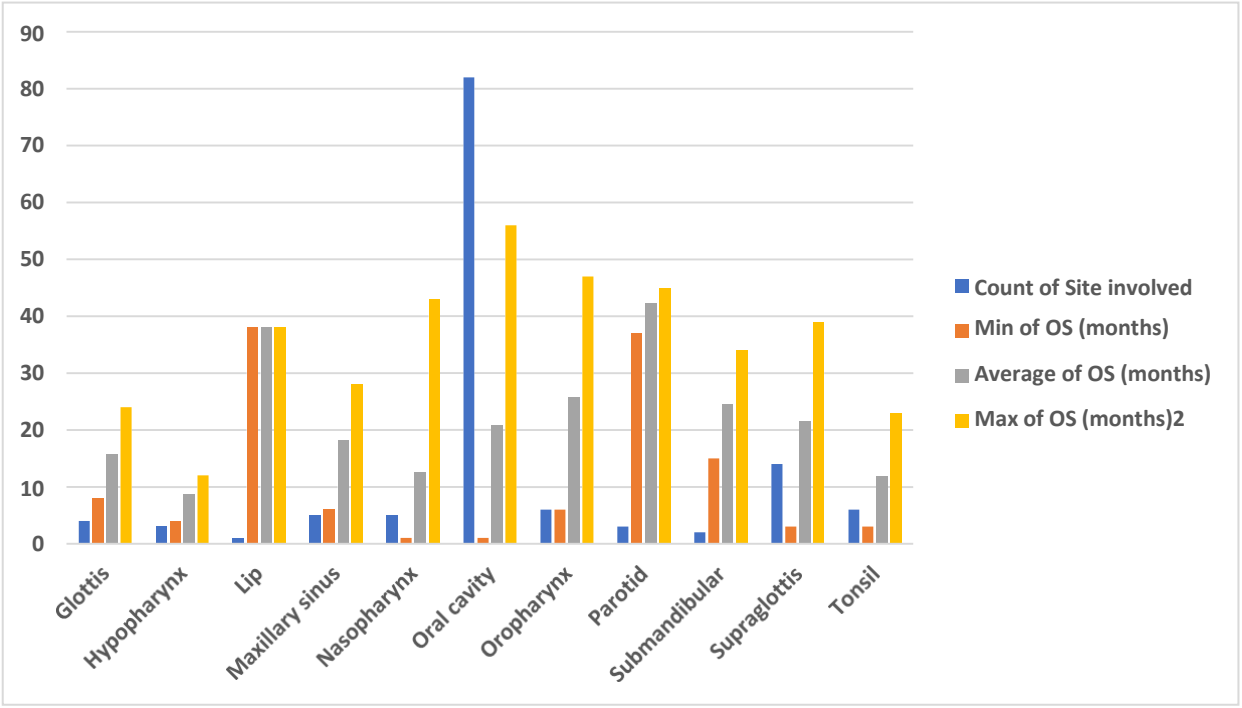
- ❖ Correlation between Depth of invasion(mm) and overall survival was done using Cox Regression test. It was found to be statistically insignificant with p value of 0.87 (95% C.I. ranging from 0.79 to 1.22).



26. <u>Site wise Overall Survival Analysis</u>-

- Log rank test was done to analyze the association between different subsites of head and neck cancer and overall survival (OS).
- There was no statistically significant difference found between overall survival of oral cavity tumors and larynx tumors, p-value was found to be 0.11.
- There was no statistically significant difference found between overall survival of oral cavity tumors and pharynx tumors, p-value was found to be 0.66.
- There was no statistically significant difference found between overall survival of larynx and pharynx tumors, p-value was found to be 0.32.

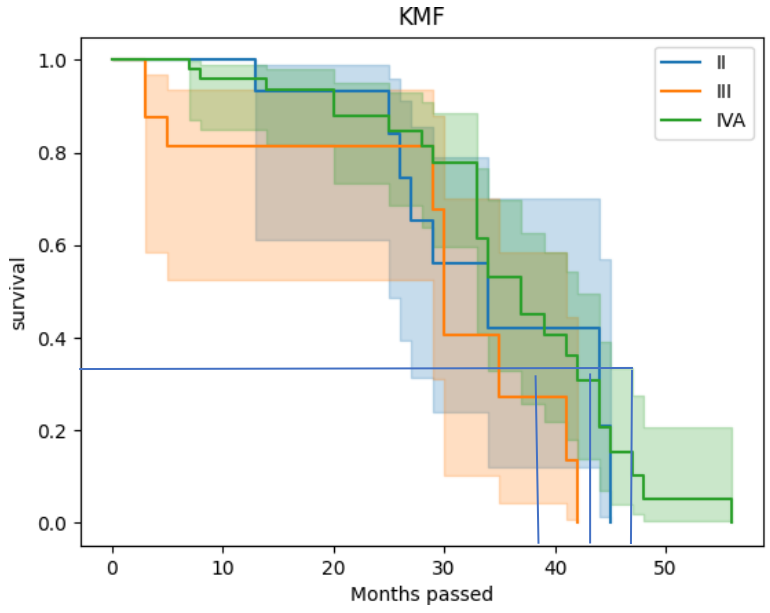

KMF
Oral
Pharynx
Larynx
survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Months passed


90
80
70
60
50
40
30
20
10
0
Glottis
Hypopharynx
Lip
Maxillary sinus
Nasopharynx
Oral cavity
Oropharynx
Parotid
Submandibular
Supraglottis
Tonsil
Count of Site involved
Min of OS (months)
Average of OS (months)
Max of OS (months)2

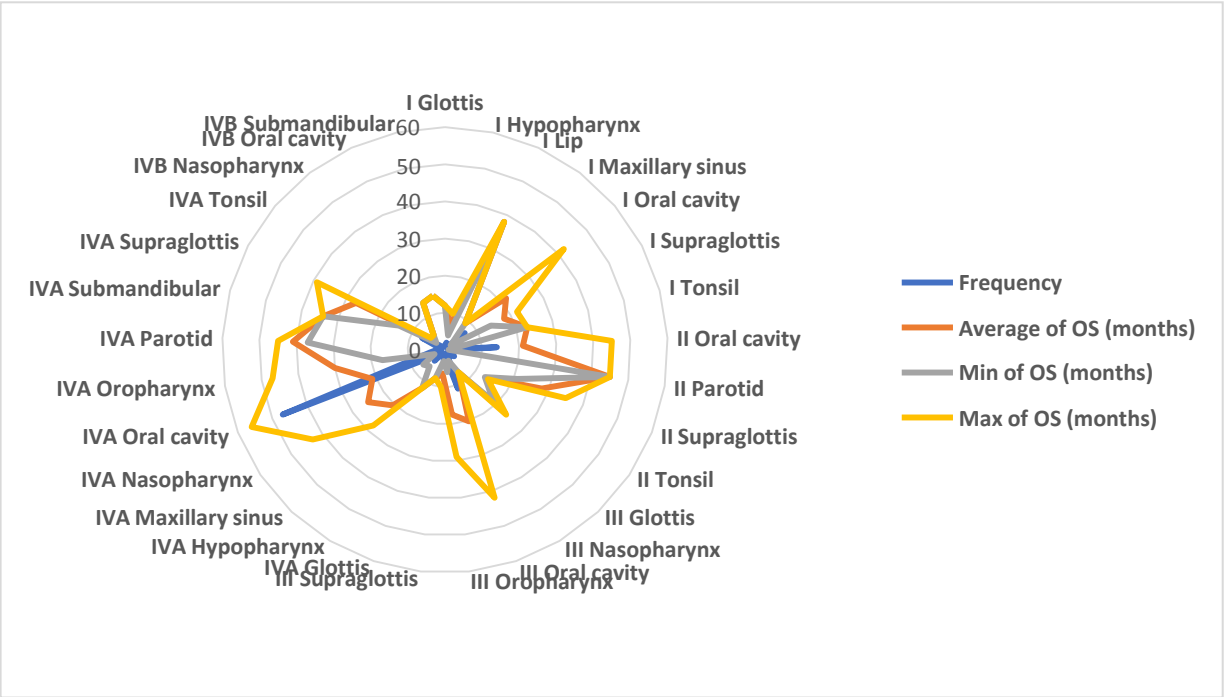
Subsite	Count of Site involved	Min of OS (months)	Average of OS (months)	Max of OS (months)
Glottis	4	8	15.75	24
Hypopharynx	3	4	8.666666667	12
Lip	1	38	38	38
Maxillary sinus	5	6	18.2	28
Nasopharynx	5	1	12.6	43
Oral cavity	82	1	20.74390244	56
Oropharynx	6	6	25.83333333	47
Parotid	3	37	42.33333333	45
Submandibular	2	15	24.5	34
Supra glottis	14	3	21.5	39
Tonsil	6	3	11.83333333	23

27. Stage wise Survival Analysis-

- Log rank test was done to analyze the association between stages of head and neck cancer and overall survival (OS).
- There was statistically significant difference in overall survival between stage III and stage IV with a p-value of 0.03.
- There was statistically insignificant difference in overall survival between stage II and stage III with a p-value of 0.23.

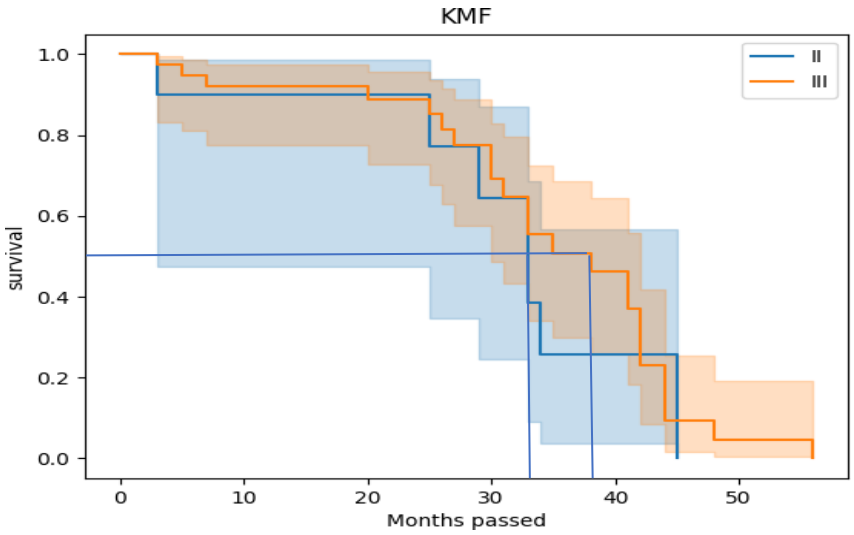


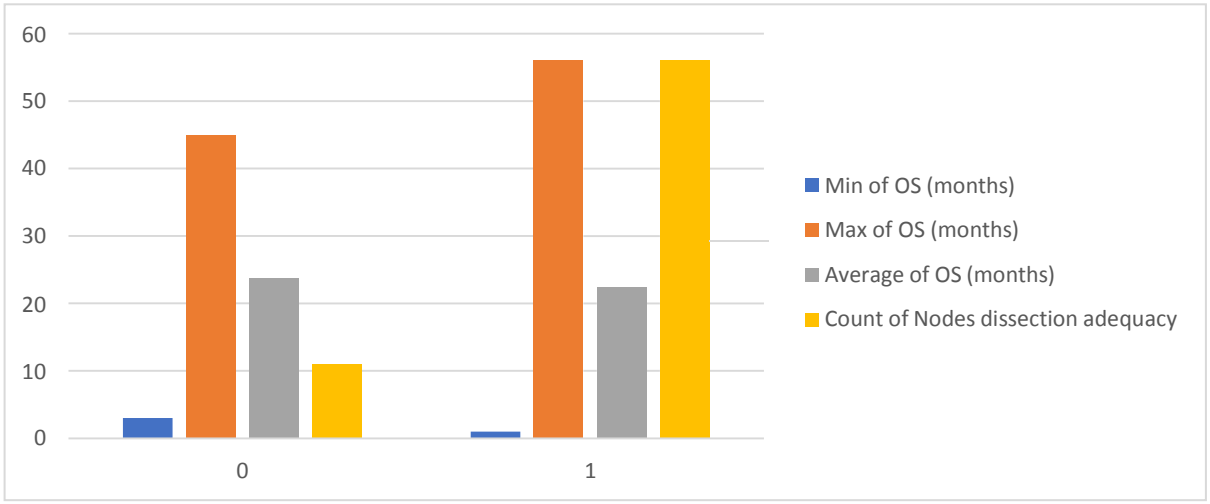
Site & Stage	Frequency	Average of OS (months)	Min of OS (months)	Max of OS (months)
I	**15**	**18.86666667**	**2**	**42**
Glottis	1	12	12	12
Hypopharynx	2	7	4	10
Lip	1	38	38	38
Maxillary sinus	1	9	9	9
Oral cavity	7	21.57142857	2	42
Supra glottis	2	18	14	22
Tonsil	1	23	23	23
II	**20**	**21.75**	**1**	**45**
Oral cavity	14	21	1	45
Parotid	1	45	45	45
Supra glottis	2	28	21	35
Tonsil	3	13.33333333	13	14
III	**19**	**17.21052632**	**3**	**42**
Glottis	2	21.5	19	24
Nasopharynx	1	7	7	7
Oral cavity	11	20.27272727	3	42
Oropharynx	2	17.5	6	29
Supra glottis	3	6.333333333	3	10
IVA	**71**	**22.16901408**	**3**	**56**
Glottis	1	8	8	8
Hypopharynx	1	12	12	12
Maxillary sinus	4	20.5	6	28
Nasopharynx	2	25	7	43
Oral cavity	47	21.0212766	3	56
Oropharynx	4	30	17	47
Parotid	2	41	37	45
Submandibular	1	34	34	34
Supra glottis	7	27.14285714	14	39
Tonsil	2	4	3	5
IVB	**3**	**11.33333333**	**5**	**15**
Nasopharynx	1	5	5	5
Oral cavity	1	14	14	14
Submandibular	1	15	15	15



28. Effect of Adequate Lymph node dissection on overall survival-

- Log rank test was done to analyze the association between lymph node dissection adequacy and overall survival (OS).
- There was no statistically significant difference found between overall survival and lymph node dissection adequacy with a p-value of 0.68.

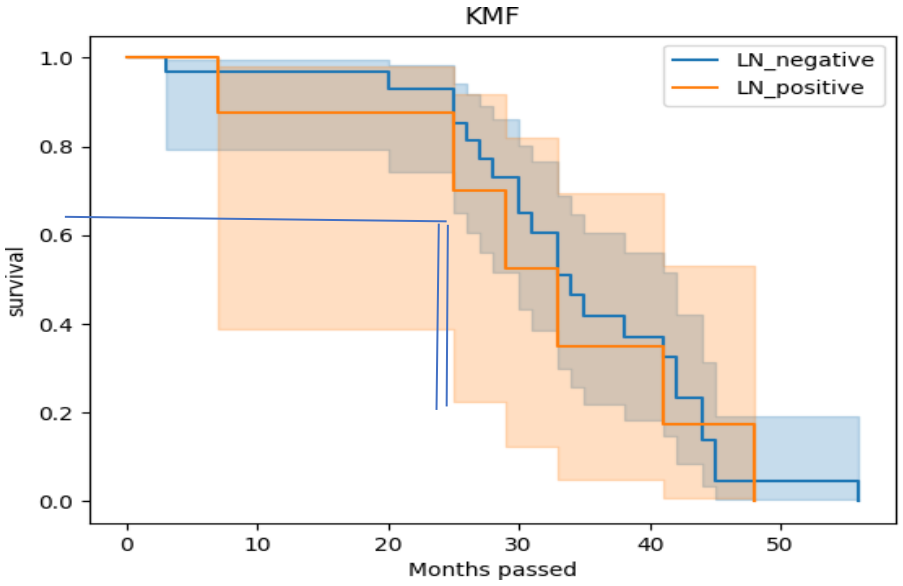


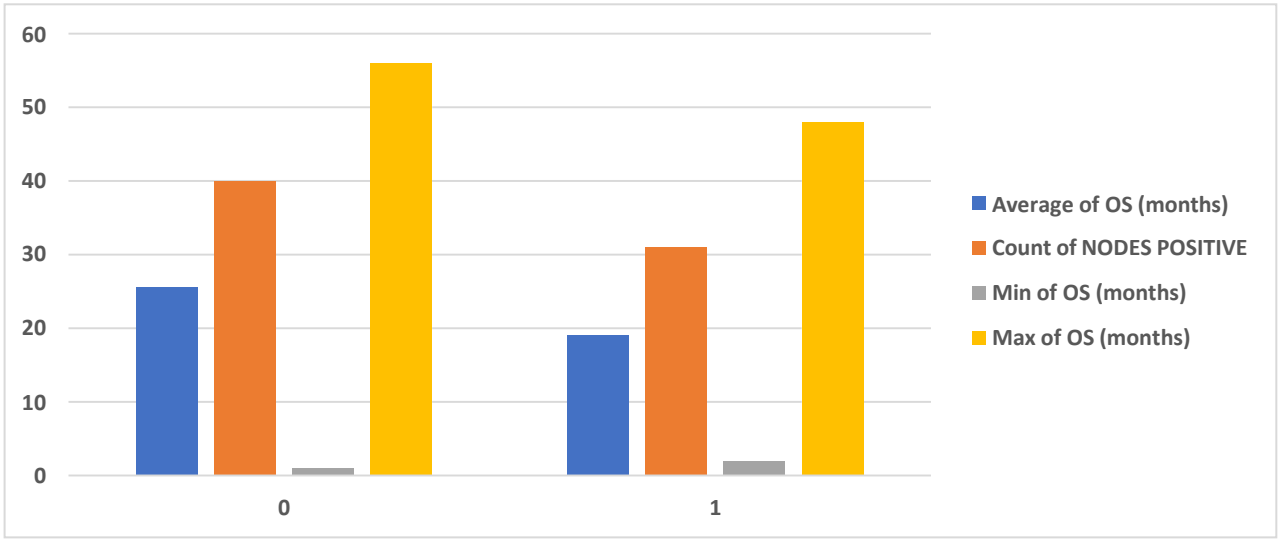


lymph node dissection adequacy	Min of OS (months)	Max of OS (months)	Average of OS (months)	Frequency
0	3	45	23.72727273	11
1	1	56	22.41071429	56
Grand Total	**1**	**56**	**22.62686567**	**67**

29. <u>Effect of node positivity on Overall Survival</u>-

- For patients who underwent surgery followed by PORT, Log rank test was done to analyze the association between lymph node positivity and overall survival (OS).
- There was no statistically significant difference found between overall survival and lymph node positivity with a p-value of 0.73.

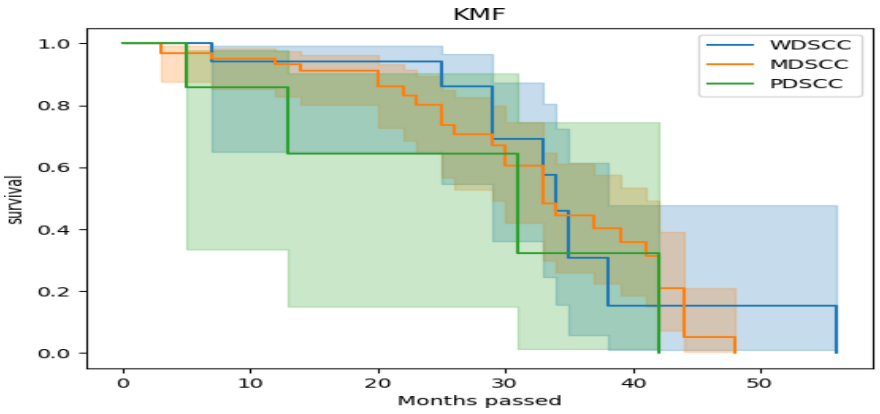


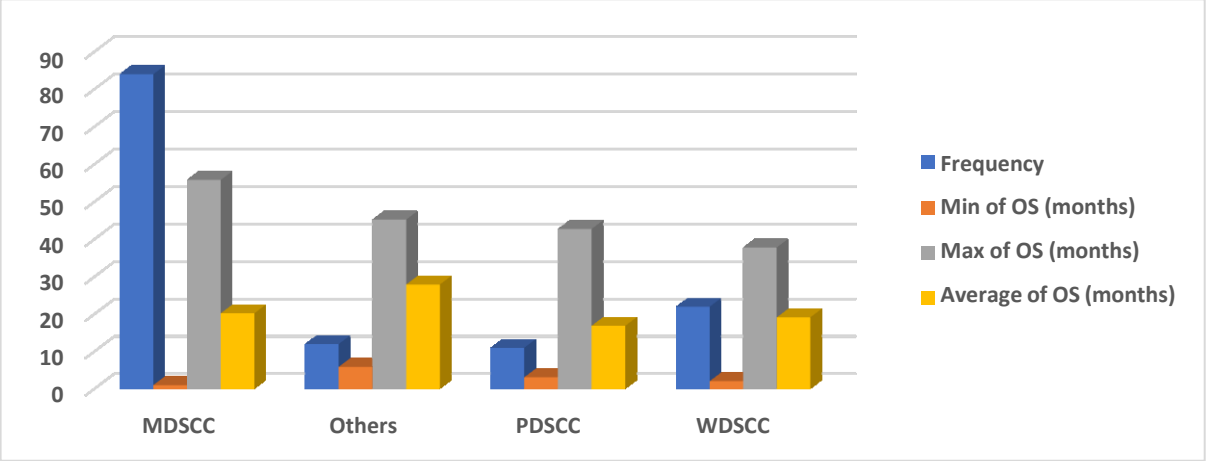


Lymph node status	Average of OS (months)	Frequency	Min of OS (months)	Max of OS (months)
0	25.63888889	40	1	56
1	19.12903226	31	2	48

30. <u>Effect of pre-op Histology on Overall Survival</u>-

- Log rank test was done to analyze the association between pre-op histology and overall survival (OS).
- There was no statistically significant difference found between overall survival of WDSCC and MDSCC with a p-value of 0.64.
- There was no statistically significant difference found between overall survival of WDSCC and PDSCC with a p-value of 0.42.
- There was no statistically significant difference found between overall survival of MDSCC and PDSCC with a p-value of 0.29.

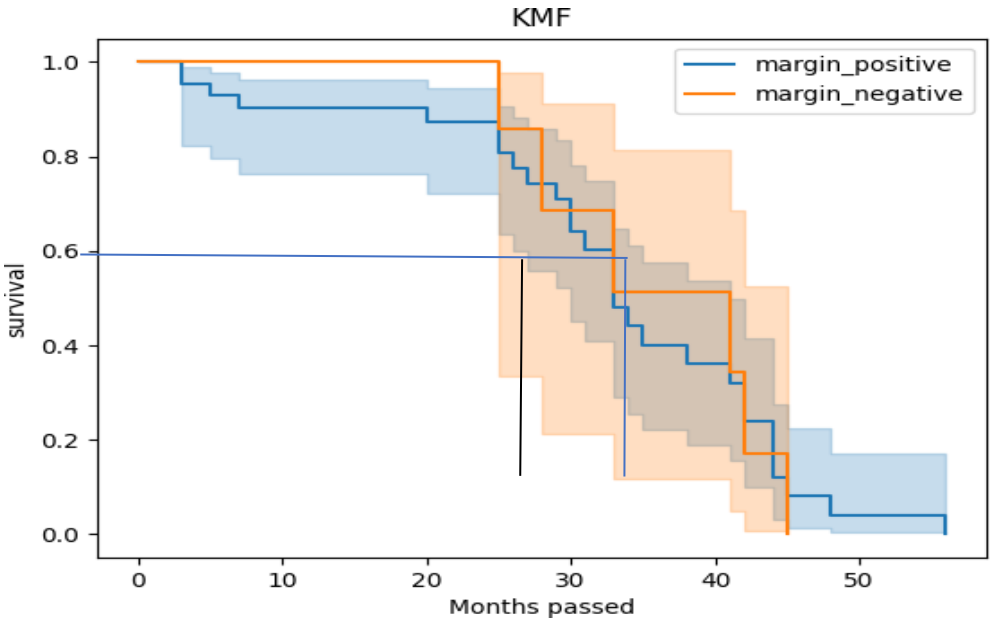


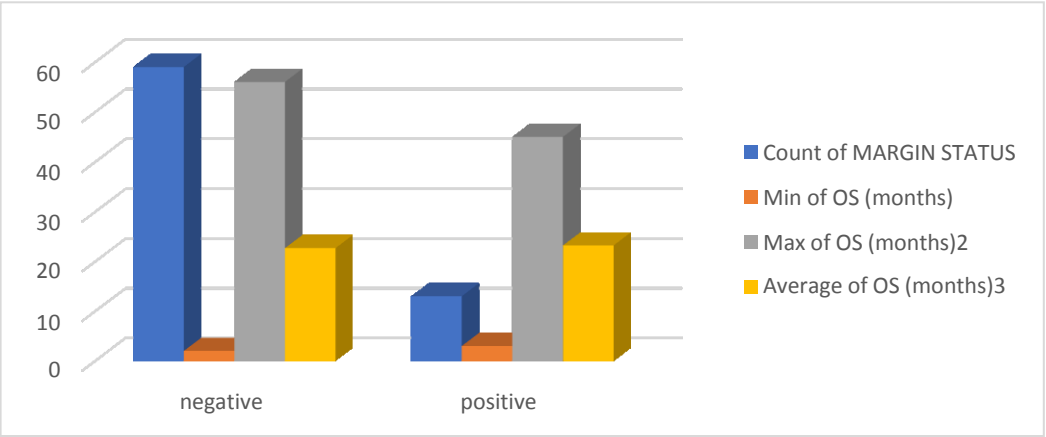


Histology	Frequency	Min of OS (months)	Max of OS (months)	Average of OS (months)
MDSCC	84	1	55.83333333	20.25079365
Others	12	5.9	45.26666667	27.96388889
PDSCC	11	3.1	42.76666667	16.92727273
WDSCC	22	2.066666667	37.83333333	19.15136364

31. <u>Effect of post-op margin status on overall survival (OS)-</u>

- Log rank test was done to analyze the association between post op margin status and overall survival (OS).
- There was no statistically significant difference found between overall survival and post op margin status with a p-value of 0.82.

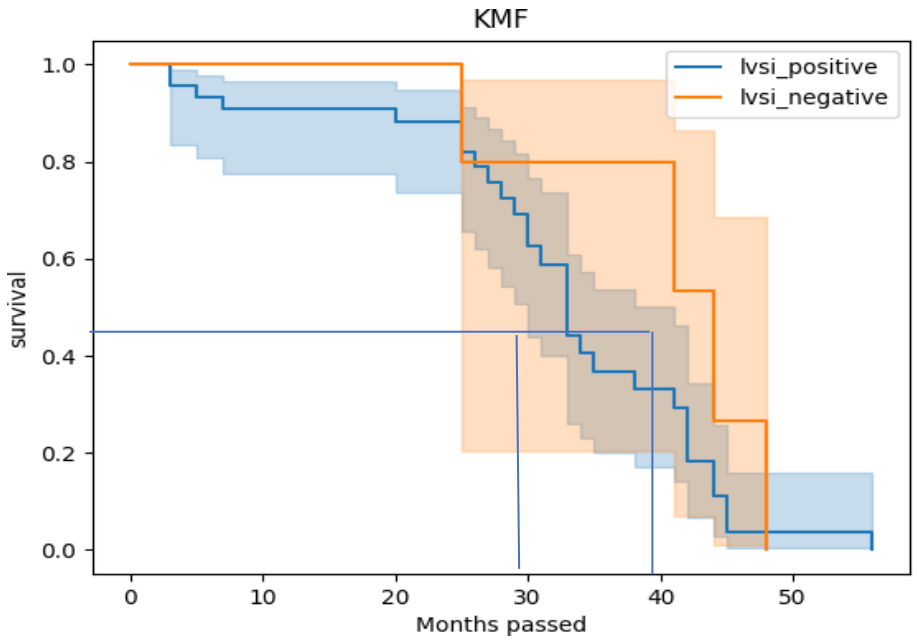


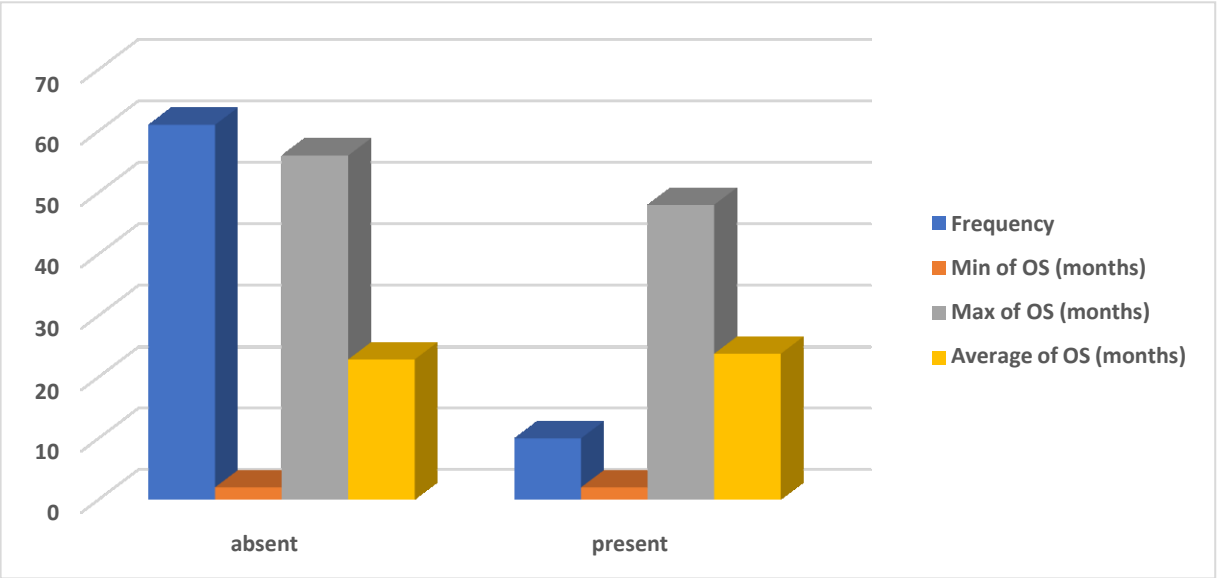


margin status	Frequency	Min of OS (months)	Max of OS (months)	Average of OS (months)
negative	59	2	56	22.67241379
positive	13	3	45	23.23076923

32. <u>Effect of LVSI on overall survival (OS)</u>-

- Log rank test was done to analyze the association between LVSI and overall survival (OS).
- There was no statistically significant difference found between overall survival and LVSI with a p-value of 0.24.

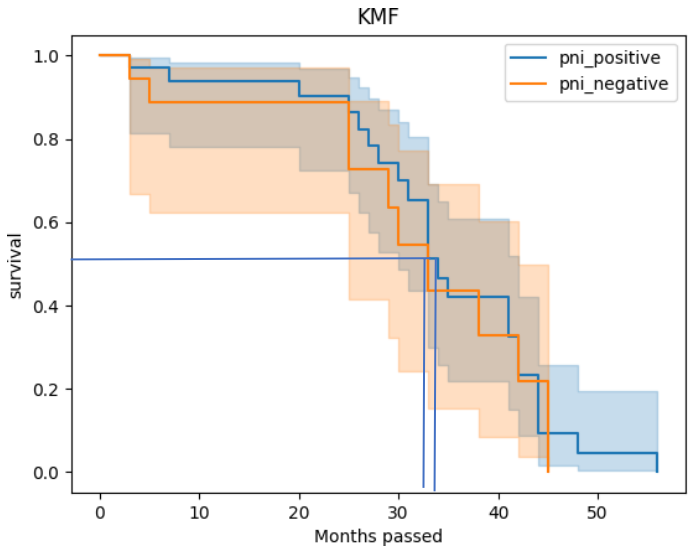


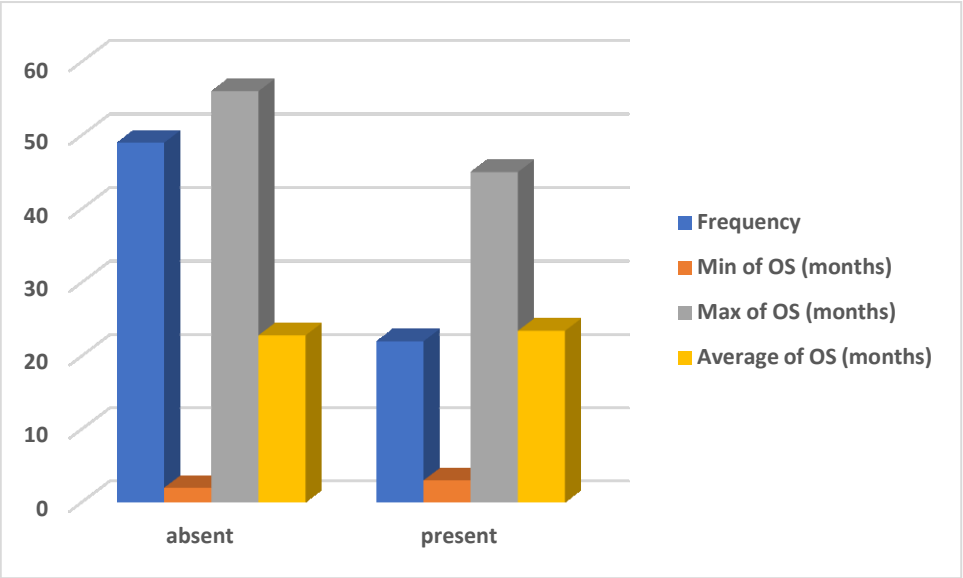


LVSI	Frequency	Min of OS (months)	Max of OS (months)	Average of OS (months)
Absent	61	2	56	22.86666667
Present	10	2	48	23.8

33. <u>Effect of PNI on Overall Survival (OS)-</u>

- Log rank test was done to analyze the association between PNI and overall survival (OS).
- There was no statistically significant difference found between overall survival and PNI with a p-value of 0.63.

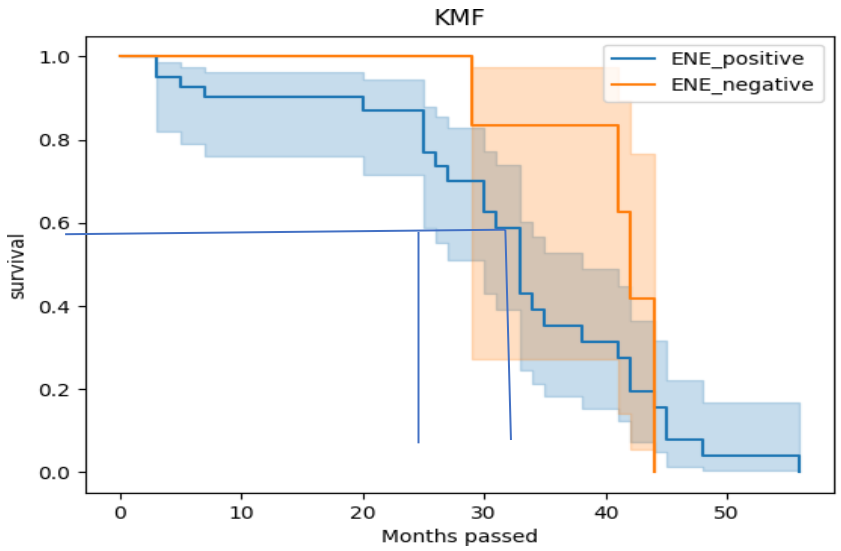


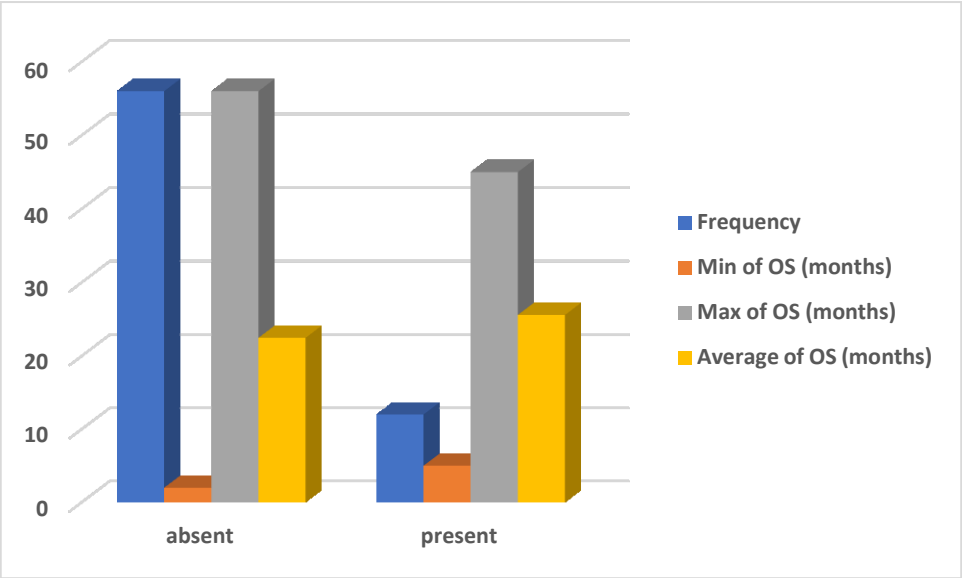


PNI	Frequency	Min of OS (months)	Max of OS (months)	Average of OS (months)
Absent	49	2	56	22.81632653
Present	22	3	45	23.42857143

34. Effect of ENE on Overall Survival (OS)-

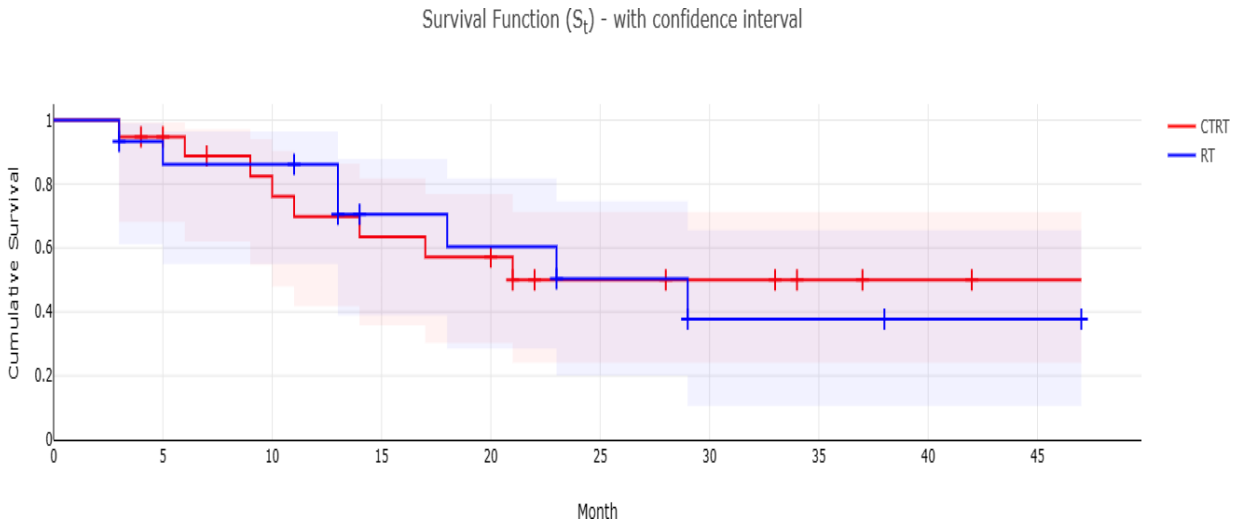
- Log rank test was done to analyze the association between ENE and overall survival (OS).
- There was no statistically significant difference found between overall survival and ENE with a p-value of 0.38.

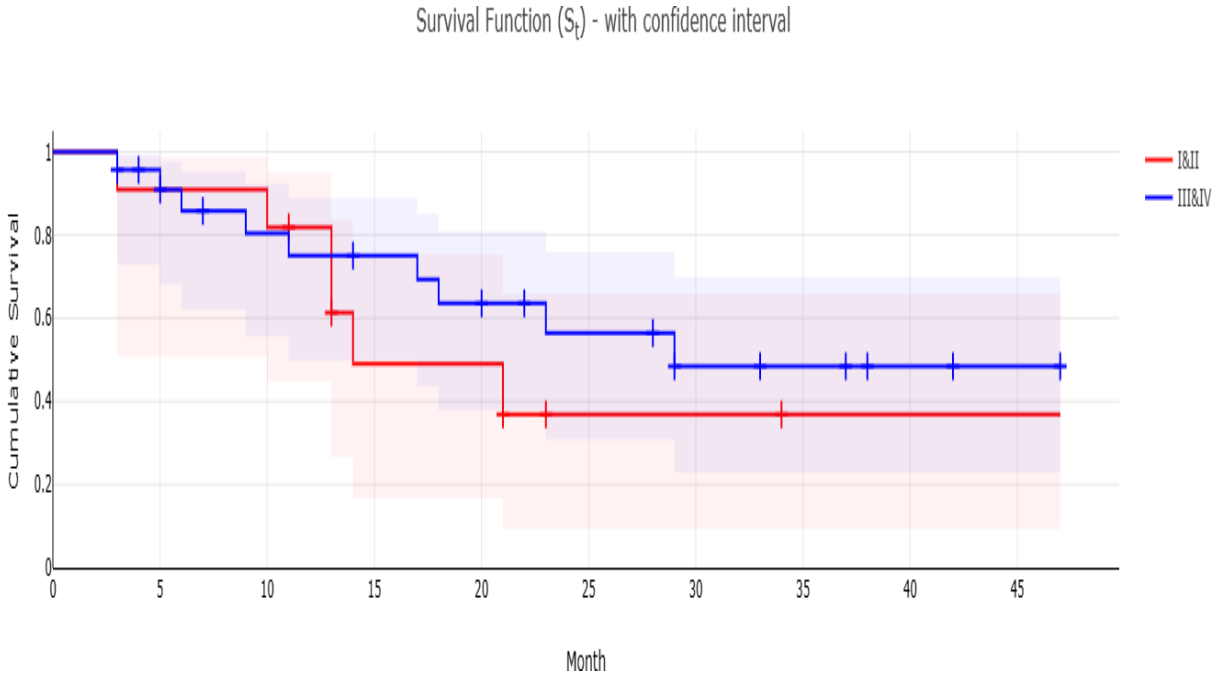




ENE	Frequency	Min of OS (months)	Max of OS (months)	Average of OS (months)
absent	56	2	56	22.47272727
present	12	5	45	25.58333333

35. <u>OVERALL SURVIVAL OF PHARYNGEAL TUMOR PATIENTS TREATED WITH EITHER RADICAL RT OR CTRT</u> :-



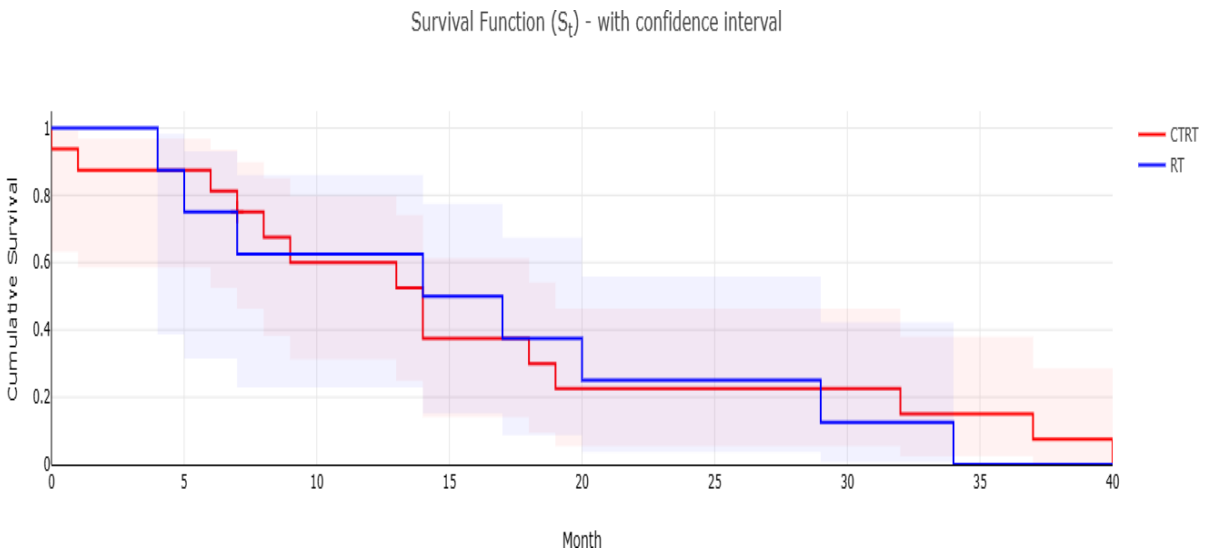


- The patients who were treated with either radical RT or CTRT were analyzed for overall survival analysis by Kaplan Meier Curve.
- Stage I & II patients were having median OS of 14 months while stage III and IV were having median OS of 29 months with a p-value of 0.42.

Site	Count of IS CONCURRENT CHEMO GIVEN	Min of OS (months)	Max of OS (months)	Average of OS (months)
Glottis	**4**	**8.166666667**	**23.93333333**	**15.68333333**
no surgery	**3**	**11.7**	**23.93333333**	**18.18888889**
no chemo	3	11.7	23.93333333	18.18888889
surgery	**1**	**8.166666667**	**8.166666667**	**8.166666667**
CTRT	1	8.166666667	8.166666667	8.166666667
Hypopharynx	**3**	**3.6**	**11.83333333**	**8.555555553**
no surgery	**3**	**3.6**	**11.83333333**	**8.555555553**
CTRT	2	10.23333333	11.83333333	11.03333333
no chemo	1	3.6	3.6	3.6
Lip	**1**	**37.83333333**	**37.83333333**	**37.83333333**
surgery	**1**	**37.83333333**	**37.83333333**	**37.83333333**
no chemo	1	37.83333333	37.83333333	37.83333333
Maxillary sinus	**5**	**5.9**	**28.3**	**18.05333333**
no surgery	**1**	**19.66666667**	**19.66666667**	**19.66666667**
no chemo	1	19.66666667	19.66666667	19.66666667

surgery	**4**	**5.9**	**28.3**	**17.65**
CTRT	1	8.666666667	8.666666667	8.666666667
no chemo	3	5.9	28.3	20.64444444
Nasopharynx	**5**	**1.533333333**	**42.76666667**	**12.81333333**
no surgery	**3**	**5.4**	**42.76666667**	**18.54444445**
CTRT	3	5.4	42.76666667	18.54444445
surgery	**2**	**1.533333333**	**6.9**	**4.216666667**
CTRT	1	6.9	6.9	6.9
no chemo	1	1.533333333	1.533333333	1.533333333
Oral cavity	**83**	**1**	**55.83333333**	**20.82922764**
No surgery	**24**	**1**	**40.93333333**	**16.26797101**
CTRT	16	1	40.93333333	15.96888889
no chemo	8	4.666666667	34.5	16.82875
surgery	**59**	**2.066666667**	**55.83333333**	**22.60734463**
CTRT	19	2.066666667	43.63333333	25.38947368
no chemo	40	2.066666667	55.83333333	21.28583333
Oropharynx	**12**	**3.1**	**47.06666667**	**18.83888889**
no surgery	**12**	**3.1**	**47.06666667**	**18.83888889**
CTRT	6	3.1	33.76666667	18.31111111
no chemo	6	5.566666667	47.06666667	19.36666667
Parotid	**3**	**37.06666667**	**45.26666667**	**42.52222222**
no surgery	**1**	**37.06666667**	**37.06666667**	**37.06666667**
no chemo	1	37.06666667	37.06666667	37.06666667
surgery	**2**	**45.23333333**	**45.26666667**	**45.25**
no chemo	2	45.23333333	45.26666667	45.25
Submandibular	**2**	**15.1**	**34.33333333**	**24.71666667**
surgery	**2**	**15.1**	**34.33333333**	**24.71666667**
CTRT	1	15.1	15.1	15.1
no chemo	1	34.33333333	34.33333333	34.33333333
Supra-glottis	**15**	**3**	**38.8**	**21.50952381**
no surgery	**14**	**3**	**38.8**	**21.51538462**
CTRT	8	6.1	37.46666667	20.61666667
no chemo	6	3	38.8	22.95333333
surgery	**1**	**21.43333333**	**21.43333333**	**21.43333333**
CTRT	1	21.43333333	21.43333333	21.43333333
Grand Total	**133**	**1**	**55.83333333**	**20.55544529**

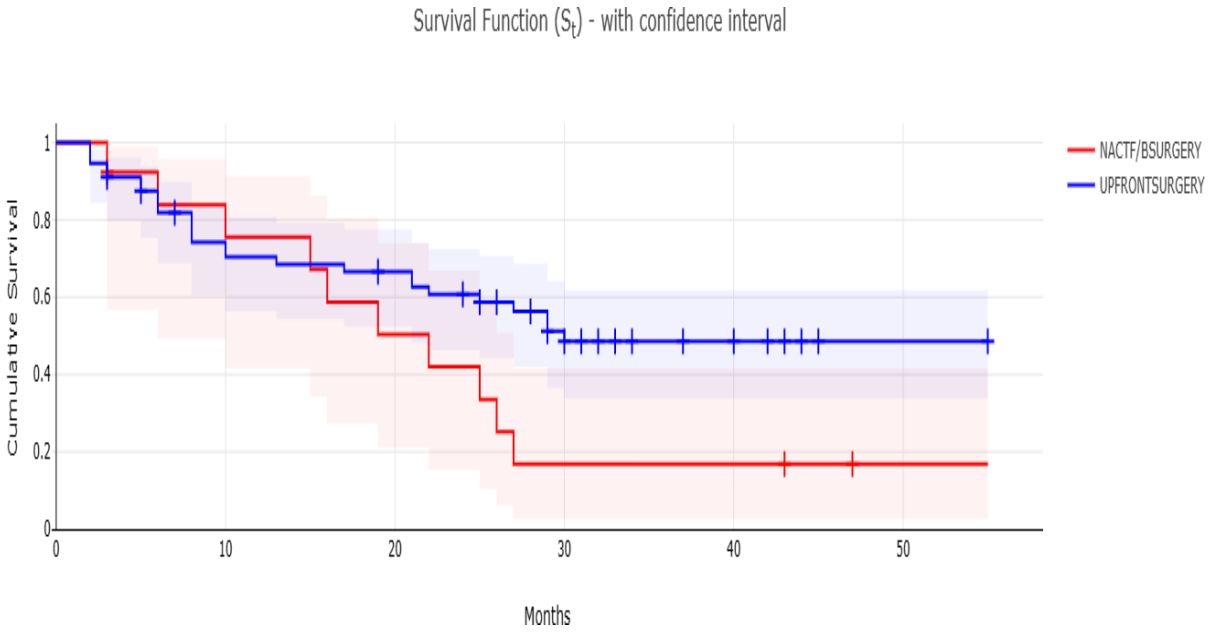
36. SURVIVAL ANALYSIS IN INOPERABLE ORAL CAVITY TUMORS-



- In patients with inoperable oral cavity tumors, median OS was calculated using Kaplan Meier curve. Median OS was found to be 13 months with p value of 0.77.

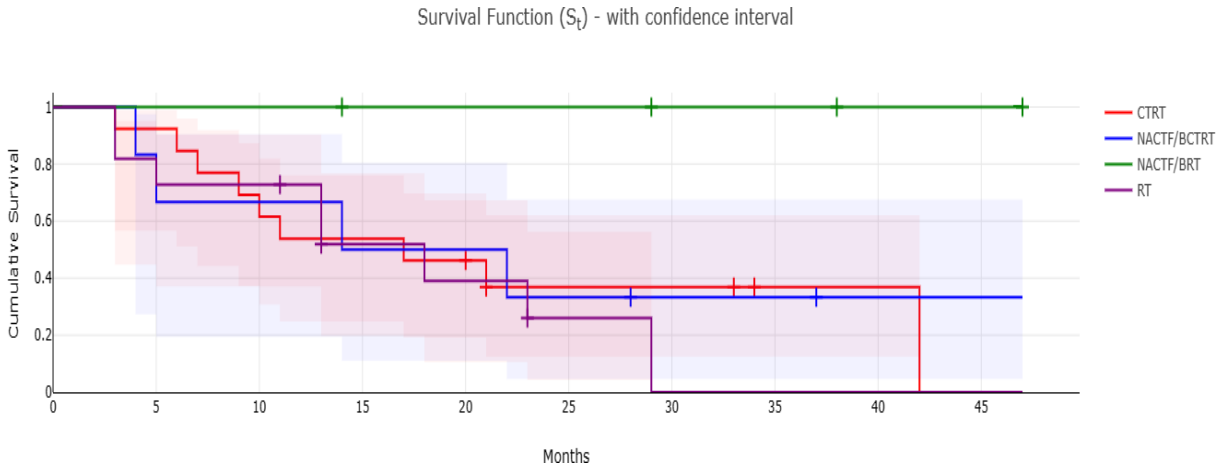
37. Effect of Induction Chemotherapy on Overall survival In HNC-

37.1 Effect of Induction Chemotherapy in Operated HNC-

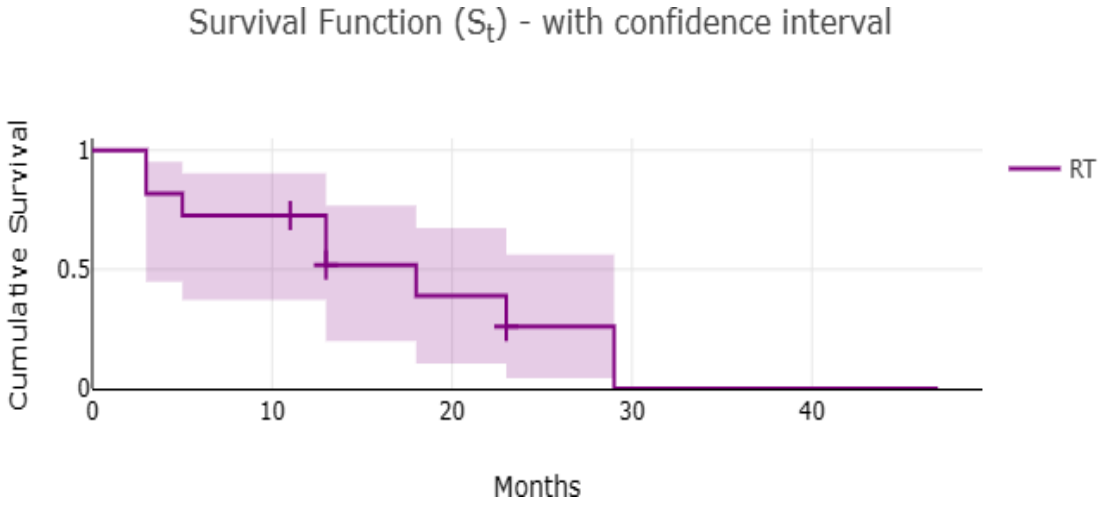


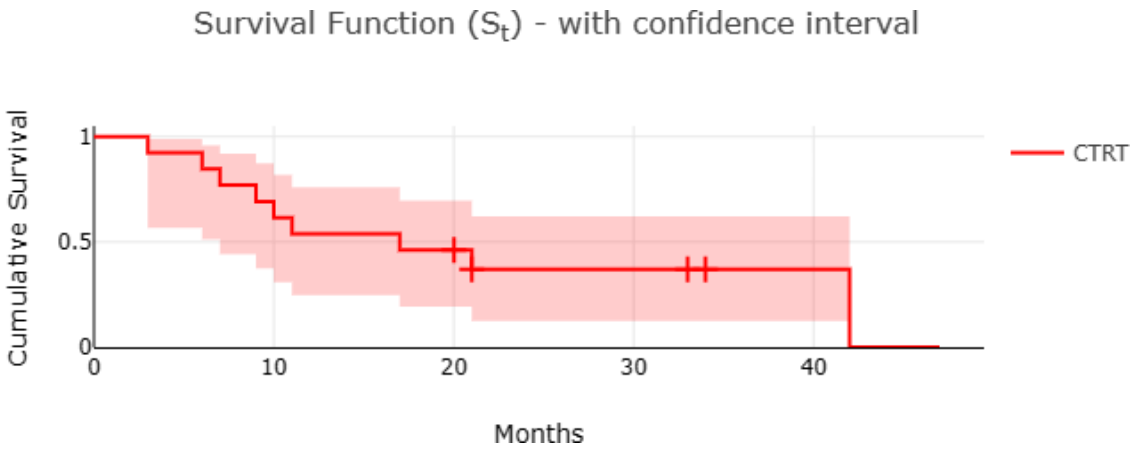
- Survival Analysis of the patients with operable subsites of HNC who received NACT or who underwent upfront surgery was done using Kaplan Meier analysis and median OS of 23 months found to be in patients who underwent NACT while median OS of 38 months who underwent upfront surgery. (p value= 0.15)

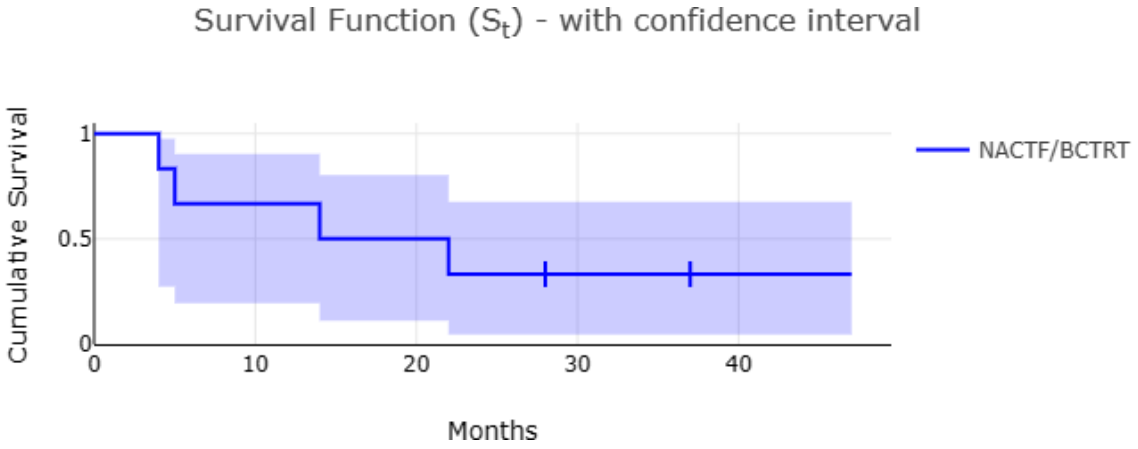
37.2 Effect of NACT in Pharyngeal tumor treated with Radical RT or CTRT –



- Effect of NACT in pharyngeal tumors who got treated wither Radical RT alone or CTRT was analyzed with Kaplan Meier Survival Analysis. Median OS in RT alone arm was found to be 13 months, 14 months in CTRT arm while 17 months in NACT f/b CTRT arm. (p value=0.07)





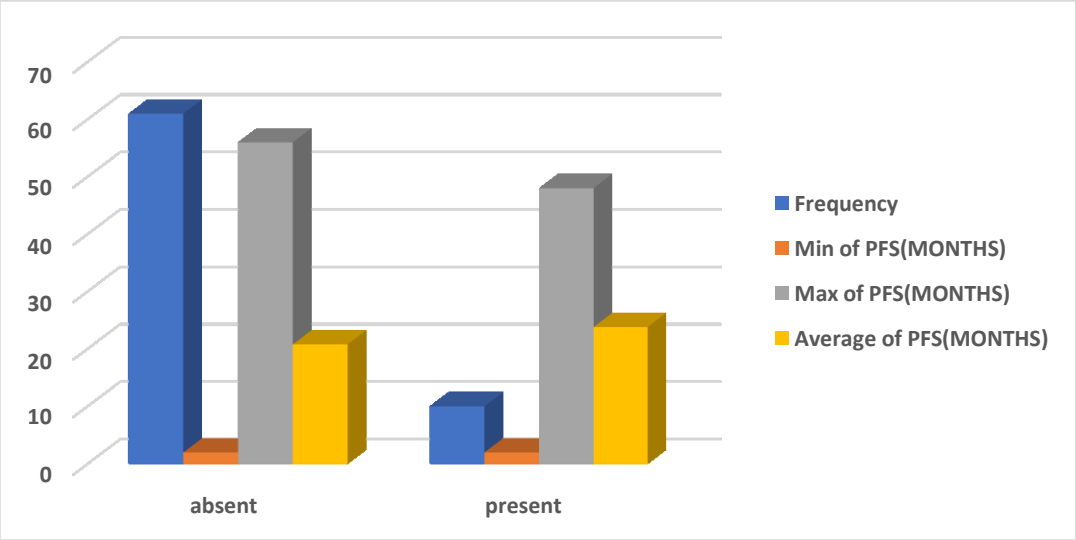


Site	Count of RECEIVED NACT?	Min of OS (months)	Max of OS (months)	Average of OS (months)
Glottis	**4**	**8.166666667**	**23.93333333**	**15.68333333**
no surgery	**3**	**11.7**	**23.93333333**	**18.18888889**
no NACT	3	11.7	23.93333333	18.18888889
surgery	**1**	**8.166666667**	**8.166666667**	**8.166666667**
no NACT	1	8.166666667	8.166666667	8.166666667
Hypopharynx	**2**	**3.6**	**10.23333333**	**6.916666665**
no surgery	**2**	**3.6**	**10.23333333**	**6.916666665**
no NACT	2	3.6	10.23333333	6.916666665
Lip	**1**	**37.83333333**	**37.83333333**	**37.83333333**
surgery	**1**	**37.83333333**	**37.83333333**	**37.83333333**
no NACT	1	37.83333333	37.83333333	37.83333333
Maxillary sinus	**5**	**5.9**	**28.3**	**18.05333333**

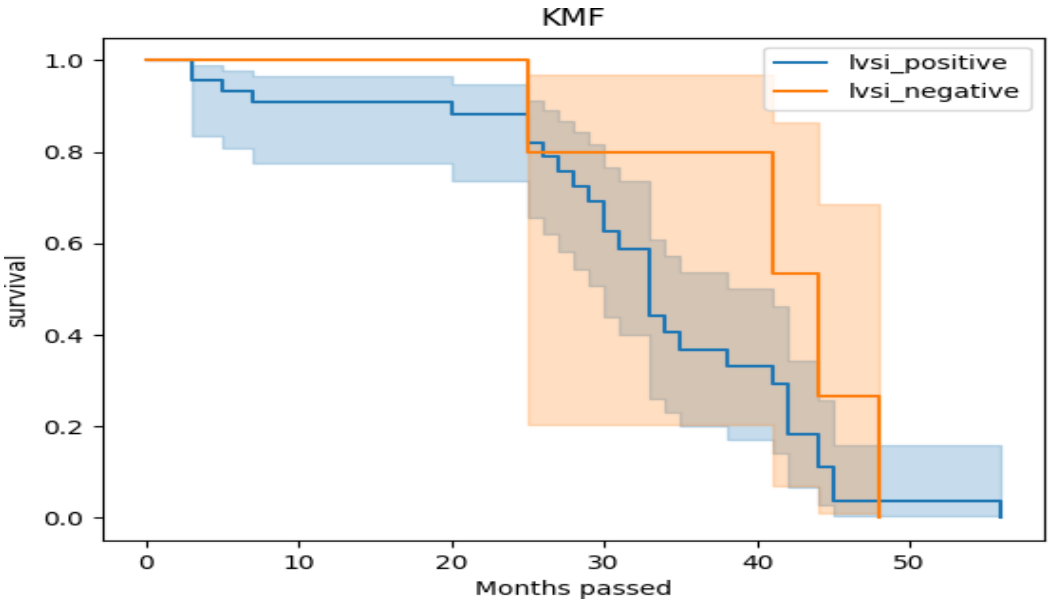
no surgery	**1**	**19.66666667**	**19.66666667**	**19.66666667**
NACT given	1	19.66666667	19.66666667	19.66666667
surgery	**4**	**5.9**	**28.3**	**17.65**
NACT given	1	27.73333333	27.73333333	27.73333333
no NACT	3	5.9	28.3	14.28888889
Nasopharynx	**4**	**5.4**	**42.76666667**	**15.63333333**
no surgery	**3**	**5.4**	**42.76666667**	**18.54444445**
NACT given	1	5.4	5.4	5.4
no NACT	2	7.466666667	42.76666667	25.11666667
surgery	**1**	**6.9**	**6.9**	**6.9**
no NACT	1	6.9	6.9	6.9
Oral cavity	**81**	**1**	**55.83333333**	**20.724125**
no surgery	**24**	**1**	**40.93333333**	**16.26797101**
NACT given	11	1	37.46666667	14.93030303
no NACT	13	4.666666667	40.93333333	17.49416667
surgery	**57**	**2.066666667**	**55.83333333**	**22.52222222**
NACT given	11	3.066666667	47.86666667	20.60606061
no NACT	46	2.066666667	55.83333333	22.98043478
Oropharynx	**12**	**3.1**	**47.06666667**	**18.83888889**
no surgery	**12**	**3.1**	**47.06666667**	**18.83888889**
NACT given	4	4.666666667	47.06666667	25.73333333
no NACT	8	3.1	33.76666667	15.39166667
Parotid	**3**	**37.06666667**	**45.26666667**	**42.52222222**
no surgery	**1**	**37.06666667**	**37.06666667**	**37.06666667**
no NACT	1	37.06666667	37.06666667	37.06666667
surgery	**2**	**45.23333333**	**45.26666667**	**45.25**
no NACT	2	45.23333333	45.26666667	45.25
Submandibular	**2**	**15.1**	**34.33333333**	**24.71666667**
surgery	**2**	**15.1**	**34.33333333**	**24.71666667**
NACT given	1	15.1	15.1	15.1
no NACT	1	34.33333333	34.33333333	34.33333333
Supra-glottis	**15**	**3**	**38.8**	**21.50952381**
no surgery	**14**	**3**	**38.8**	**21.51538462**
NACT given	6	14.06666667	38.8	26.74
no NACT	8	3	34.66666667	18.25
surgery	**1**	**21.43333333**	**21.43333333**	**21.43333333**
no NACT	1	21.43333333	21.43333333	21.43333333

38. <u>Effect of LVSI on Progression free survival (PFS)</u>-

- Log rank test was done to analyze the association between LVSI and progression free survival (PFS).
- There was no statistically significant difference found between progression free survival and LVSI with a p-value of 0.14.

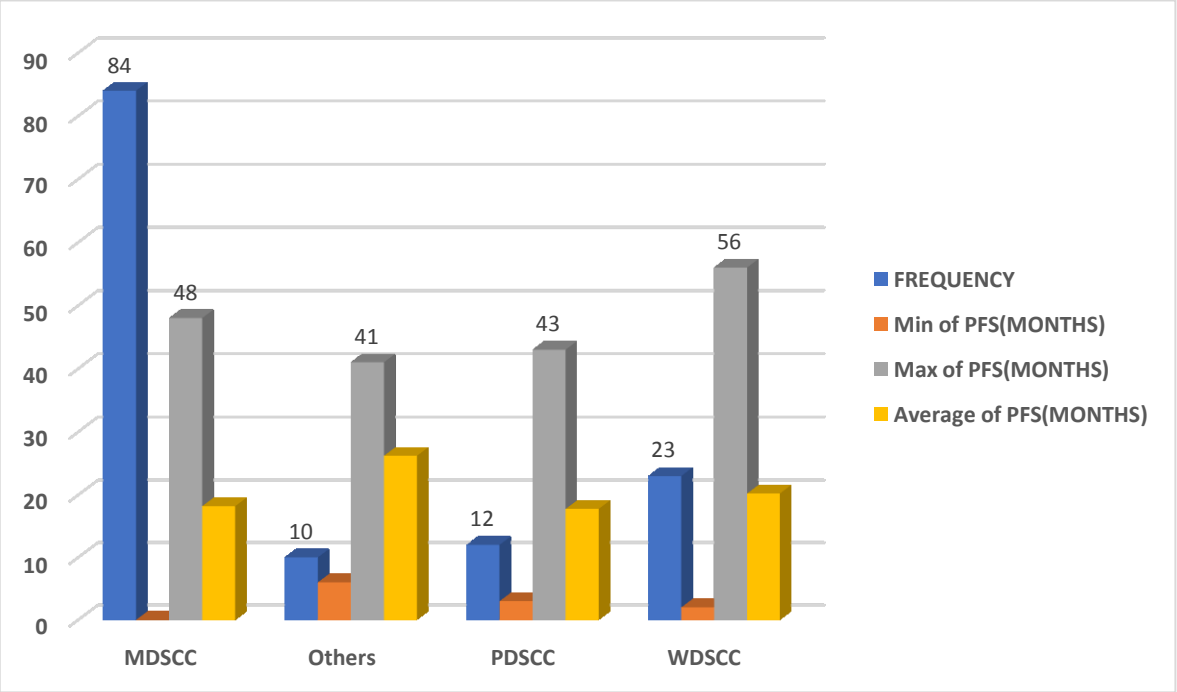


LVSI	Frequency	Min of PFS(MONTHS)	Max of PFS(MONTHS)	Average of PFS(MONTHS)
absent	61	2	56	20.78688525
present	10	2	48	23.8

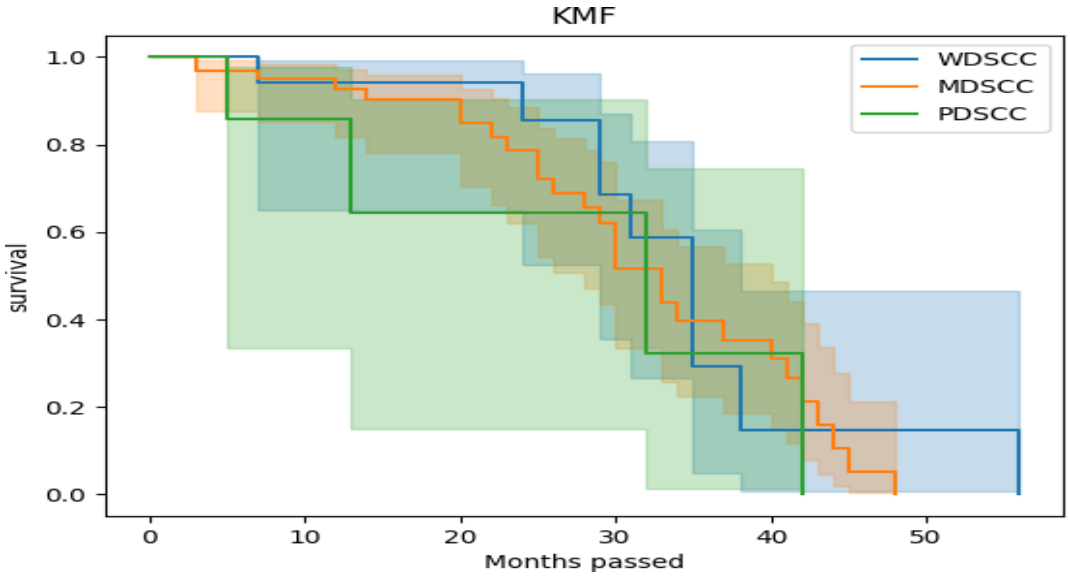


39. <u>Effect of Tumor Histology on PFS</u>-

- Log rank test was done to analyze the association between pre-op histology and progression free survival (PFS).
- There was no statistically significant difference found between PFS of WDSCC and MDSCC with a p-value of 0.47.
- There was no statistically significant difference found between PFS of WDSCC and PDSCC with a p-value of 0.46.
- There was no statistically significant difference found between PFS of MDSCC and PDSCC with a p-value of 0.39.

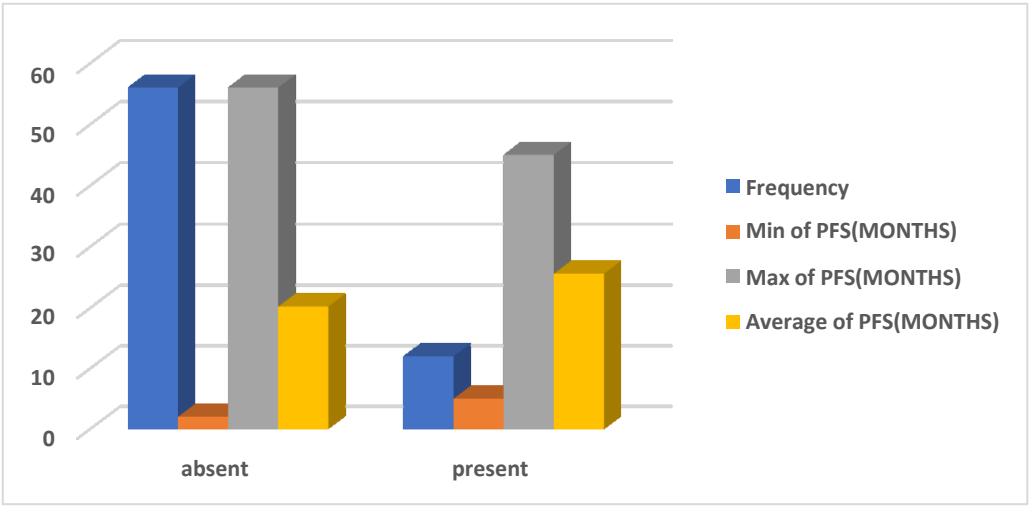


HISTOLOGY	FREQUENCY	Min of PFS (MONTHS)	Max of PFS(MONTHS)	Average of PFS(MONTHS)
MDSCC	84	0	48	18.19047619
Others	10	6	41	26.2
PDSCC	12	3	43	17.75
WDSCC	23	2	56	20.2173913

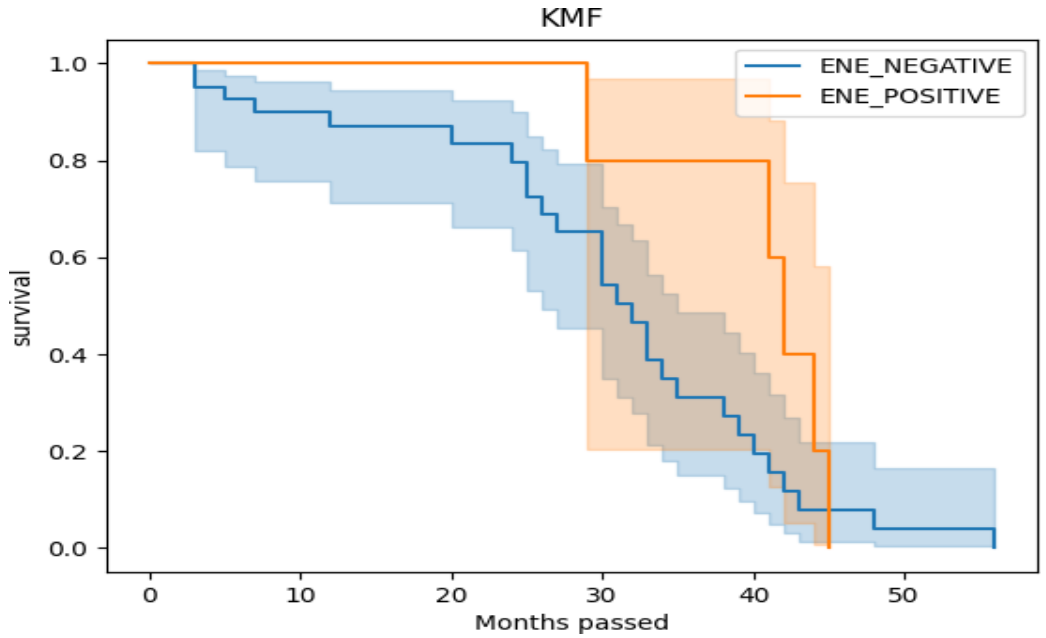


40. <u>Effect of ENE on PFS</u>-

- Log rank test was done to analyze the association between ENE and progression free survival (PFS).
- There was no statistically significant difference found between progression free survival and ENE with a p-value of 0.13.

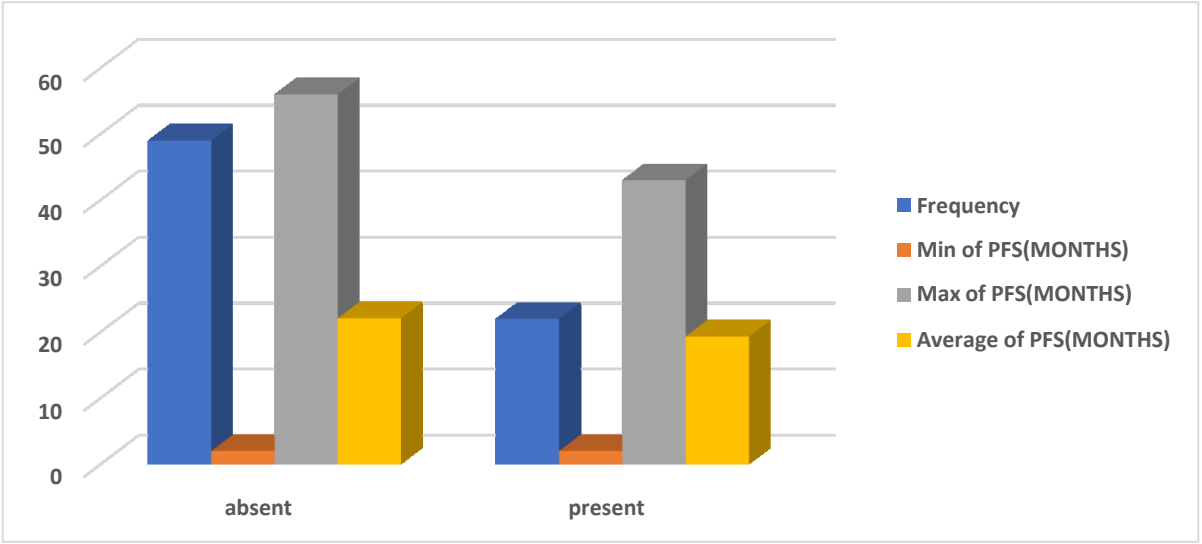


ENE	Frequency	Min of PFS(MONTHS)	Max of PFS(MONTHS)	Average of PFS(MONTHS)
absent	56	2	56	20.21428571
present	12	5	45	25.58333333

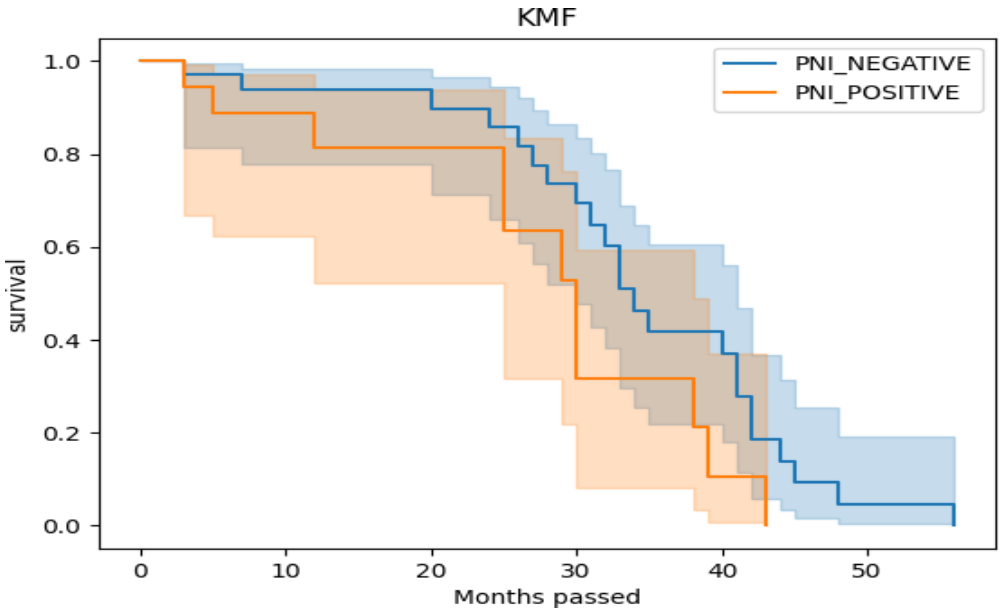


41. <u>Effect of PNI on PFS</u>-

- Log rank test was done to analyze the association between PNI and progression free survival (PFS).
- There was no statistically significant difference found between progression free survival and PNI with a p-value of 0.07.

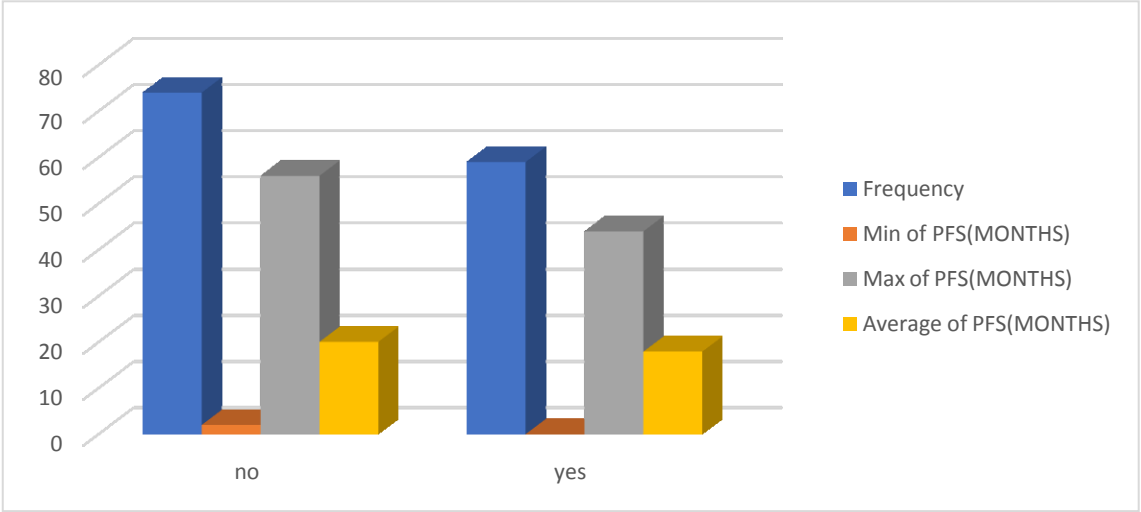


PNI	Frequency	Min of PFS(MONTHS)	Max of PFS (MONTHS)	Average of PFS(MONTHS)
absent	49	2	56	22.06122449
present	22	2	43	19.31818182

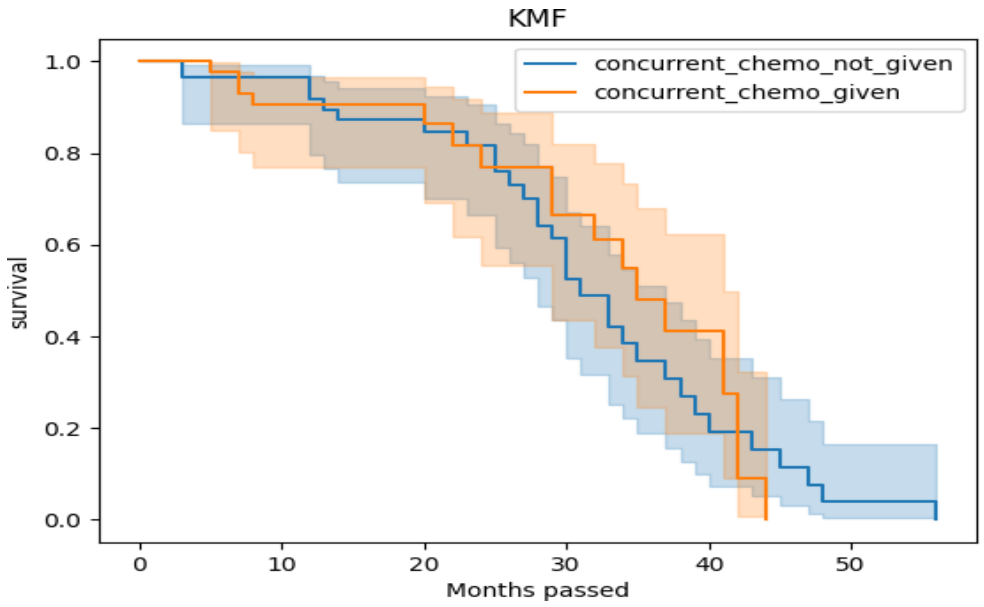


42. <u>Effect of concurrent chemotherapy on PFS</u>-

- Log rank test was done to analyze the association between concurrent chemotherapy and progression free survival (PFS).
- There was no statistically significant difference found between progression free survival and concurrent chemotherapy with a p-value of 0.8.

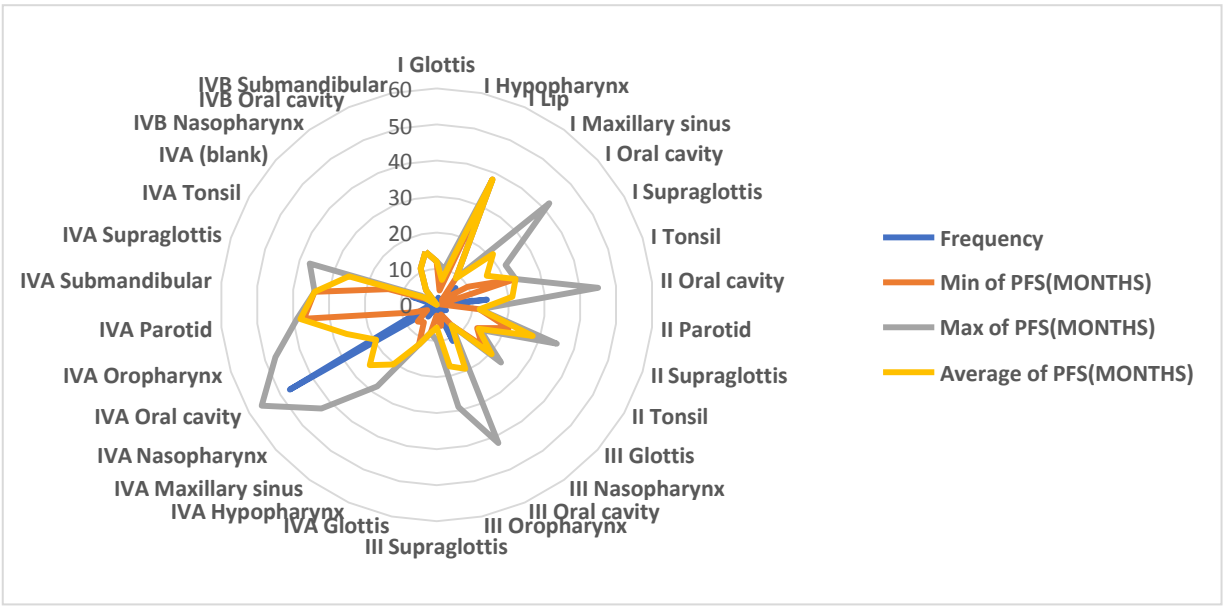


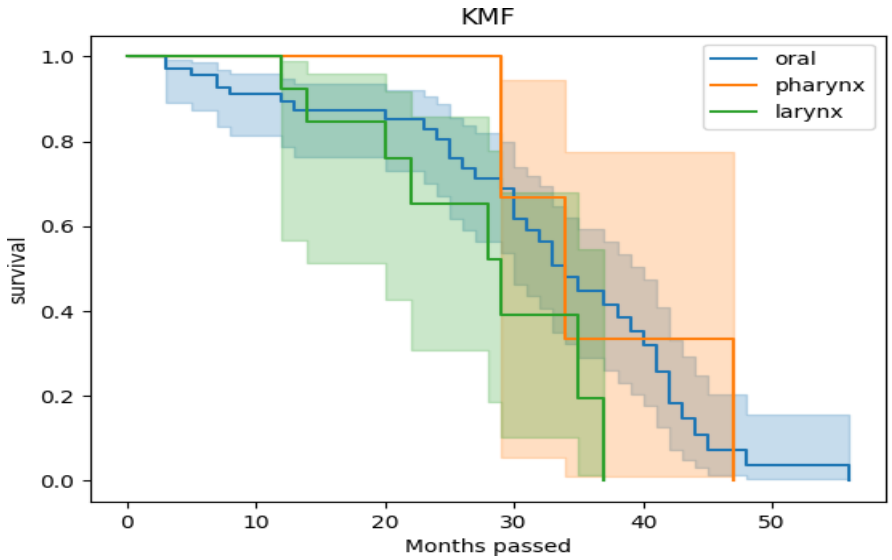
Concurrent chemo	Frequency	Min of PFS(MONTHS)	Max of PFS(MONTHS)	Average of PFS(MONTHS)
no	74	2	56	20.06849315
yes	59	0	44	17.94915254



43. <u>Stage wise Progression free survival analysis</u>-

- Log rank test was done to analyze the association between stages of head and neck cancer and progression free survival (PFS).
- There was statistically insignificant difference in PFS between stage III and stage IV with a p-value of 0.1.
- There was statistically insignificant difference in PFS between stage II and stage III with a p-value of 0.54.



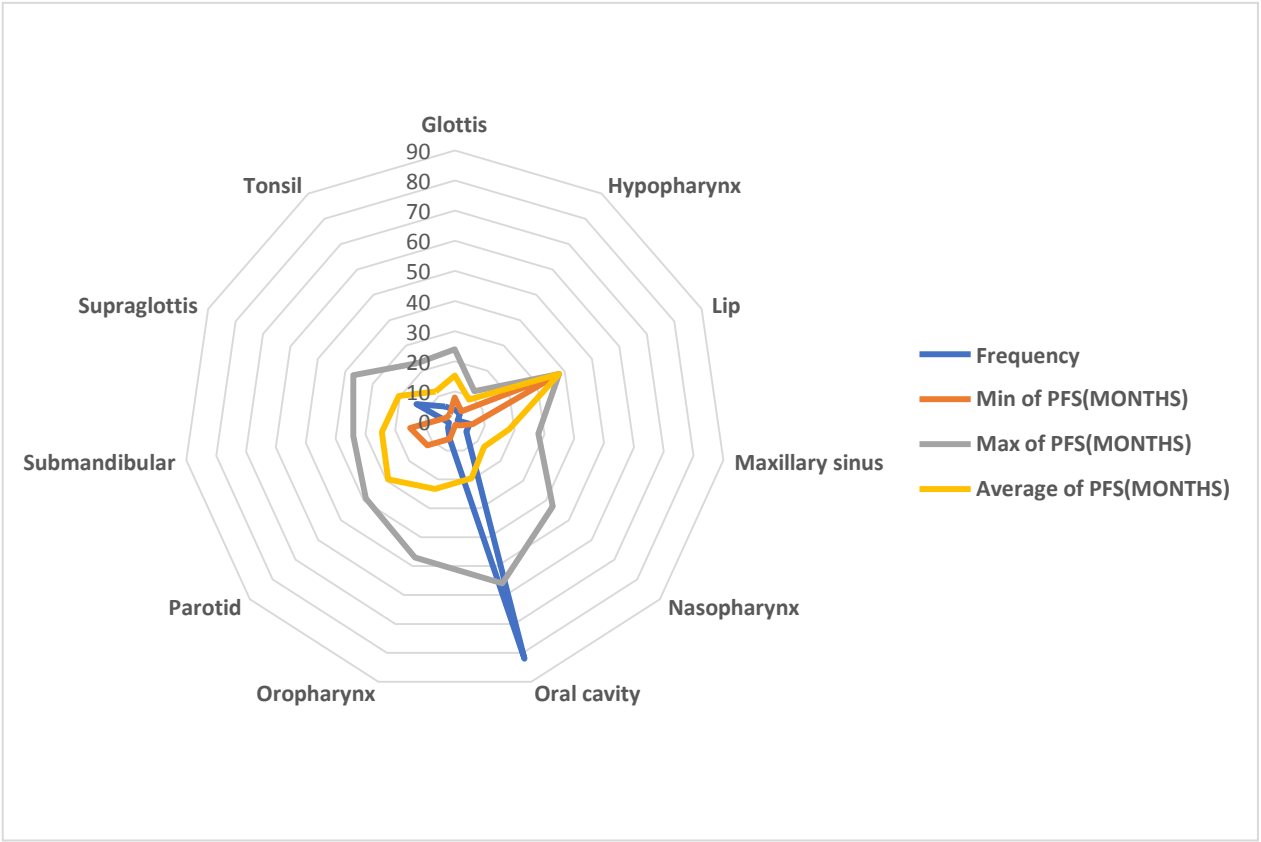


Stage & Site	Frequency	Min of PFS (MONTHS)	Max of PFS (MONTHS)	Average of PFS(MONTHS)
I	**15**	**2**	**42**	**18.33333333**
Glottis	1	12	12	12
Hypopharynx	2	4	10	7
Lip	1	38	38	38
Maxillary sinus	1	9	9	9
Oral cavity	7	2	42	21
Supra glottis	2	10	22	16
Tonsil	1	23	23	23
II	**20**	**1**	**45**	**20.15**
Oral cavity	14	1	45	21.07142857
Parotid	1	12	12	12
Supra glottis	2	21	35	28
Tonsil	3	13	14	13.33333333
III	**19**	**3**	**42**	**16.63157895**
Glottis	2	17	24	20.5
Nasopharynx	1	7	7	7
Oral cavity	11	3	42	19.45454545
Oropharynx	2	6	29	17.5
Supra glottis	3	3	10	6.333333333
IVA	**71**	**0**	**56**	**20.36111111**
Glottis	1	8	8	8
Hypopharynx	1	12	12	12
Maxillary sinus	4	6	28	20.5
Nasopharynx	2	7	43	25
Oral cavity	47	3	56	19.40425532
Oropharynx	4	7	47	26.25

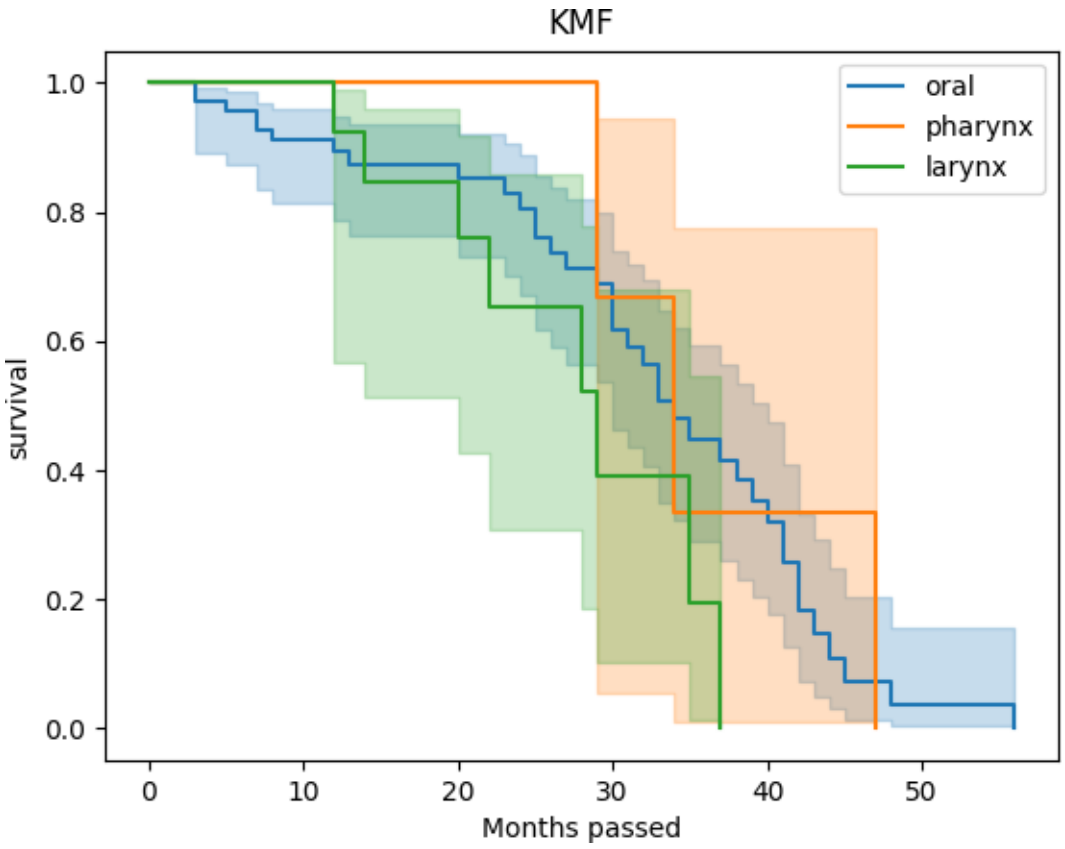
Parotid	2	37	39	38
Submandibular	1	34	34	34
Supra glottis	7	14	37	25.57142857
Tonsil	2	3	5	4
(blank)		0	0	0
IVB	**3**	**5**	**15**	**10.33333333**
Nasopharynx	1	5	5	5
Oral cavity	1	11	11	11
Submandibular	1	15	15	15

44. Site wise Progression free Survival Analysis-

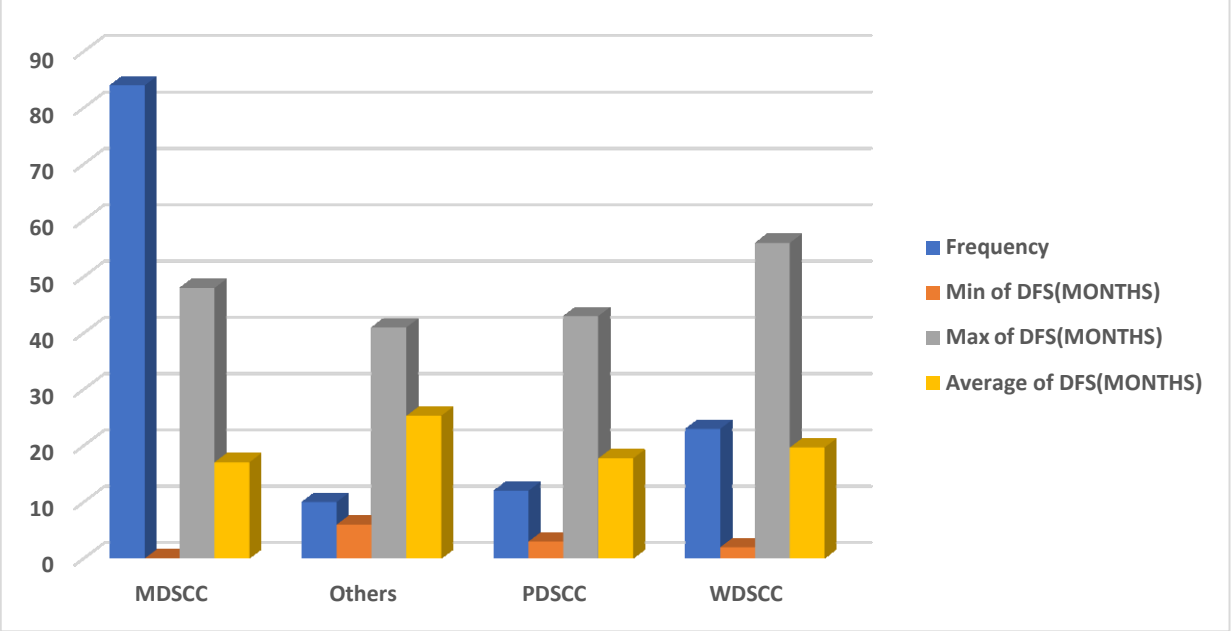
- Log rank test was done to analyze the association between different subsites of head and neck cancer and PFS.
- There was no statistically significant difference found between PFS of oral cavity tumors and larynx tumors, p-value was found to be 0.12.
- There was no statistically significant difference found between PFS of oral cavity tumors and pharynx tumors, p-value was found to be 0.59.
- There was no statistically significant difference found between PFS of larynx and pharynx tumors, p-value was found to be 0.27.



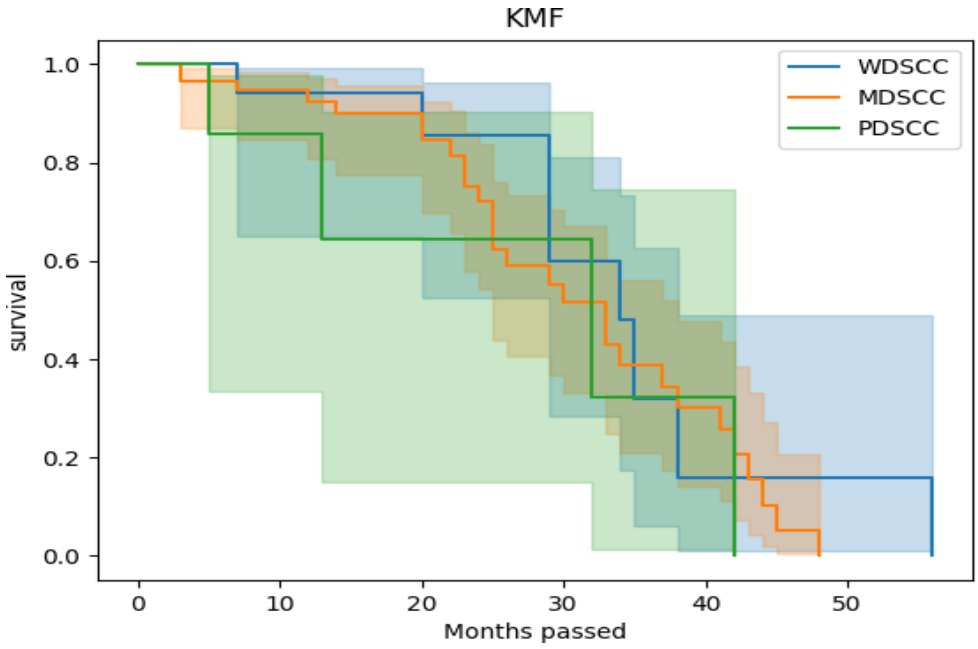
Subsite	Frequency	Min of PFS (MONTHS)	Max of PFS (MONTHS)	Average of PFS (MONTHS)
Glottis	4	8	24	15.25
Hypopharynx	3	4	12	8.666666667
Lip	1	38	38	38
Maxillary sinus	5	6	28	18.2
Nasopharynx	5	2	43	12.8
Oral cavity	82	1	56	19.63414634
Oropharynx	6	6	47	23.33333333
Parotid	3	12	39	29.33333333
Submandibular	2	15	34	24.5
Supra glottis	14	3	37	20.42857143
Tonsil	6	3	23	11.83333333



45. Effect of tumor histology on Disease free survival (DFS)-

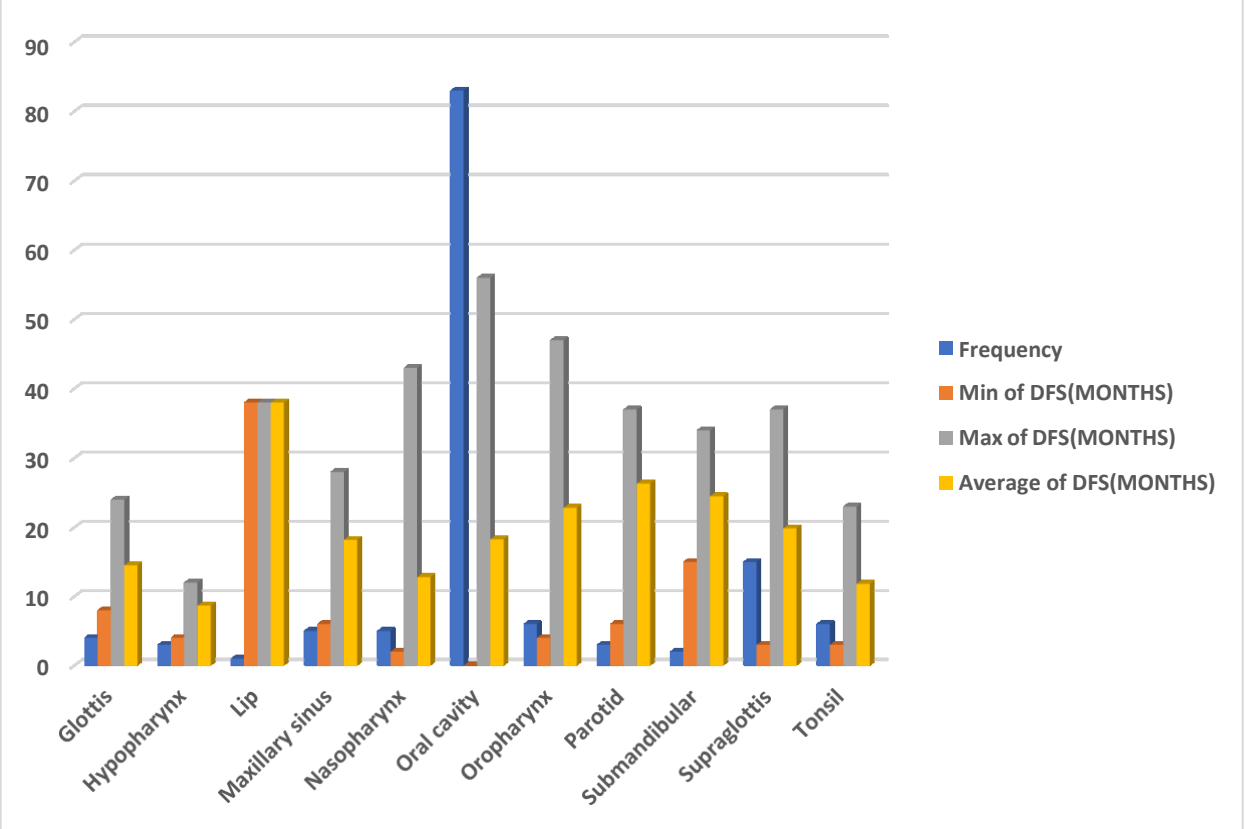


Histology	Frequency	Min of DFS (MONTHS)	Max of DFS (MONTHS)	Average of DFS (MONTHS)
MDSCC	84	0	48	17.05555556
Others	10	6	41	25.30666667
PDSCC	12	3	43	17.75277778
WDSCC	23	2	56	19.67391304



- Log rank test was done to analyze the association between pre-op histology and disease-free survival (DFS).
- There was no statistically significant difference found between DFS of WDSCC and MDSCC with a p-value of 0.47.
- There was no statistically significant difference found between DFS of WDSCC and PDSCC with a p-value of 0.43.
- There was no statistically significant difference found between DFS of MDSCC and PDSCC with a p-value of 0.41.

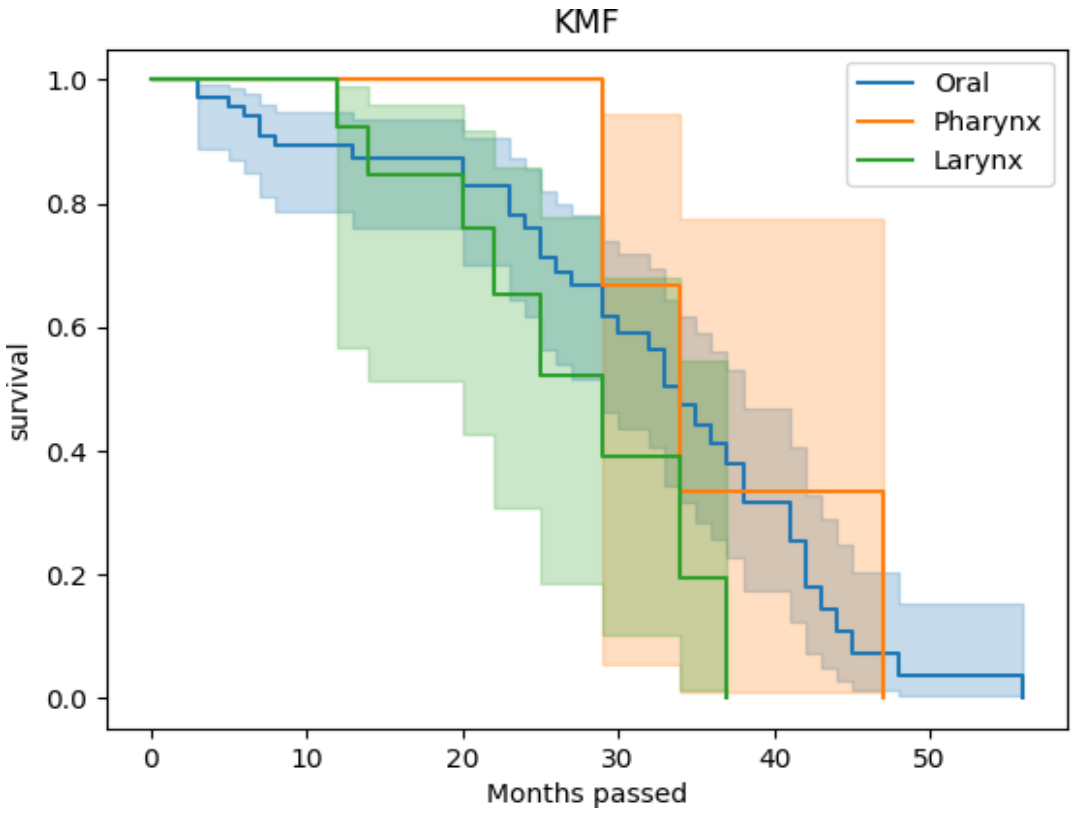
46. <u>Site-wise disease-free survival analysis</u>-



Subsite	Frequency	Min of DFS (MONTHS)	Max of DFS (MONTHS)	Average of DFS (MONTHS)
Glottis	4	8	24	14.5
Hypopharynx	3	4	12	8.666666667
Lip	1	38	38	38
Maxillary sinus	5	6	28	18.2
Nasopharynx	5	2	43	12.8

Oral cavity	83	0	56	18.27710843
Oropharynx	6	4	47	22.83333333
Parotid	3	6	37	26.33333333
Submandibular	2	15	34	24.5
Supra glottis	15	3	37	19.85714286
Tonsil	6	3	23	11.83333333

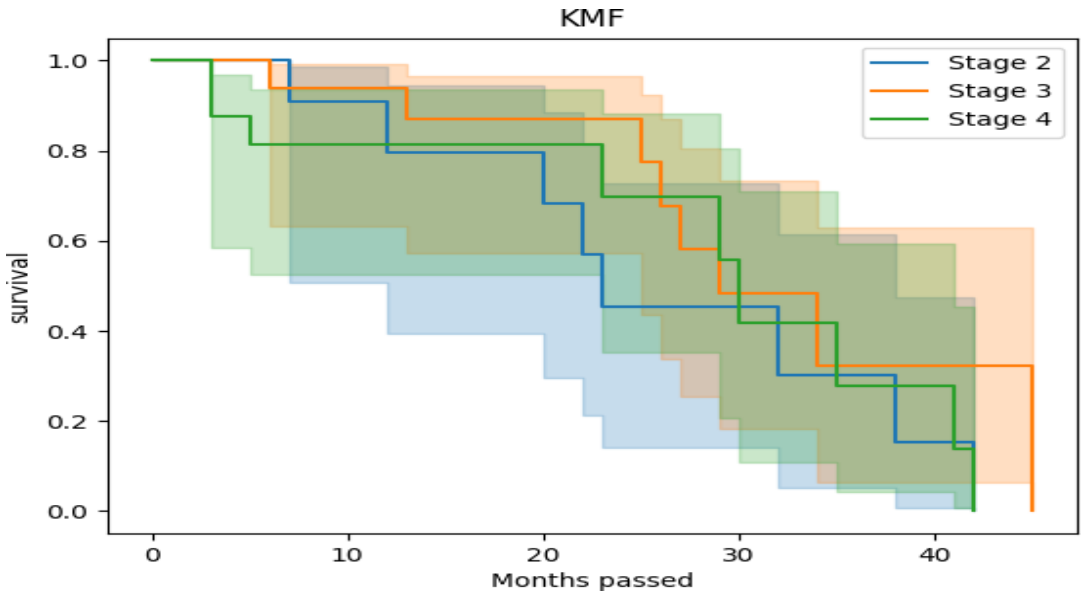
- Log rank test was done to analyze the association between different subsites of head and neck cancer and DFS.
- There was no statistically significant difference found between DFS of oral cavity tumors and larynx tumors, p-value was found to be 0.16.
- There was no statistically significant difference found between DFS of oral cavity tumors and pharynx tumors, p-value was found to be 0.53.
- There was no statistically significant difference found between DFS of larynx and pharynx tumors, p-value was found to be 0.26.

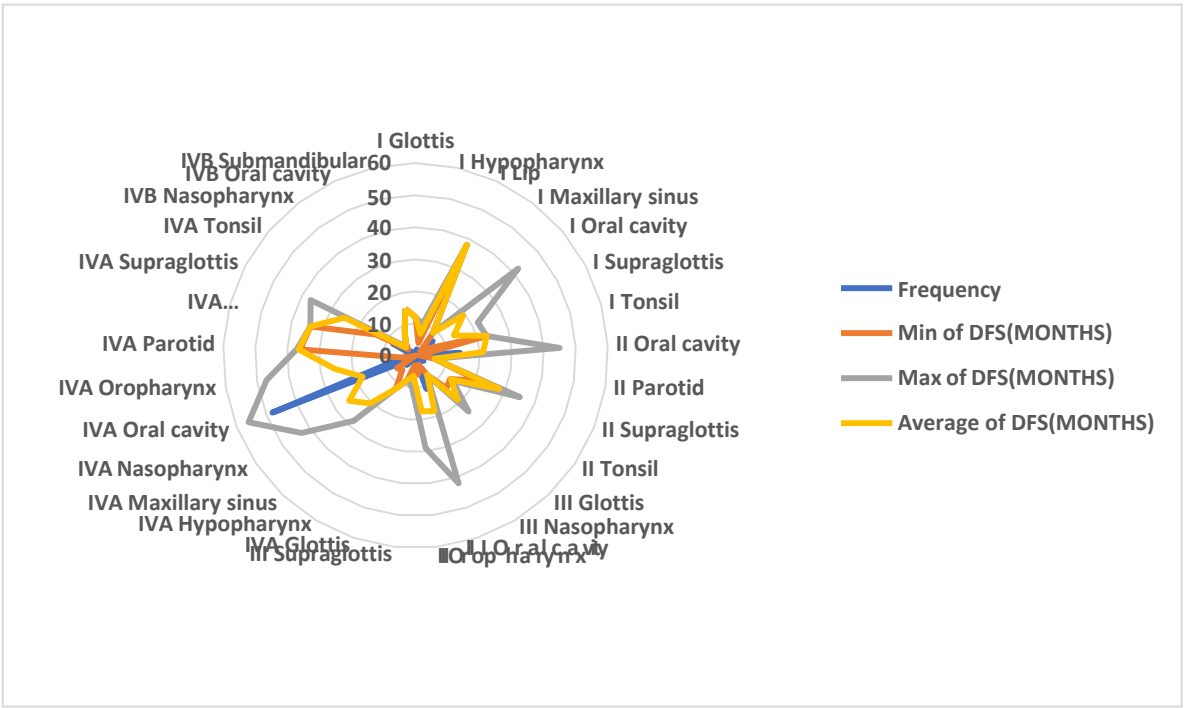


47. <u>Stage wise DFS analysis</u>-

Site & Stage	Frequency	Min of DFS (MONTHS)	Max of DFS (MONTHS)	Average of DFS (MONTHS)
I	**15**	**2**	**42**	**17.26666667**
Glottis	1	12	12	12
Hypopharynx	2	4	10	7
Lip	1	38	38	38
Maxillary sinus	1	9	9	9
Oral cavity	7	2	42	19.42857143
Supra glottis	2	5	22	13.5
Tonsil	1	23	23	23
II	**20**	**1**	**45**	**19.85**
Oral cavity	14	1	45	21.07142857
Parotid	1	6	6	6
Supra glottis	2	21	35	28
Tonsil	3	13	14	13.33333333
III	**19**	**3**	**42**	**15.78947368**
Glottis	2	14	24	19
Nasopharynx	1	7	7	7
Oral cavity	11	3	42	18.27272727
Oropharynx	2	6	29	17.5
Supra glottis	3	3	10	6.333333333
IVA	**73**	**0**	**56**	**19.40277778**
Glottis	1	8	8	8
Hypopharynx	1	12	12	12
Maxillary sinus	4	6	28	20.5
Nasopharynx	2	7	43	25
Oral cavity	48	0	56	17.75
Oropharynx	4	4	47	25.5
Parotid	2	36	37	36.5
Submandibular	1	34	34	34
Supra glottis	8	14	37	25.14285714
Tonsil	2	3	5	4

IVB	3	5	15	9.333333333
Nasopharynx	1	5	5	5
Oral cavity	1	8	8	8
Submandibular	1	15	15	15

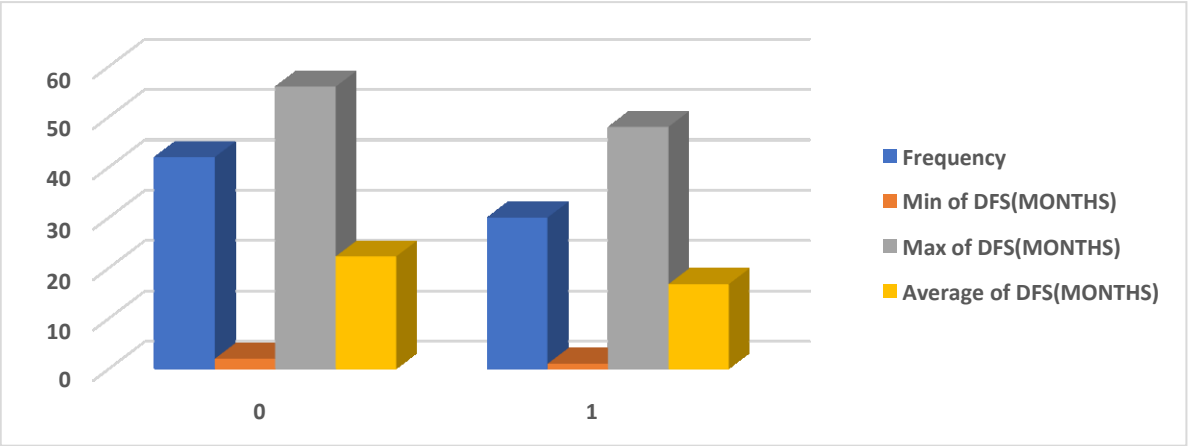




- Log rank test was done to analyze the association between stages of head and neck cancer and disease-free survival (DFS).

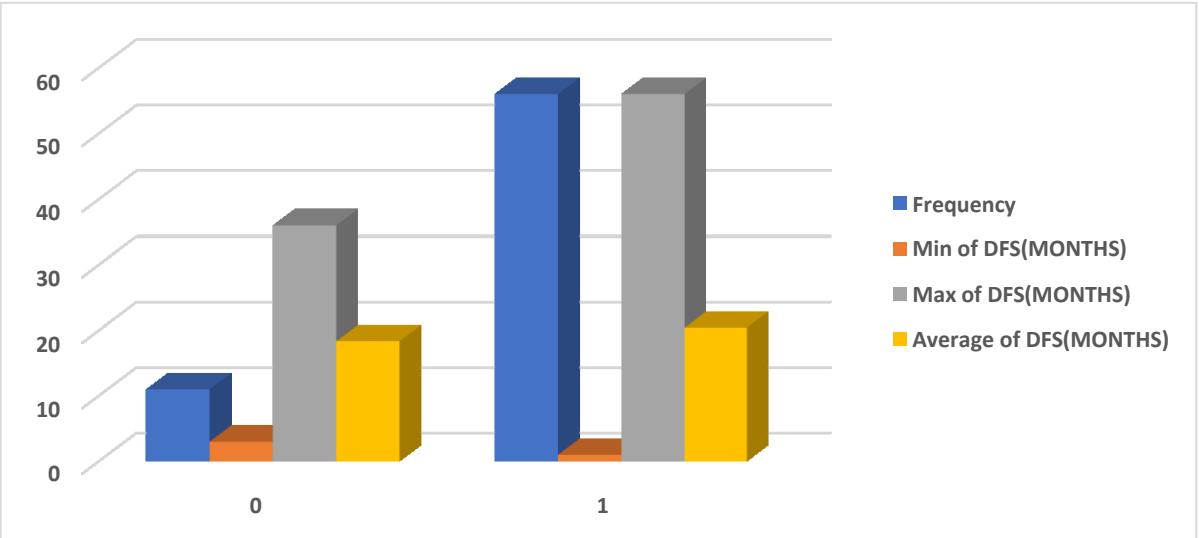
- There was statistically insignificant difference in DFS between stage I and stage II with a p-value of 0.35.
- There was statistically insignificant difference in DFS between stage II and stage III with a p-value of 0.52.
- There was statistically insignificant difference in DFS between stage I and stage III with a p-value of 0.91.

48. <u>Effect of Lymph node positivity on DFS</u>-



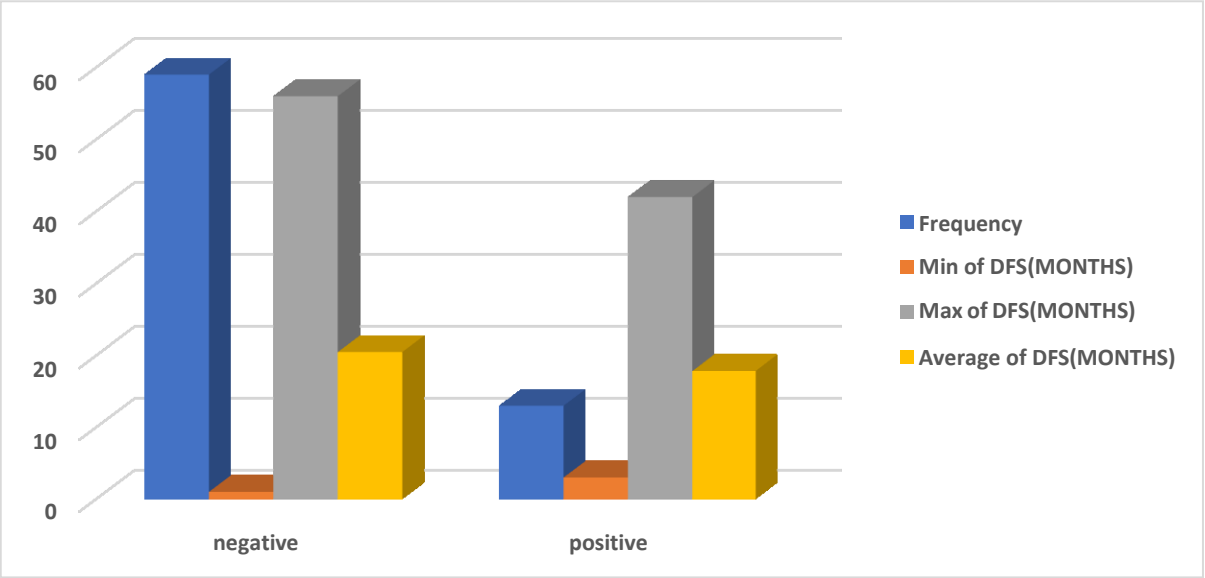
LN POSITIVITY	Frequency	Min of DFS (MONTHS)	Max of DFS (MONTHS)	Average of DFS (MONTHS)
0	42	2	56	22.30952381
1	30	1	48	16.8

49. <u>Effect of Lymph node dissection adequacy on DFS-</u>

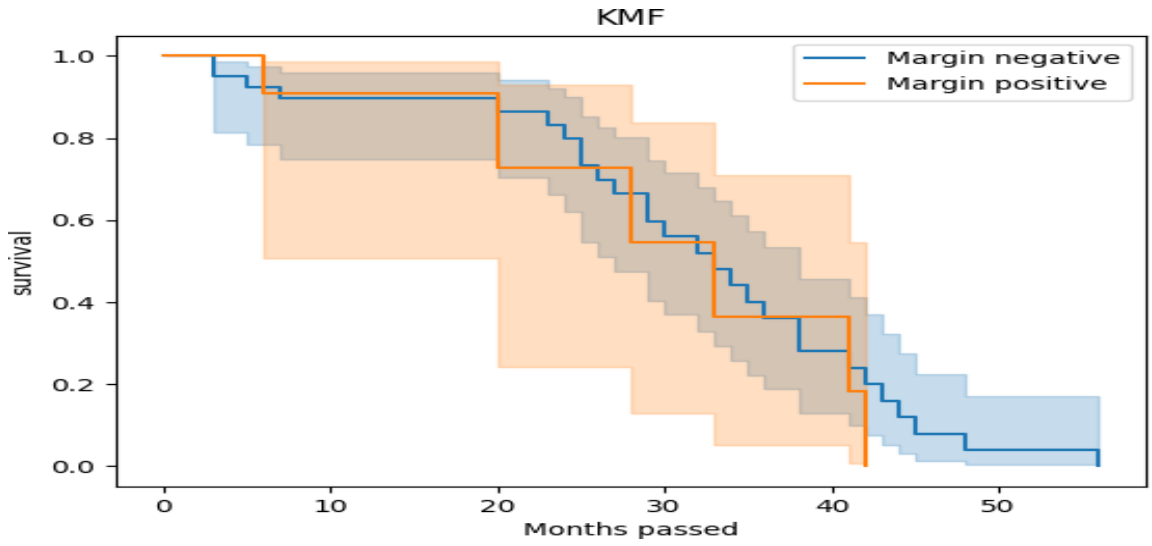


Lymph node dissection adequacy	Frequency	Min of DFS (MONTHS)	Max of DFS (MONTHS)	Average of DFS(MONTHS)
0	11	3	36	18.36363636
1	56	1	56	20.44642857

50. <u>Effect of post op margin status on DFS-</u>

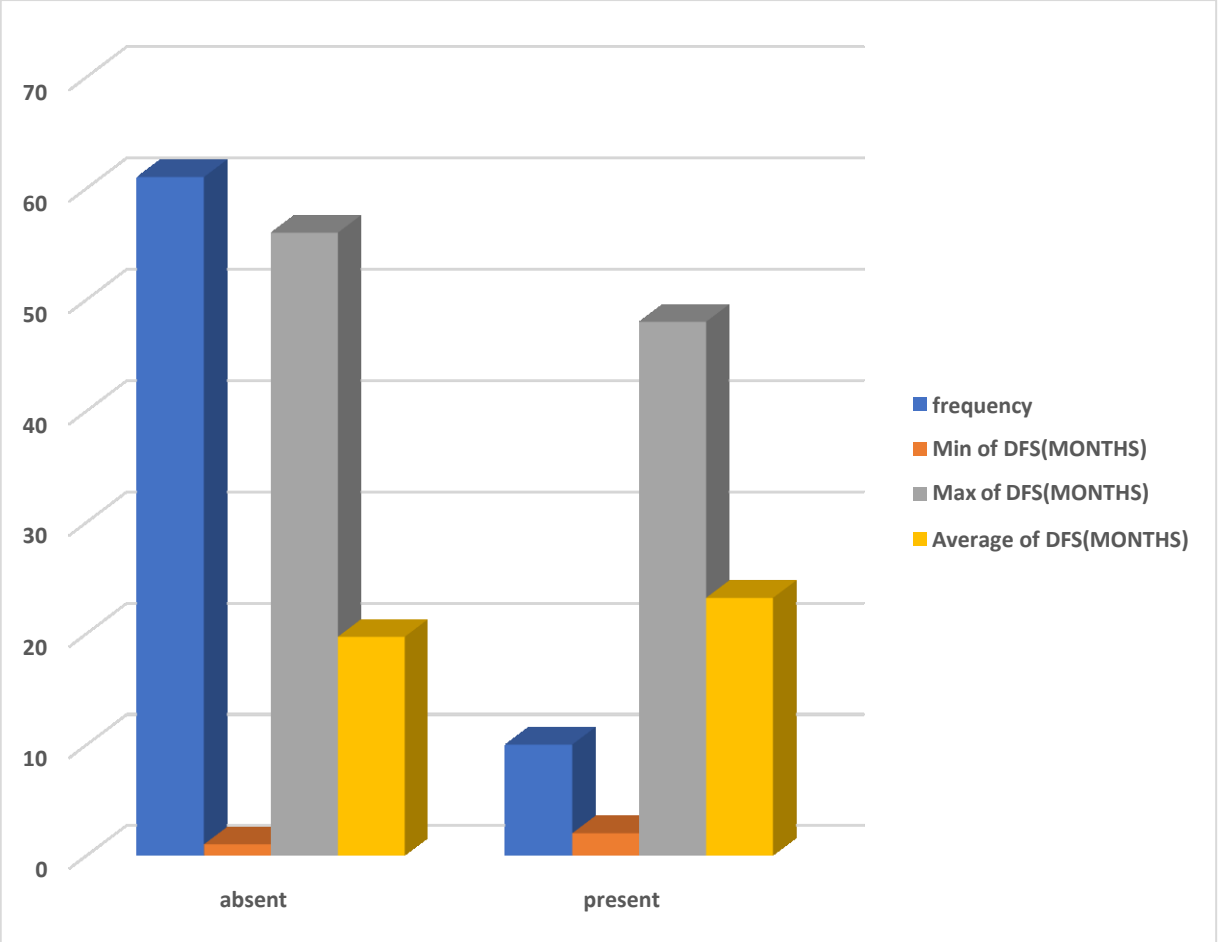


Margin status	Frequency	Min of DFS (MONTHS)	Max of DFS (MONTHS)	Average of DFS (MONTHS)
negative	59	1	56	20.49152542
positive	13	3	42	17.84615385



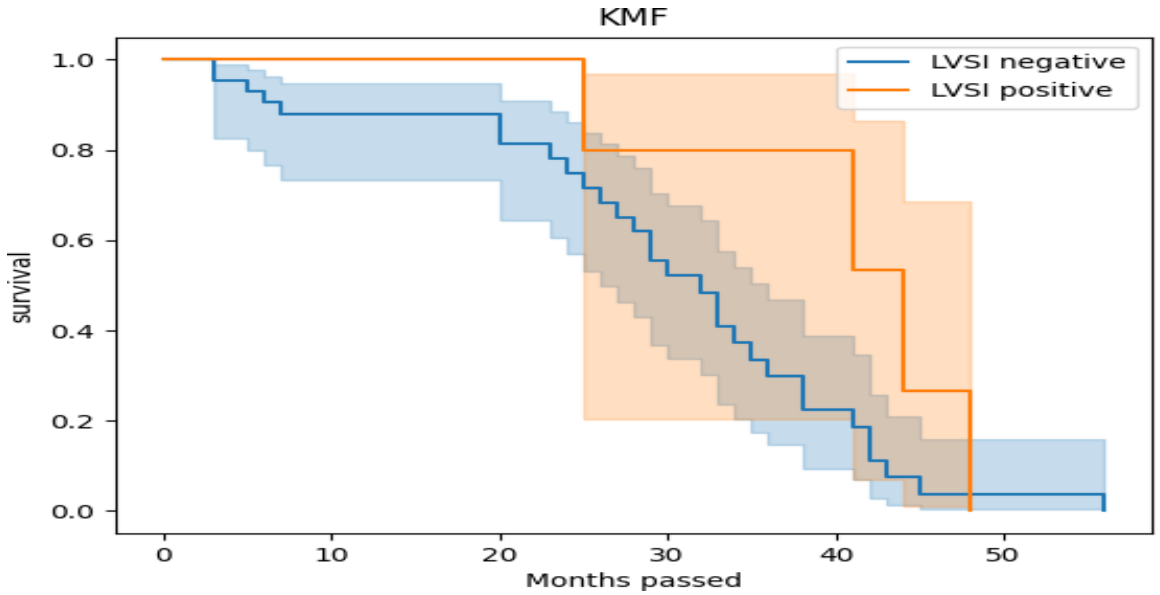
- Log rank test was done to analyze the association between post op margin status and disease-free survival (DFS).
- There was no statistically significant difference found between disease-free survival and post op margin status with a p-value of 0.63.

51. <u>Effect of LVSI on DFS</u>-

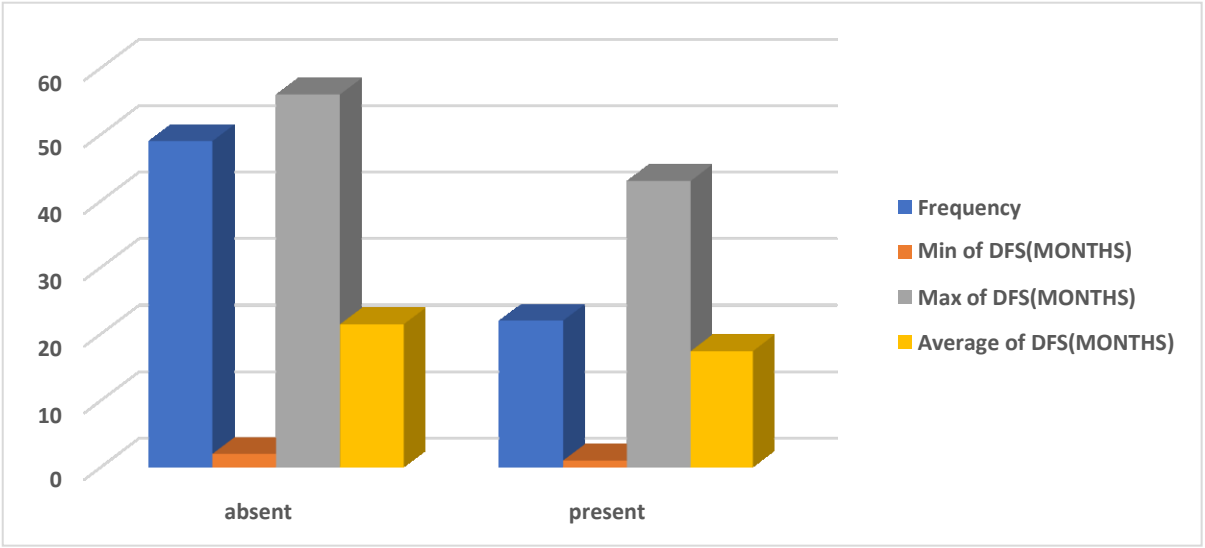


LVSI	frequency	Min of DFS (MONTHS)	Max of DFS (MONTHS)	Average of DFS (MONTHS)
absent	61	1	56	19.70491803
present	10	2	48	23.2

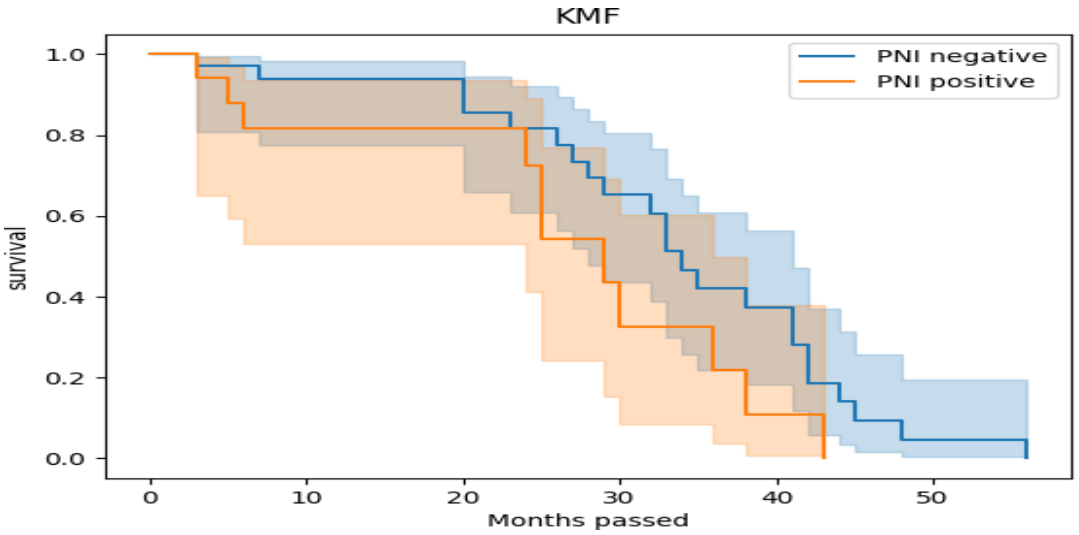
- Log rank test was done to analyze the association between LVSI and disease-free survival (DFS).
- There was no statistically significant difference found between disease-free survival (DFS) and LVSI with a p-value of 0.12.



52. <u>Effect of PNI on DFS</u>-

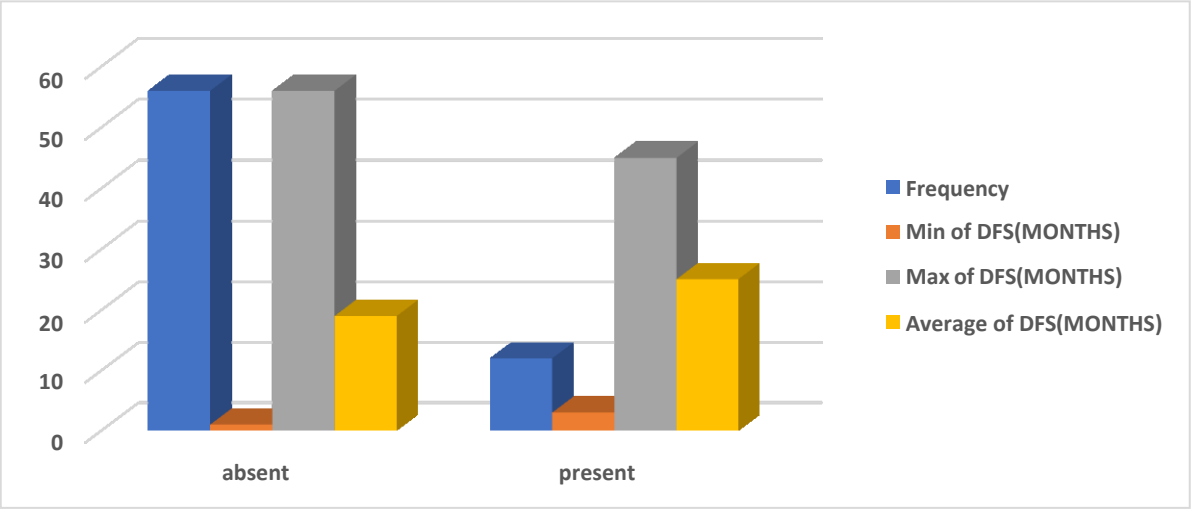


PNI	Frequency	Min of DFS (MONTHS)	Max of DFS (MONTHS)	Average of DFS(MONTHS)
absent	49	2	56	21.44897959
present	22	1	43	17.40909091



- Log rank test was done to analyze the association between PNI and disease-free survival (DFS).
- There was no statistically significant difference found between disease free survival and PNI with a p-value of 0.08.

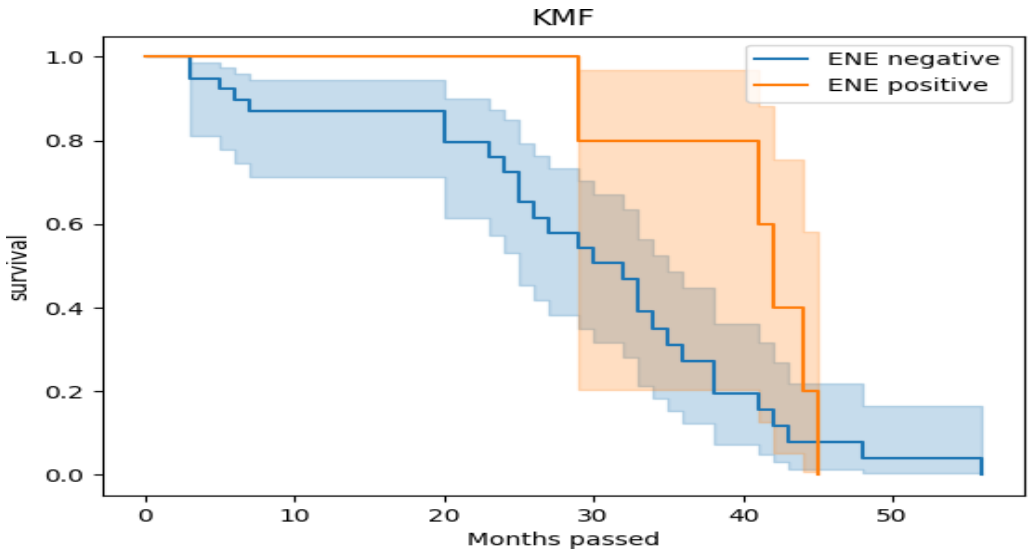
53. <u>Effect of ENE on DFS</u>-



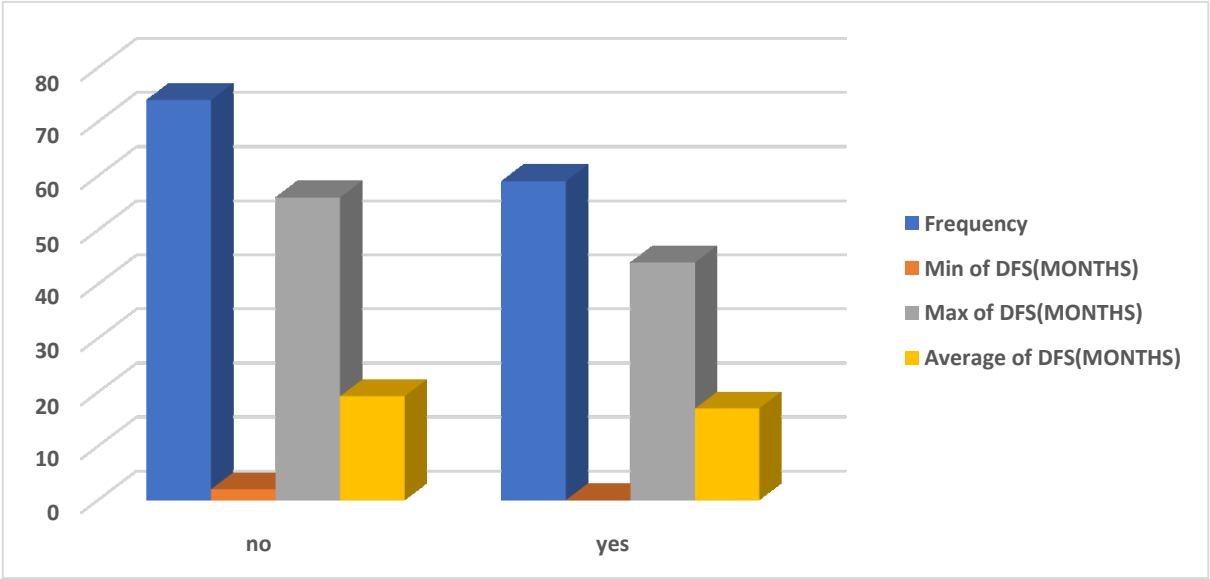
ENE	Frequency	Min of DFS (MONTHS)	Max of DFS (MONTHS)	Average of DFS(MONTHS)
absent	56	1	56	19.03571429
present	12	3	45	25.08333333

- Log rank test was done to analyze the association between ENE and disease-free survival (DFS).

- There was no statistically significant difference found between disease-free survival and ENE with a p-value of 0.11.



54. <u>Effect of concurrent chemotherapy on DFS</u>-



Concurrent chemo	Frequency	Min of DFS(MONTHS)	Max of DFS(MONTHS)	Average of DFS(MONTHS)
no	74	2	56	19.26027397
yes	59	0	44	16.98305085

DISCUSSION

Head and neck cancers (HNCs) are malignant tumors of the upper aerodigestive tract including the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx. Squamous cell carcinoma (SCC) constitutes >90% of HNCs.

PATIENT CHARACTERISTICS-

After getting clearance from Institute Ethical Committee, the study started which includes follow-up of the head and neck cancer patients who received Definitive/Palliative Radiotherapy either in adjuvant or definitive setting at our Institute from 2018 to 2020. Full data could be collected for 133 patients.

Similar to other studies, most of our patients were male (73%) as compared to female (27%). Epidemiological data from studies by GLOBOCAN 2020 and ICMR Cancer Atlas etc. have also shown that three-fourths of head and neck cancer cases in India are males(11–13).

Similar to other studies, most of the patients (82%) were in their late forties while the rest of the patients (18%) were of age less than forty years(14–16).

Most of the patients (90%) were from western Rajasthan, while the remaining were from eastern Rajasthan (7%), from Uttar Pradesh (2.5%) and Delhi (1%)(17). Our Institute is the major multispecialty treatment center catering to the population in the North-western part of India

Previous studies conclude that height is having inverse association with the incidence of head and neck cancer(18). while in our database, most of the patients (92%) had the height of >=150cm and the rest of 8% had the height of <150cm.

There is no definitive causal association to be defined between Body Mass Index (BMI) and the incidence of occurrence of head and neck cancers. However, obesity is a known risk factor for many other cancers such as breast and colorectal etc. In Our study, As per the Definition of obesity for the Asian population, only 24% were obese (BMI >=25kg/m^2) while 76% were non-obese patients (19,20).

In concordance with previous studies, most of the patients (62%) were having oral cavity involved while others were having other sites involved as pharynx, larynx, maxillary sinus

etc.(21,22). This may be related to the high prevalence of oral tobacco chewing in South East Asia including India.

Clinical presentation of the patient depends upon the primary site involved as most patients in the study group were having oral cavity involved so main initial presentation was ulcer (51%) along with pain (20%). Patient with nasopharyngeal cancer presented with complaint of nasal blockage associated with lymphadenopathy. Patients with oropharyngeal and hypopharyngeal cancer presented with complaint of dysphagia while those with laryngeal involvement presented with hoarseness of voice.

Clinical presentation time of patients with head and neck cancer is usually late, contributing due to multiple factors as literacy rate, approach to medical resources, social stigma etc. In the literature mean time interval of patients was approximately three months. In our study also, the median time of clinical presentation was four months in concordance with previous studies(23).

Consumption of alcohol and tobacco has been implicated in the pathogenesis of head and neck cancers. In countries like India, there is an increased prevalence of tobacco consumption that is associated with a relatively increased incidence of head and neck cancers as compared to the Western Population. Tobacco is considered a preventable cause of head and neck cancer pathogenesis. In our study group, most (64%) had a history of tobacco consumption, while 27% were having a history of alcohol consumption(24–26).

As history of comorbidities is of utmost significance because proper management of the malignancy includes oncological intervention to cure malignancy along with optimum control of the co-morbid condition. Studies suggest that the degree of comorbid burden may have an impact on the treatment delivered, with up to 20% receiving suboptimal regimens. Comorbidity has been cited as one of the factors implicated in treatment modification. In our study group, about 36% were having co-morbid conditions out of which 14% were having hypertension, 11% were having diabetes, and the rest were having other co-morbid condition as chronic kidney disease(CKD), cardiac disease etc.(27).

In India, most head and neck cancer patients present at a very advanced stage due to lack of awareness, education or the presence of social stigma. These patients with advanced disease do require a multi-disciplinary treatment paradigm with the involvement of Chemotherapy, radiotherapy, surgical intervention along with supportive care measures. As consistent with

other studies, in our study group, most (72%) presented with the locally advanced disease, while only 28% presented with early disease(21,28,29).

Similar to other studies performed, our study group showed the presence of mostly (90%) squamous cell carcinoma and the rest (10%) with other Histology as adenoid cystic carcinoma, pleomorphic adenoma, spindle cell and basaloid variant of SCC(30,31).

TREATMENT STRATEGY-

Many cancers of the head and neck can be cured, especially if they are found early. Although eliminating cancer is the primary goal of treatment, preserving the function of the nearby nerves, organs, and tissues is also very important. During planning treatment, consideration of how treatment might affect a person's quality of life, such as how a person feels, looks, talks, eats, and breathes, is also made. Treatment options and recommendations depend on several factors, including the site, type and stage of head and neck cancer, possible side effects, and the patient's preferences and overall health.

TREATMENT STRATEGY IN OPERABLE SUBSITES-

In operable sites such as lip and oral cavity, surgery followed by postoperative radiation therapy is indeed the current standard and preferred strategy. Concomitant chemotherapy to postoperative radiation therapy is added on the basis of adverse factors of the surgical histopathology report. In surgical histopathology reports, various risk factors are paid attention to. The most important of these are margin status and Extra Nodal Extension (ENE) and sometimes LVSI, PNI, histology, pathological staging, lymph node status, etc., according to which adjuvant treatment is decided. Presence of positive margin status and extra-nodal extension are considered to be indication for adjuvant concurrent chemoradiotherapy(32,33).

In our study, majority of oral cavity cancer (72%) underwent surgical intervention. Out of those 25% underwent adjuvant chemoradiation while 75% underwent adjuvant radiation therapy alone. 28% patients of oral cavity were inoperable, underwent definitive chemoradiation or radiotherapy alone. Pharyngeal tumors were treated with the current standard treatment of radical chemoradiation or radiation therapy alone.

In locally advanced operable sites of head and neck cancers, although the standard treatment guidelines do not include use of NACT as in most of the studies, it has failed to increase the OS, there is always an attraction for downstaging the disease, increasing the probability of R0 resections, sometimes preservation of mandible and reducing the morbidity of the surgery. In those patients who have pCR, an advantage in survival is also possible(34,35). In our study, total 25 patients (24 oral cavity and 1 maxillary sinus) underwent NACT with intent of downstaging. 23 of these patients were stage IVA. 2 patients were early stage but received NACT as bridging therapy in view of waiting list for the OT. Out of 23 patients given NACT for the downstaging, 13 could be operated while rest of the patients continued for radiation therapy as a main treatment and were not operated. Thus, out of 50% patients who were operated, received induction chemotherapy with either two drug regimen or three drug-regimen. 48% Patients received two drugs Platinum and Taxane while 30% received triple drug regimen of docetaxel, Cisplatin and 5FU (TPF). Out of 24 patients, 11 patients did not undergo surgical intervention due to tumor location at either floor of mouth or tumor of tongue encroaching posterior 1/3rd and with unsatisfactory regression. 1 patient was having tumor at floor of mouth opted for lesser morbid radical chemoradiation, so induction chemotherapy was followed by radiation therapy , currently doing well(31–35).

Lymph node metastases in the neck are considered to be a major prognostic factor in patients with head and neck squamous cell carcinoma (HNSCC). Assessment and treatment of lymph nodes in the neck are of great significance. Inappropriate management of lymph node metastases can result in regional failure as well as distant failure. Radical neck dissection has been and is still considered the "gold standard" for the surgical management of lymph node metastases of HNSCC. Adequate lymph node dissection is to be considered if >=18 LNs have been dissected and has been associated with better outcome. Short axis diameter (SAD) of Lymph node is also considered to a prognostic factor in Head and neck cancer patients. In our study, almost 77% were having adequate lymph node dissection. In our database, SAD of LN ranges from 0.4 cm to 3.8 cm with a median value of 1.22cm(41,42).

FACTORS AFFECTING OUTCOME-

Various factors have been implicated in prediction of prognosis of head and neck cancer patients which include stage at presentation, Lymph node status, site involved, treatment

strategy, risk factors in pathological staging as presence of PNI, LVSI, ENE, WPOI, margin status along with some patient related factors as age, comorbidity status, performance status, BMI etc.

Various studies have showed association of **body mass index (BMI)** with overall survival and found out that increased BMI is a predictor of better overall survival. Low BMI has been found to be associated with higher incidence of locoregional relapse along with impaired overall survival. In our study, correlation between BMI and overall survival was found to be statistically insignificant with a p-value of 0.99 and hazard ratio of 1.00(43–45).

In **Operated Patients** in our study, we found **Histopathological Features** such as LVSI, PNI, ENE, margin status etc. were found to have an impact on patient outcome.

Depth of invasion (DOI) has been included in AJCC staging system to upstage or downstage the cancer on the basis of DOI. Literature has concluded DOI as a strong predictor of lymph nodal recurrence and overall survival also. In our study, DOI was found be associated with overall survival with a p-value of 0.87 (95% C.I. ranging from 0.79 to 1.22)(46).

As there are multiple **subsites in head and neck cancers** and site involved determines the management strategy to a greater extent as the sites which are surgically accessible are primarily managed by surgical intervention while sites which are not accessible by surgery are to be managed with Chemoradiation or Radiation alone protocol. Prognosis is also determined to a greater extent by site involved while other factors like stage, performance status, comorbidity status, treatment modality used etc. also determines the prognosis of the patients. As per literature, lip, oral cavity, larynx, nasopharynx subsites are to be considered sites with better prognosis. In our study ,Patients with oral cavity has slightly better prognosis than pharyngeal tumors(median OS of 35 vs 32 months; p=0.66) while patients with pharyngeal and laryngeal tumors were having almost similar overall survival (median survival 32 months ; p value of 0.32) (47–50).

The patients who got operated for oral cavity tumors were having 3-year cumulative survival rate of 50% which is in concordance to multi-institutional study conducted by ICMR (49).

In countries like India, due to either lack of awareness or due to lack of resources, mostly patients with head and neck cancer usually present in locally advanced **stage** for which management include multimodality treatment with surgery + either RT alone or chemoradiation. Advanced disease patients do have dismal prognosis as compared to early-

stage disease due to treatment related complications or higher incidence of metastasis. However due to better radiation technique and including concurrent chemotherapy with radiation has improved survival outcome to a much larger extent as compared to earlier. In our study also, stage IVA patients were having better OS as compared to stage III(median OS of 38 months vs 30 months ;p=0.03) (47,49,51,52).

Lymph node metastasis is considered to be an independent factor in predicting survival in patients with head and neck cancers. Various factors related to lymph node dissection affect outcome in the patients as adequacy of lymph node dissection, lymph node positivity, lymph node yield and density. Adequate lymph node dissection (>=18 LN) has been found to be associated with better outcome as compared to inadequate lymph node dissection(41). Increased lymph node yield is associated with better outcome while increased lymph node density is associated with poorer outcome(53) (54). Similar to literature, in our study also, lymph node positivity was found to be associated with dismal outcome (median OS of 32 vs 33 months; p=0.73) while adequate lymph node dissection was found to be an indicator of better outcome (median OS of 38 vs 32 months; p=0.68).

Post operative **surgical margin status** is found to be an important prognostic factor in patients with head and neck cancer who underwent surgical intervention. With reference to optimal distance between tumor and the surgical margin, recent reports recommended cutoffs less than 5mm. While assessing surgical margin, if margin is found to be involved by cancerous cells, it confers poor prognosis to the patients and requires more intensive treatment either re-resection or concurrent chemoradiotherapy. While those without margin involvement are associated with favorable outcome and doesn't require concurrent chemotherapy for management. Recent National Comprehensive Cancer Network (NCCN) guidelines define a clear margin as invasive tumor that is at least 5 mm from the resected margin, a close margin as invasive tumor that is nearer than 5 mm, and a positive margin as invasive tumor at the margin of resection. In our study also, although statistically not significant, margin positivity besides intensive treatment with adjuvant chemoradiation was associated with poor prognosis (median OS 32m vs 41m ;p=0.82)as compared to margin negativity(55–59).

The presence of **lympho-vascular invasion (LVSI)** is considered a prognostic determinant for different malignancies and is frequently taken into consideration by surgeons and oncologists to determine patients' treatment. Various studies have concluded presence of lympho-vascular invasion as a poor prognostic factor in patients with head and neck cancers.

In our study also, presence of LVSI was associated with a poor outcome (median OS of 32.5 months vs 42.5 months; p=0.24) despite intensive treatment as compared to its absence in surgical specimen(60,61).

Perineural invasion (PNI) is a mechanism of tumor dissemination that can provide a challenge to tumor eradication and is a common pathologic finding in head and neck cancer that is associated with poor clinical outcomes. PNI is a histologic finding of tumor cell infiltration and is distinct from perineural tumor spread (PNTS), which is macroscopic tumor involvement along a nerve extending from the primary tumor that is by definition more advanced, being radiologically or clinically apparent. In our study, PNI was present in about one third of the operated patients and was associated with poor prognosis(median OS of 31 vs 32 months; p=0.63) as compared to the patients with absence of PNI(62–66).

Extra-nodal extension (ENE) is a significant prognostic factor in head and neck squamous-cell carcinoma and is classified as N3b by AJCC 8th edition. It represents one of the most important adverse prognostic factors for survival in patients with head and neck squamous cell carcinoma. Stratification of ENE has been done into ENEmi (minor, up-to 2mm) and ENEma (major, over 2mm). Presence of ENEmi was associated with better outcome as compared to ENEma. The clinical significance of surgical extra-nodal extension was much greater for patients with laryngeal/hypopharyngeal cancer than oral cancer. In our study also, Presence of ENE was associated with poor outcome(median OS of 32 vs 42 months ; p= 0.38)as compared to patients with ENE negative(67–70).

Historically unresectable head and neck cancer patients were treated with radiotherapy alone. Following which concept of using low dose chemotherapy drugs as radiosensitizers came that helped in increasing survival outcome at the cost of increasing toxicities. Many chemotherapy drugs have been investigated in concurrent setting for example Cisplatin, carboplatin, cetuximab. Many recent landmark trials have showed concurrent cisplatin as standard of care as compared to concurrent cetuximab in HPV positive oropharyngeal cancer in terms of better outcome and toxicity profile. How-ever there is lack of consensus on schedule of chemotherapy interval as 3 weekly vs weekly regimens are having different toxicity, compliance profile. In our study, **concurrent chemotherapy** was associated with slightly dismal outcome as compared to patients who did not receive concurrent chemoradiotherapy (median OS of 32 vs 33 months ;p=0.73), However it was statistically insignificant(38,71–76).

TREATMENT STRATEGY IN PHARYNGEAL TUMORS AND INOPERABLE SUBSITES-

Cancers as nasopharynx, oropharynx and hypopharynx, concurrent chemoradiation or radiation therapy alone is the mainstay of treatment based on disease stage and patients tolerability(77).

In our study also, mostly patients with these subsites underwent either definitive radiotherapy alone or chemoradiation. Out of total 133 patients, we had total 59 patients who underwent radical radiotherapy/chemoradiotherapy. Out of these, 24 patients were of inoperable oral cavity cancer while 35 patients were of other subsites as pharynx and larynx. Majority of patients were cancer of supra-glottis (8%) followed by Oropharynx (3%). Only 2% patients had glottic cancer. 100% of these patients received 66Gy-70Gy/33-35 Fr/6-7 weeks 6MV 3DRCT/IMRT. 17 patients received radiation therapy alone while 18 patients received concomitant chemotherapy too.

Out of these 17 patients who received radiation therapy alone, response assessment imaging data was available for 6 patients, all of them had complete response and 100% of them were relapse free. Only 1 patient died due to some unrelated cause. Out of these 7 patients are dead while 10 patients are alive. Out of total 35 patients treated, the median OS is 20 months and without any measurable statistically significant difference between those treated with radiation therapy alone or chemoradiation. The survival thus flattens out at 50% at 36 months. Biologically too, most recurrence happen in head and neck cancers in the initial 24 months. This result is in concordance to a multi-institutional study (12 institutes) conducted by Indian Council of Medical Research (ICMR) which shows 3-year survival of about 30-50% in patients with locally advanced oropharyngeal tumors(49).

Out of the patients received concurrent chemoradiotherapy, response assessment data was available for 8 patients our of which 4 patients were having CR, 3 patients were having PR while 1 patient was having progressive disease.

In patients with inoperable oral cavity tumors either base of tongue involvement or posterior third involvement, 16 patients received concurrent chemoradiation while 8 received radiation therapy alone. Median OS for these patients was found to be 13 months (34). This data is in concordance to a multi-institutional study (12 institutes) by ICMR which shows 3-year cumulative survival of about 50% in these patients(49).

CONCLUSION

Head and Neck Squamous Cell Cancers are the major cause of morbidity and mortality in India as well as many other countries of Asia. Tobacco is the main preventable cause of this disease. Only very few patients present with stage I or II disease which can be cured in using Surgery or Radiation Therapy. Unfortunately, due to menace of tobacco and unawareness, majority (75%) patients present in locally advanced stage, at which they are either not amenable to upfront radical treatment with surgery or radiation therapy or have high incidence of local recurrence after their primary treatment. The locally advanced or recurrent head and neck cancers seriously compromise the quality of life (QOL) of patients besides limiting the survival to mere months. The multimodal treatment strategies for such patients have important goals of holding or improving the quality of life till patients live, and add ameagre amount of survival of a few months.

Despite various meticulously planned aggressive surgeries and high technology radiation therapy, patients of these locally advanced head and neck cancer carry a dismal prognosis, a finding in our study too.

Various factors contribute to the prognosis of the patients with head and neck cancers as the general condition and nutritional status of the patients, age, co-morbidity status, stage at initial presentation, treatment offered, treatment cost, availability of various treatment modalities, and in those patients who get operated, pathologic risk factors. Patient should be offered best available treatment modality for his best management and along with proper counselling about the disease status and treatment approach.

In patients who recur despite use of intensive treatment modality, there is not much advantage on survival of adding immunotherapy and other targeted agents. With such a plateauing in outcomes despite multimodal treatments it is unclear how more the needs of such patients who are in the most productive age group in the community can be met.

The current study also draws attention to three urgencies where head and neck cancers are concerned:

1. Urgent need to explore newer, more effective and affordable treatments for locally advanced and recurrent head and neck cancers.
2. More honest efforts for tobacco control for primary prevention and reduce the burden of head and neck cancers.
3. Aggressive efforts at increasing awareness and screening of oral cancers as has been initiated in the Non-Communicable Disease Control (NCDCPS) programs by the Government of India.

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ANNEXURES

ANNEXURE-1

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/3548 Date: 12/03/2021

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3383**

Project title: **"Prognostic factors in head and neck cancer patients treated with radiotherapy: A retrospective analysis"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**D.M. Dissertation**
Student Name:	**Dr. Atul Kumar Gupta**
Guide:	**Dr. Puneet Pareek**
Co-Guide:	**Dr. Poonam Elhence & Dr. Jeewan Ram Vishnoi**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary

Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

ANNEXURE-2

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR
(Department of Radiation Oncology)

PERFORMA FOR DATA COLLECTION

Name of the patient: Age: Sex: REG. ID:

Education: Occupation: Monthly Income:

Religion:

Residence:

Mobile No:

ECOG:

Ht: Wt: BSA: AT START OF TREATMENT

Ht: Wt: BSA: AT END OF TREATMENT

DIAGNOSIS:

DATE OF DIAGNOSIS:

TUMOR VOLUME:

NODAL VOLUME:

SYMPTOMS AT PRESENTATION:

DURATION OF SYMPTOMS:

ADDICTION HISTORY:

HISTORY OF CO-MORBIDITIES AND PAST HISTORY:

PERFORMANCE STATUS:

CLINICAL FINDINGS:

IMAGING AT DIAGNOSIS (Tumor and node volume, level of node involvement, ENE, necrosis):

DISEASE STAGE AT PRESENTATION:

TREATMENT RECEIVED:

1. SURGERY:

    a) **DATE:**

    b) **TYPE:**

    c) **NODAL DISSECTION LEVELS:**

    d) **NODES DISSECTED:**

    e) **PATHOLOGIC STAGE/MARGINS/ENE:**

2. CHEMOTHERAPY:

INTENT	START	END	CYCLES	AGENTS	CUM. DOSE

Significant toxicities if available:

3. RADIOTHERAPY:

a) **TECHNIQUE:**

b) **DOSE AND FRACTIONATION:**

c) **GAPS IN TREATMENT:**

d) **CONCURRENT CHEMOTHERAPY (AGENT/CYCLES/CUM. DOSE):**

e) **TARGET SPECIFICATION**

CTV	DEFINITION	VOLUME
HIGH		
INTERMEDIATE		
LOW		

f) **DVH PARAMETERS**

a. **PTV_HR 95%-**

b. **PTV_IR 95%-**

c. **PTV_LR 95%-**

d. **OAR PARAMETERS-**

RESPONSE ASSESSMENT

a) DATE:
b) MODALITY:
c) STATUS:

CURRENT DISEASE STAGE:

RELAPSE/PROGRESSION:

a) DATE:
b) DISTAL/LOCAL(SITE AND NUMBER):

c) TREATMENT OFFERED:

DATE OF DEATH:

CAUSE OF DEATH:

ANNEXURE-3

Table 1
American Joint Committee on Cancer (AJCC)
TNM Staging Classification for the Oral Cavity (including mucosa of lip) (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage, mucosal melanoma, and cutaneous squamous cell carcinoma of the vermilion lip are not included)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor ≤2 cm with depth of invasion (DOI)* ≤5 mm
T2	Tumor ≤2 cm, with DOI* >5 mm and ≤10 mm *or* tumor >2 cm and ≤4 cm, with DOI* ≤10 mm
T3	Tumor >2 cm and ≤4 cm, with DOI* >10 mm *or* tumor >4 cm, with DOI* ≤10 mm
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor >4 cm, with DOI* >10 mm *or* tumor invades adjacent structures only (eg, through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face) Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4.
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

*DOI is depth of invasion and *not* tumor thickness.

Regional Lymph Nodes (N)

Clinical N (cN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(–)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension, and ENE(–)
N2b	Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Table 1 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging Classification for the Oral Cavity (including mucosa of lip) (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage, mucosal melanoma, and cutaneous squamous cell carcinoma of the vermilion lip are not included)

Regional Lymph Nodes (N)

Pathological N (pN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, ENE(−)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension, and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastases in multiple ipsilateral node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); *or* a single contralateral node of any size and ENE (+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); *or* a single contralateral node of any size and ENE (+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)

GX	Cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Prognostic Stage Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1,T2	N1	M0
	T3	N0,N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

ANNEXURE-4

Table 2
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Nasopharynx (8th ed., 2017)
(The following types of cancer are not included: Mucosal melanoma, lymphoma, sarcoma of the soft tissue, bone and cartilage.)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No tumor identified, but EBV-positive cervical node(s) involvement
Tis	Carcinoma *in situ*
T1	Tumor confined to nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumor with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/ or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)
A grading system is not used for NPCs.

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T0,T1	N1	M0
	T2	N0,N1	M0
Stage III	T0,T1,T2	N2	M0
	T3	N0,N1,N2	M0
Stage IVA	T4	N0,N1,N2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Table 3
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Oropharynx (p16-)

TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*
T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

**Note:* Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Hypopharynx

TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor limited to one subsite of hypopharynx and/or 2 cm or smaller in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures larger than 2 cm but not larger than 4 cm in greatest dimension without fixation of hemilarynx
T3	Tumor larger than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophageal mucosa
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophageal muscle or central compartment soft tissue*
T4b	Very advanced local disease Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

**Note:* Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

ANNEXURE-5

Table 3 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Regional Lymph Nodes (N):
Pathological N (pN) - Oropharynx (p16-) and Hypopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+) *or* a single contralateral node of any size and ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Prognostic Stage Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Table 3 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Regional Lymph Nodes (N)
Clinical N (cN) - Oropharynx (p16-) and Hypopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Table 4
American Joint Committee on Cancer (AJCC)
TNM Staging System for HPV-Mediated (p16+) Oropharyngeal Cancer (8th ed., 2017)
(Not including: P16-negative (p16-) cancers of the oropharynx)

Primary Tumor (T)
T0 No primary identified
T1 Tumor 2 cm or smaller in greatest dimension
T2 Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3 Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4 Moderately advanced local disease
Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond*
Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Regional Lymph Nodes (N)
Clinical N (cN)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 One or more ipsilateral lymph nodes, none larger than 6 cm
N2 Contralateral or bilateral lymph nodes, none larger than 6 cm
N3 Lymph node(s) larger than 6 cm

Pathological N (pN)
NX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in 4 or fewer lymph nodes
pN2 Metastasis in more than 4 lymph nodes

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)
No grading system exists for HPV-mediated oropharyngeal tumors

Prognostic Stage Groups
Clinical

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3	N0,N1,N2	M0
Stage III	T0,T1,T2,T3	N3	M0
	T4	N0,N1,N2,N3	M0
Stage IV	Any T	Any N	M1

Pathological

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3,T4	N0,N1	M0
Stage III	T3,T4	N2	M0
Stage IV	Any T	Any N	M1

Table 3 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Regional Lymph Nodes (N):
Pathological N (pN) - Oropharynx (p16-) and Hypopharynx

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
	N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
	N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
	N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3		Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)
	N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
	N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+) *or* a single contralateral node of any size and ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Prognostic Stage Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

ANNEXURE-6

Table 5
American Joint Committee on Cancer (AJCC) TNM Staging System for the Larynx (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone and cartilage, and mucosal melanoma of the lip and oral cavity are not included)

Primary Tumor (T)

TX Primary tumor cannot be assessed

Tis Carcinoma *in situ*

Supraglottis

T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility

T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx

T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage

T4 Moderately advanced or very advanced

T4a Moderately advanced local disease
Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis

T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility

T1a Tumor limited to one vocal cord

T1b Tumor involves both vocal cords

T2 Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility

T3 Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage

T4 Moderately advanced or very advanced

T4a Moderately advanced local disease
Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Subglottis

T1 Tumor limited to the subglottis

T2 Tumor extends to vocal cord(s) with normal or impaired mobility

T3 Tumor limited to larynx with vocal cord fixation and/or inner cortex of the thyroid cartilage

T4 Moderately advanced or very advanced

T4a Moderately advanced local disease
Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Continued

Table 5 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Larynx (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

Regional Lymph Nodes (N)

Clinical N (cN)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(–)

N2 Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–);
or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–);
or metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)

N2a Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)

N2b Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)

N2c Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)

N3 Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(–);
or metastasis in any lymph node(s) with clinically overt ENE(+)

N3a Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−)

N3b Metastasis in any lymph node(s) with clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Table 5 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Larynx (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

Pathological N (pN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(–)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node, 3 cm or smaller in greatest dimension and ENE(+); *or* metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−); *or* metastasis in a single ipsilateral node, larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral lymph nodes and any with ENE(+); *or* a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node, larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral lymph nodes any with ENE(+); or a single contralateral node of any size and ENE(+)

**Note:* A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Prognostic Stage Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1