QUALITY OF LIFE IN PATIENTS RECEIVING PALLIATIVE SEQUENTIAL METRONOMIC CHEMOTHERAPY AND RADIOTHERAPY IN ADVANCED AND RECURRENT HEAD AND NECK CANCERS

Thesis

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DECLARATION

I hereby declare that the thesis titled "**Quality of life in patients receiving palliative sequential metronomic chemotherapy and radiotherapy in advanced and recurrent head and neck cancers**" embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled "**Quality of life in patients receiving palliative sequential metronomic chemotherapy and radiotherapy in advanced and recurrent head and neck cancers**" is a record of the bonafide research work of Dr. Sanjay Santhyavu carried out under our guidance and supervision in the Department of Radiation Oncology, Department of Surgical Oncology and Department of Otorhinolaryngology, All India Institute of Medical Sciences, Jodhpur, Rajasthan. Dr Sanjay Santhyavu has learned and performed all the clinical and analytical procedures involved in the study under guidance and supervision.

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TO

MY GRANDFATHER SOLOMON

ACKNOWLEDGEMENT

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

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Sanjay Santhyavu

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 TREATMENT OF CANCER
HRQOL	HEALTH RELATED QUALITY OF LIFE
NCCN	NATIONAL COMPREHENSIVE CANCER NETWORK
5FU	5 FLUORO-URACIL
GY	GRAY
IV	INTRAVENOUS
RCT	RANDOMISED CONTROLLED TRIAL
CEP	ENDOTHELIAL PROGENITOR CELL
T_{REG}	T REGULATORY CELLS
CD	CLUSTER OF DIFFERENTIATION

NK	NATURAL KILLER
CPA	CYCLOPHOSPHAMIDE
DNA	DEOXYRIBO NUCLEIC ACID
4-D	4-DIMENSION
MTD	MAXIMUM TOLERABLE DOSE
EC	ENDOTHELIAL CELL
BSC	BEST SUPPORTIVE CARE
PFS	PROGRESSION FREE SURVIVAL
OS	OVERALL SURVIVAL
GLOBOCAN	GLOBAL CANCER OBSERVATORY
PBCR	POPULATION-BASED CANCER REGISTRY
HBCR	HOSPITAL-BASED CANCER REGISTRY
ESMO	EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY.
WHO	WORLD HEALTH ORGANISATION
EML	MODEL LIST OF ESSENTIAL MEDICINES
PF	PLATINUM AND 5 FLUORO-URACIL
TPF	TAXANE, PLATINUM AND 5 FLUORO-URACIL
ICT	INDUCTION CHEMOTHERAPY
RTOG	RADIATION THERAPY ONCOLOGY GROUP
LA	LOCALLY ADVANCED
LRC	LOCOREGIONAL CONTROL

CTRT	CONCURRENT CHEMORADIOTHERAPY
SS	SALVAGE SURGERY
PL	PHARYNGOLARYNGECTOMY
BD/BID	TWICE DAILY
SBRT	STEREOTACTIC BODY RADIOTHERAPY
R/M	RECURRENT OR METASTATIC
GC	GENERAL CONDITION
DCR	DISEASE CONTROL RATE
MCT	METRONOMIC CHEMOTHERAPY
OBD	OPTIMUM BIOLOGICAL DOSE
FACT	FUNCTIONAL ASSESSMENT OF CANCER THERAPY
QLQ	QUALITY OF LIFE QUESTIONNAIRE
ECOG PS	EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS
LFT	LIVER FUNCTION TEST
KFT	KIDNEY FUNCTION TEST
CBC	COMPLETE BLOOD COUNT
CPMS	COMPUTERISED PATIENT MANAGEMENT SYSTEM
CECT	CONTRAST ENHANCED COMPUTED TOMOGRAPHY
PA	POSTERIOR-ANTERIOR
IEC	INSTITUTE ETHICS COMMITTEE

OPD	OUTPATIENT DEPARTMENT
MTX	METHOTREXATE
CXB	CELECOXIB
PD	PROGRESSIVE DISEASE
PR	PARTIAL RESPONSE
CTCAE	COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS
NSAID	NON STEROIDAL ANTI INFLAMMATORY DRUG
PK	PAIN KILLERS
WL	WEIGHT LOSS
OM	MOUTH OPENING
SS	STICKY SALIVA
SP	SPEECH
SO	SOCIAL EATING
PA	PAIN
DR	DRY MOUTH
SW	SWALLOWING
TE	TEETH
FI	FELT ILL
SC	SOCIAL CONTACT
SE	SENSES
NU	NUTRITIONAL SUPPLEMENTS

CO	COUGH
SX	SEXUALITY
FE	FEEDING TUBE
WG	WEIGHT GAIN
NBSC	NON BEST SUPORTIVE CARE
ICMR	INDIAN COUNCIL OF MEDICAL RESEARCH
G-CSF	GRANULOCYTE COLONY STIMULATING FACTOR
MTHFR	METHYLENETETRAHYDROFOLATE REDUCTASE
NCDC	NON COMMUNICABLE DISEASE CONTROL

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INTRODUCTION

INTRODUCTION

THE PROBLEM

The term '*Head and Neck Cancers (HNC)*' refers to cancers of upper aerodigestive tract, including the lips, oral cavity, oropharynx, sinonasal cavities, larynx, hypopharynx and salivary glands(1). HNC is the major cause of morbidity and mortality in India. It affects mostly at the age of 30-69 years of age, which is the main productive age group in Asia and India(2,3). This is mainly attributed to preventable causes as use of tobacco, areca nut, alcohol. In 2020, tobacco related cancers are estimated to contribute 3.7 lakhs (27.1%) of the total cancer burden. HPV infection is also one of the leading causes for HNC in the present times. In India, 75% of patients present with advanced disease as compared to 40% in western countries. Oral cavity cancers are the most common amongst all head and neck squamous cell cancers (HNSCC). Head and neck cancer contributes to 15.19% of the cancer-related mortality in the country(3). The estimated mortality rates per 1000 patients in head and neck cancers are higher in a rural population as compared to urban population. The lack of adequate treatment facilities and manpower coupled with the lack of social security may be responsible for this disparity(4).

MANAGEMENT PARADIGM

HNSCC have lower incidence of systemic distant metastasis 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. The face and its expressions have evolutionary importance for the psychosocial roles of the person and HNSCC affects it seriously. Overall HNSCC affects the quality of life (QOL) of a patient. While the early stage HNSCC can be cured using a single modality as surgery or radiation therapy, locally advanced tumours need multimodal therapy. The management of unresectable HNSCC revolves around use of radiation therapy (RT) and systemic agents as platinum based chemotherapy etc. Radiation Therapy is often combined with platinum based chemotherapy for those patients who are fit for same. Majority of patients either progress or recur. Once HNSCC is inoperable, progresses, recurs or metastasize, systemic agents are also used in the treatment strategy. systemic agents have been explored in clinical trials as EXTREME in which the anti-Epidermal Growth Factor

(EGFR) monoclonal antibody was shown to have increased the progression free survival to meagre 3.5 to 5 months(5). Even the most recent immunotherapy studies as KEYNOTE 048 exploring use of Pembrolizumab or Checkmate-141 exploring Nivolumab are unable to increase the survival(6,7). The cost of these systemic agents for palliative patients is increasing more than cost of treatment of curative patient with high incidence of adverse effects. Most patients with poor performance status are not suitable for any oncological interventions are candidates for best supportive care alone.

HNSCCs are moderately chemo sensitive precluding use of chemotherapy as the principle treatment modality. Role of chemotherapy is established mainly either in combination with RT for organ preservation or in the adjuvant setting to improve loco regional control. Use of neo adjuvant chemotherapy (NACT) either for chemo selection (European Organization for Research and Treatment of Cancer – larynx preservation) or for downsizing the tumour is still largely investigational. In recurrent or locally advanced head and neck cancers, palliative chemotherapy has a significant role, however with only very modest survival benefits.

The complexity of HNSCC is, in part, due to the heterogeneity in the anatomic and physiological functions of the organs and thereby demanding a multimodality approach. In addition, the patient population (often elderly and/or patients with smoking and alcohol habits) 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 favourable risks of cure; and on the optimization of multi-modality regimens among patients with worse prognostic risks.

OTHER ASPECTS OF DISEASE AND QOL

Another important factor to be considered is the symptoms from the tumour (such as pain and difficulty swallowing) and its treatments often result in significant physical impairment (e.g. loss of taste), functional impairment (e.g. difficulty breathing, as well as voice, speech and hearing impairment), and psychosocial problems (e.g. depression, social isolation, and delays returning to work); all of which can have a negative impact on all aspects of patients' health-related quality of life (HRQOL)

ECONOMIC BURDEN

In Low and middle income countries, common difficulties that preclude the management of cancer includes cultural barriers or previous consultation with traditional practitioners, distance to nearest oncology centre, availability of drugs and treatment facilities, compliance with treatment, and cost of anticancer treatments. Delay in diagnosis and irregular follow-up, which contribute to poor prognosis also are important hurdles in management. The agents as Cetuximab or Immunotherapy are not affordable by most of these poor patients.

COMPLIANCE

One of the important factors which determine the progression of disease in head and neck cancers is timely presentation to health care facility and regular follow up. Most of the patients presents to a health care facility at an advance stage. The compliance to treatment is low in mostly elderly and poor economic strata of the patient population. Poor compliance and loss to follow up results in disease progression which further cuts down the available treatment options.

AVAILABLE TREATMENT OPTIONS

The accessibility to targeted therapy and checkpoint inhibitors is low in low income and middle-income countries. Palliative systemic therapy is used to treat recurrent, relapsed, metastatic or newly diagnosed head and neck cancers with good performance status that are not amenable to upfront surgery or radiotherapy. The current standard options for palliative systemic therapy, according to the US National Comprehensive Cancer Network (NCCN) guidelines are the EXTREME trial regimen (cisplatin, fluorouracil, and cetuximab and the KEYNOTE-048 trial regimen (Pembrolizumab with or without cisplatin and fluorouracil). Interestingly, these treatment options with very high cost to benefit ratio, are not at all useful in India where the incidence of HNSCC is highest, in Asia and India! Palliative Radiation Therapy (RT), Platinum Based Chemotherapy (Cisplatin, Carboplatin singlets, doublets with 5FU or paclitaxel or docetaxel), Methotrexate Based Oral Metronomic Chemotherapy, inexpensive EGFR blockers as Gefitinib and Best Supportive Care are the most common choices available to patients in this region(8).

SUPPORTIVE TREATMENT

Supportive care measures are equally important along with anti-cancer therapy in palliation of symptoms associated with cancer. The main symptoms encountered are pain, dysphagia, dyspnoea, bleeding, ulceration besides problems in social eating and psychosocial and nutritional issues. Given the critical importance of the tissues of the head and neck to basic life function, such symptoms significantly affect quality of life. Pain management with medications, anticholinergic blockade of secretions, and tracheostomy for airway protection and feeding tube placement for nutritional supplementation represent some of the common forms of care provided. For few symptomatic patients with more expected survival, judicious and limited use of invasive procedures as palliative surgery (debulking) or embolization of bleeding vessels can also be performed. Best supportive care is associated with a median survival of between 3 to 5 months (shorter for patients who have received prior therapy)

PALLIATIVE RADIOTHERAPY AND BEST SUPPORTIVE CARE

Palliative radiation is used in locally advanced disease and recurrent disease for symptom palliation like pain, bleeding and functional impairment due to disease bulk. Historically it is one of the oldest treatment which has stood the test of the time(9). Palliative Radiation Therapy (RT) reduces pain, bleeding, and foul discharges and may palliate most symptoms due to locally advanced treatment naïve or recurrent HNSCC. Most of the palliative RT regimens are hypo fractionated in order to reduce the treatment time and hospital visits. Various regimens have been studied like the QUAD shot, hypo trial, 40Gy in 10 fractions, 24 Gy in 3 weekly fractions, 40 Gy in 16 fractions .These studies showed significant palliation of symptoms with hypo fractionated radiation therapy(10–12).

METRONOMIC CHEMOTHERAPY

Palliative systemic therapy has shown to improve survival over supportive care alone, as demonstrated by the median survival of 10.1 months with the EXTREME regimen (cisplatin/carboplatin, 5-fluorouracil, and cetuximab) and of 14.9 months with Pembrolizumab(5,6). However, the use of these regimens is low (less than 1–3%) in low and middle income countries because of their cost. IV chemotherapy alone is therefore

commonly used in these countries. Also patient outcomes with these regimens are modest and associated with a high incidence of adverse events. With 75% of the global population located in low and middle income countries and 70% of all deaths due to cancer occurring in these countries there is a need to develop a more accessible and less toxic alternative therapy for patients with head and neck cancer who require palliative systemic therapy

The term metronomic has been derived from the 'metronome' an instrument mostly used by musicians and dancers to produce rhythmic beats. As per Merriam Webster's dictionary *'metronome is a device used by musicians that marks time at a selected rate by giving a regular tick'*. Metronomic chemotherapy (the chronic administration of chemotherapy at low, minimally toxic doses on a frequent schedule of administration, with no prolonged drug-free breaks) has recently emerged as a potential strategy to control advanced or refractory cancer. It is an alternative to toxic and costly systemic chemotherapy for patients with cancer living in developing countries. This low-cost, well-tolerated, and easy to access strategy is an attractive therapeutic option. Interestingly well conducted phase 3 randomized controlled trials (RCT) have shown that regimen of oral metronomic chemotherapy based on Methotrexate and Celecoxib is non-inferior to injectable IV Platinum based regimens and rather may be superior to same in safety profile, response rates and modest improvement of progression free survival(13). Studies may thus gradually change the current standard of treatment of such HNSCC to Oral Metronomic Chemotherapy.

MECHANISM OF ACTION OF METRONOMIC CHEMOTHERAPY

Metronomic chemotherapy uses multiple sites as targets inside the cell. Metronomic chemotherapy exerts both direct as well as indirect effects on tumour cells and their microenvironment. It can inhibit tumour angiogenesis, stimulate anticancer immune response and also induces tumour dormancy.

Anti-angiogenic properties

Metronomic chemotherapy works mainly by inhibiting tumour angiogenesis.

The mechanisms of anti-angiogenic activity of metronomic chemotherapy include:

- Induction of apoptosis of activated endothelial cells is selectively inhibited.
- Increase in the expression of thrombospondin-1, an endogenous inhibitor of angiogenesis
- Selective inhibition of migration of endothelial cell,
- Decrease in the levels and viability of bone marrow-derived endothelial progenitor cells (CEPs).

Activation of immunity

The neoplastic control by the immune system depends on both, the innate and adaptive immunity. The effect on regulatory T cells (T_{reg}) is very important for metronomic treatments. T_{reg} are $CD4^+ CD25^+ Foxp3^+$ lymphocytes that can inhibit antigen-specific immune response in respect to cytokine-dependent and cell contact-dependent manner. T_{reg} thus inhibits anti-tumour immune response by suppressing the activity of tumour-specific ($CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T helper cells) and tumour-unspecific effector cells (natural killer [NK] and NK T cells. Impairment of T_{reg} activity by either specific blockade or depletion is a method to enhance immune response against tumour-related antigens. Many studies (preclinical and clinical) have shown the effect of low dose Cyclophosphamide on T_{reg} cells. It reduces the number and function of T_{reg} cells and increases both lymphocyte proliferation and memory T cells(1,14).

Induction of tumour dormancy

Cell-cycle arrest is one of the most common mechanism of tumour dormancy. It can also be a result of a dynamic equilibrium state wherein cell proliferation is balanced by induction of apoptosis. Tumour dormancy can be observed during the early phase of cancer progression and also after completion of anticancer treatments during the remission phase where tumours can resume their growth from remaining residual disease. Apoptosis of malignant cells, suppression of angiogenesis and immune-surveillance are three main methods by which metronomic chemotherapy induces tumour dormancy

Induction of senescence

Lower grade of damage by chemotherapeutic agents may not activate the cascades of caspase that induce cellular apoptosis but however may induce senescence associated with anti-proliferative responses. DNA damage leading to single- and double-strand breaks have been induced by many senescence-inducing drugs. The induction of senescence in tumours can be achieved by repetitive, low-dose regimens of cytostatic drugs.

Four-dimensional effect

André and Pasquier hypothesized a drug driven dependency/deprivation or a 4-D phenomenon, so as to explain the efficacy of the drug regimens using intermittent drug interruptions. According to this hypothesis, tumour cells become dependent on chemotherapeutic agents during long exposures and sudden withdrawal or replacement therapy may lead to cell death(15).

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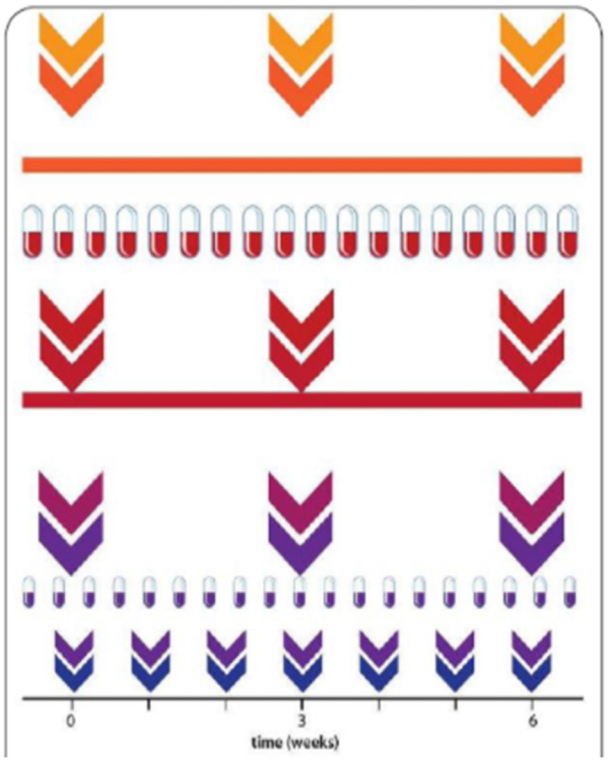
<td> 
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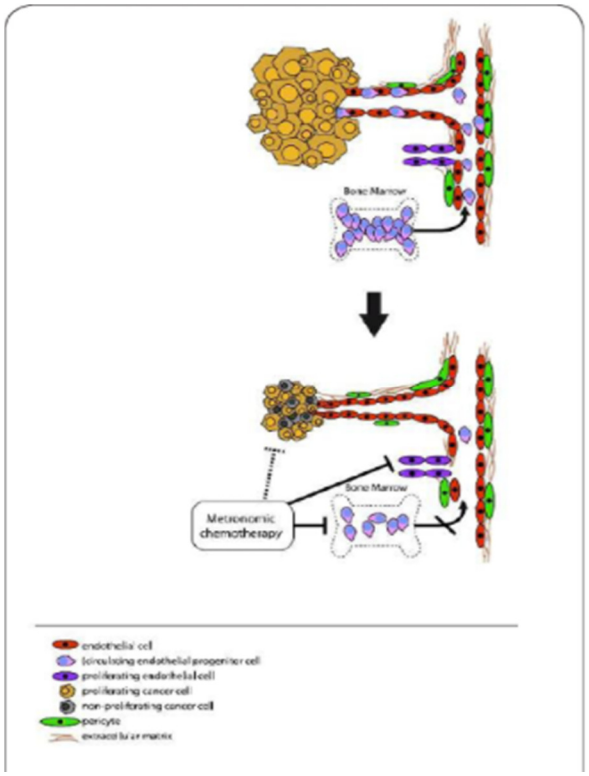
<td> 
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<td>Figure shows typical metronomic chemotherapies in comparison to standard procedure (repetitive infusions or bolus near resp. at the MTD)
From above to below :-

1st row figures a classical q3w schedule at the MTD

2nd row shows a continuous infusion at the MTD

3rd row presents a metronomic(daily) oral therapy

4th row displays a contiunous infusion together with a q3w application of iv chemotherapy

5th row depicts a q2w iv chemotherapy combined with a metronomic low-dose concept

6th row shows a weeky chemotherapy</td>
<td>Metronomic chemotherapy reduces the rapidly proliferating angioblasts like CEPs (circulating and growing out from bone marrow) and possibly inhibits proliferating ECs(most of the ECs of old vessels do not proliferate)</td>
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Figure 1: Comparison of metronomic chemotherapy with standard procedures *(15)*

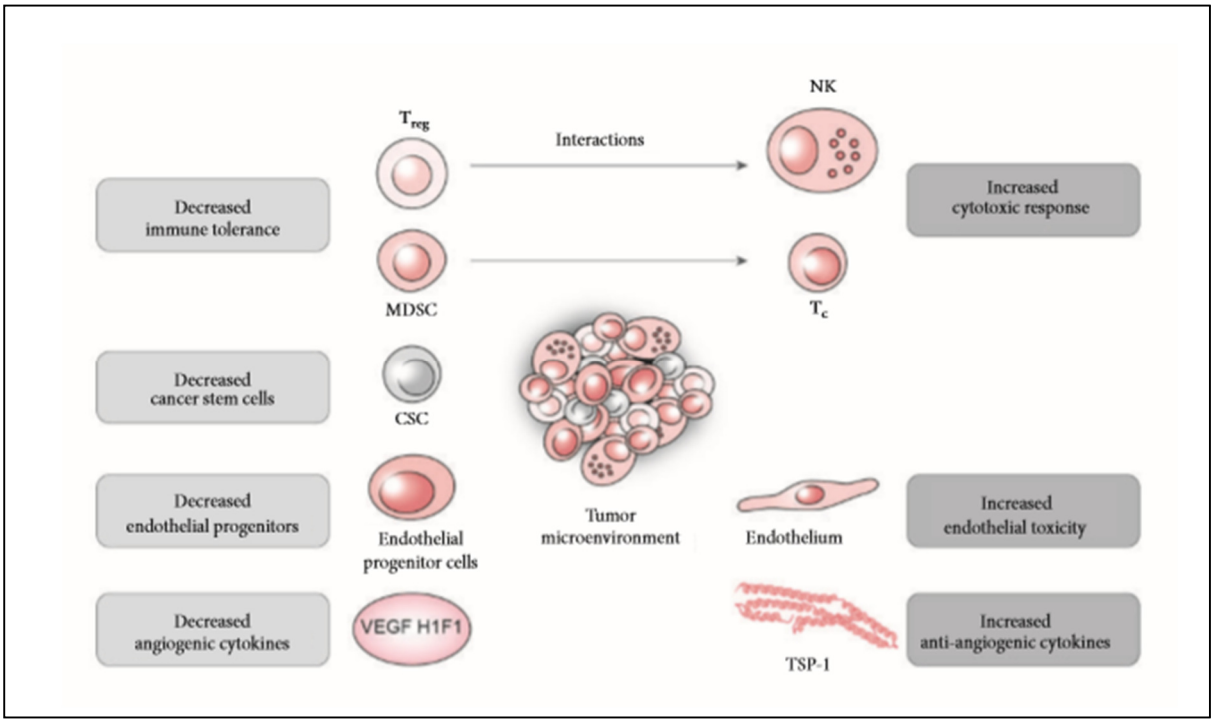


Figure 2: Proposed mechanism of action of metronomic chemotherapy*(16)*

RATIONALE FOR THE PRESENT STUDY

In absence of any clear evidence for the right sequencing of treatment modalities for locally advanced, recurrent and metastatic HNSCC and impracticality of costly treatments as Cetuximab or Immunotherapy for most of the patients in Asia and India, oral metronomic chemotherapy appears quite attractive. Moreover in real life situations, clinicians make treatment decisions creating a sequence of feasible treatment options for a patient from palliative radiation therapy, platinum based chemotherapy and metronomic chemotherapy(13,16–18). The present study explored in such HNSCC patients, the use of treatment initiated with the oral methotrexate-celecoxib based metronomic chemotherapy and further sequenced with other treatment options based on patients' wishes and performance status and judgement of the treating clinician.

AIM & OBJECTIVES

AIM AND OBJECTIVES

Aim of the study:

To assess the effect and toxicity of palliative metronomic methotrexate and celecoxib based chemotherapy in advanced and recurrent head and neck cancers. Patients progressing on metronomic regimen being offered best supportive care (BSC), palliative radiation therapy (if not given earlier radiation recently) or palliative platinum based chemotherapy as per their performance status and clinical judgment.

Objectives:

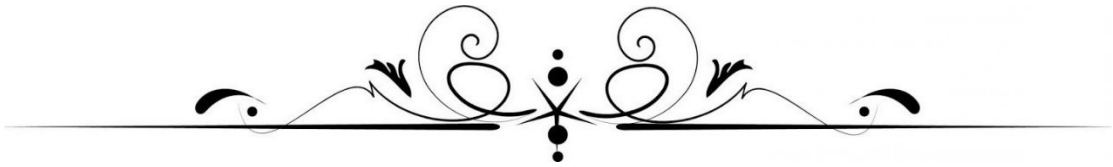
Primary Objective:

In patients with the diagnosis of locally advanced, recurrent or metastatic squamous cell cancer of head and neck, being treated with the study protocol with palliative intent:

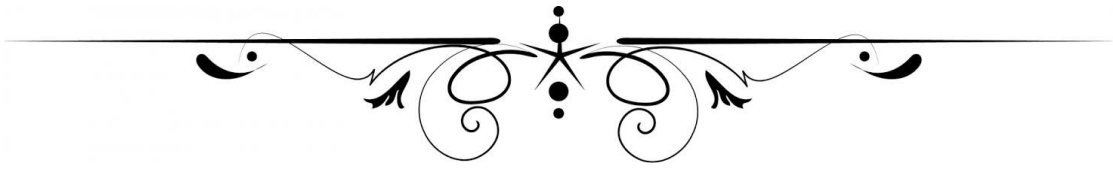
To assess the change in quality of life of Patients.

Secondary Objectives

1. To assess the progression free survival (PFS)
2. To assess the toxicity
3. To assess the overall survival(OS)
4. To assess the response of the treatment (clinical/radiological)



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(3).

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 Programme–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%)(4).

N I Cherny et al in the ESMO International Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in countries outside of Europe concluded that low- and low-middle-income countries have significant lack of availability and high out-of-pocket expenditures for cancer medicines on the WHO EML (Model List of Essential Medicines), with much less availability of new, more expensive targeted agents compared with high-income countries(19).

MANAGEMENT OF UNRESECTABLE LOCALLLY ADVANCED HEAD AND NECK CANCERS

TAX 323/EORTC 24971 with 358 patients with Unresectable disease compared PF → RT versus TPF → RT which showed that PFS: higher PFS and OS in TPF arm. However, more grade 3/4 leukopenia and neutropenia in the TPF arm. More grade 3/4 thrombocytopenia, nausea, vomiting, stomatitis, and hearing loss in the PF arm. Rates of death from toxicity: 2.3% versus 5.5% in TPF versus PF arms(20).

PARADIGM study conducted with 145 patients of unresectable disease compared TPF → chemo-RT versus cisplatin-RT showed no OS difference between both arms but febrile neutropenia was numerically more common in the ICT → chemo-RT arm than in the chemo-RT arm(21).

RTOG 91-11 study conducted with 520 patients with Glottis/supraglottic stages III–IV LA SCC compared PF → RT/surgery + RT versus cisplatin-RT versus RT showed that the Laryngectomy free survival was similar between PF → RT and cisplatin-RT however Higher rate of non–treatment-/disease-related death occurred with cisplatin-RT versus PF → RT and RT alone(22).

Misiukiewicz et al compared TPF → cisplatin-RT or cetuximab-RT versus cisplatin-RT or cetuximab-RT in 414 patients of Stages III–IV disease of the oral cavity, oropharynx, hypopharynx showed that OS and LRC was higher with addition of TPF as Induction chemotherapy(23).

Fausto Petrelli et al in a systematic review and meta-analysis of 15 published studies consisting of a total of 1808 patients demonstrated that for the treatment of locally advanced HNSCC, platinum-based CTRT is associated with a better OS and PFS compared to RT+Cetuximab . Thus, platinum-based CTRT should remain the standard of care until equivalence with RT+cetuximab can be prospectively demonstrated(24).

Jian Guan et al in a meta-analysis comparing cisplatin-based to carboplatin-based chemotherapy in moderate to advanced squamous cell carcinoma of head and neck showed that patients with cisplatin based CT can achieve a higher OS, but there is no significant difference in LRC. The cisplatin based CT is associated with fewer hematological toxicities but more gastrointestinal toxicities and nephrotoxicity compared to the carboplatin arm(25).

MANAGEMENT OF RECCURENT HEAD AND NECK CANCERS

Mark E Zafereo et al in his study retrospectively reviewed 1681 consecutive patients who completed definitive therapy for primary SCC oropharynx and identified 168 patients with locally recurrent SCC oropharynx who underwent salvage surgery (41 patients), reirradiation or brachytherapy (18 patients), palliative chemotherapy (70 patients), or supportive care (39 patients). Twenty-six of 39 patients (67%) developed a second recurrence after salvage surgery. The 3-year overall survival rate for patients who underwent salvage surgery or received reirradiation, palliative chemotherapy, or supportive care were 48.7%, 31.6%, 3.7%, and 5.1%, respectively(26).

Salvage surgery in recurrent head and neck cancers

Marc Hamoir et al in his paper about the role of salvage surgery in head and neck cancer mentioned that because 50% of advanced stage patients relapse after nonsurgical primary treatment, the role of salvage surgery (SS) is critical because surgery is generally regarded as the best treatment option in patients with recurrent resectable HNSCC. Wide local excision to achieve clear margins must be balanced with the morbidity of the procedure, the functional consequences of organ mutilation, and the likelihood of success. Patients with a high comorbidity index, advanced oropharyngeal or hypopharyngeal primary tumours, and both

local and regional recurrence have a very limited likelihood of success with salvage surgery and should be strongly considered for other treatments(27).

Takahide Taguchi et al in his study about treatment results and prognostic factors for advanced squamous cell carcinoma of the head and neck treated with salvage surgery after concurrent chemo radiotherapy concluded that salvage surgery is the best therapeutic option for failure after CTRT for SCCHN because of its good survival rate, although a high surgical complication rate is seen(28).

Goodwin et al , 2000; Putten et al., 2015 from their studies concluded that outcome in recurrent laryngeal cancer is relatively good, specifically in early stage recurrences(29,30).

Elbers et al., 2019; Putten et al., 2015; concluded that outcome in recurrent hypopharyngeal SCC is inferior to recurrent laryngeal SCC. Complication rate is higher in salvage PL probably due to high percentage of prior chemotherapy and the notoriously poor outcome of hypopharynx cancer(30,31). **Putten et al**. also found a 5-year OS of 27% for salvage pharyngo laryngectomy after primary chemo radiation(30).

Chung, Park, et al found that for an isolated neck recurrence OS drops to below 20% at 18 months. Radical salvage neck dissection is often difficult to achieve, specifically in case of extra capsular spread amidst of fibrosis with limited or no options for re-irradiation(32).

Tam et al reported the recurrence rates in oral cavity cancers to be 25- 45% and even 50% for advanced stage disease. Loco regional recurrence after salvage surgery is around 60%(33).

In general, a non- laryngeal recurrence is considered a relative negative prognosticator.

Reirradiation in recurrent head and neck cancers

Langer C.J. et al conducted a Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck (RTOG PROTOCOL 9911) in 105 patients. Patients received twice-daily radiation (1.5 Gy per fraction bid x 5 days every 2 weeks x4), plus cisplatin 15 mg/m^2 intravenously (IV) daily x 5 and paclitaxel 20 mg/m^2 IV daily x 5 every 2 weeks x4 .the study showed that the median survival time was 12.1 months, with estimated 1-

and 2-year OS rates of 50.2% and 25.9%. Grade 4 or worse acute toxicity occurred in 28%, grade 4 or worse acute hematologic toxicity in 21%. Eight treatment-related deaths (8%) occurred: five in the acute setting, three late (including two carotid haemorrhages). Thus the study concluded that Despite a high incidence of grade 3 and 4 toxicity, 1- and 2-year OS rates for split-course bid radiation therapy and concurrent cisplatin/paclitaxel exceed results generally seen with chemotherapy alone(34).

Sharon A Spencer et al conducted a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck in 86 patients to determine acute and late toxicity as well as 2-yr OS. The worst acute toxicity was grade 4 in 17.7% and grade 5 in 7.6%. Grade 3 and 4 late toxicities were found in 19.4% and 3.0%, respectively. The estimated cumulative incidence of grade 3 to 4 late effects occurring at >1 year was 9.4% at 2 and 5 years. The 2- and 5-year cumulative incidence for grade 4 toxicity was 3.1%. The estimated 2- and 5-year survival rates were 15.2% and 3.8% respectively. Patients who entered the study at >1 year from initial radiotherapy (RT) had better survival than did those who were <1 year from prior RT (median survival, 9.8 months versus 5.8 months; p = .036). No correlation was detected between dose received and overall survival(35).

Primož Strojan et al in 2015 analysed the literature on the efficacy and toxicity of photon/electron-based external beam reirradiation for previously irradiated patients with HNSCC of non-nasopharyngeal origin. Results showed that with improved dose distribution and adequate imaging support, including positron emission tomography-CT, modern radiotherapy techniques may improve local control and reduce toxicity of reirradiation. A reirradiation dose of ≥60 Gy and a volume encompassing the gross tumour with up to a 5-mm margin are recommended. Concomitant administration of systemic therapeutics and reirradiation is likely to be of similar benefit as observed in large randomized studies of upfront therapy(36).

Mark W McDonald et al did a study in Reirradiation of Recurrent and Second Primary Head and Neck Cancer with Proton Therapy. The study reported a 2-year overall survival estimate was 32.7%, and the median overall survival was 16.5 months(37).

Mustafa Cengiz et al did a study Salvage reirradiation with stereotactic body radiotherapy with cyber knife for locally recurrent head-and-neck tumors in 46 patients. Ultimate local disease control was achieved in 31 patients (83.8%). The overall survival was 11.93 months

in and the median progression free survival was 10.5 months. One-year progression-free survival and overall survival were 41% and 46%, respectively. Carotid blow out occurred only in patients with tumor surrounding carotid arteries and carotid arteries receiving all prescribed dose(38).

John A Vargo et al reported that SBRT with concurrent cetuximab appears to be a safe salvage treatment for recurrent HNSCC with short overall treatment time. The median overall survival was 10 months with a 1-year overall survival of 40% and 1-year local PFS rate was 60%(39).

Systemic therapy in advanced, recurrent and metastatic head and neck cancers

J B Vermorken et al in review article published in 2010 about Optimal treatment for recurrent/metastatic head and neck cancer concluded that the majority of patients presenting in a more advanced disease stage and very often treated with a form of combined modality treatment, will eventually relapse, either loco regionally only, at distant sites only or both. A few patients with a loco regional recurrence can be salvaged by surgery or reirradiation. However, most patients with recurrent or metastatic (R/M) disease only qualify for palliative treatment. Treatment options in these patients include supportive care only, or in addition single agent chemotherapy, combination chemotherapy or targeted therapies either alone or in combination with cytotoxic agents(40).

Best supportive care is associated with a median survival of between 3 to 5 months. It is shorter for patients who have received prior therapy. The use of palliative systemic therapy has the potential to improve survival over supportive care alone, as demonstrated by the median survival of 10.1 months with the EXTREME regimen (cisplatin/carboplatin, 5-fluorouracil, and cetuximab) and of 14.9 months with Pembrolizumab(5,6).

Platinum-based chemotherapy plus cetuximab in head and neck cancer

Jan B. Vermorken, et al compared platinum based chemotherapy with 5FU with and without addition of cetuximab. Adding cetuximab to platinum-based chemotherapy with fluorouracil (platinum–fluorouracil) significantly prolonged the median overall survival from 7.4 months

in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab .The addition of cetuximab prolonged the median progression-free survival time from 3.3 to 5.6 months and increased the response rate from 20% to 36% thus concluding that cetuximab along with cisplatin/carboplatin and 5 FU is a better option for first-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck(5).

F. Pontes et al published his data on the survival outcomes and survival predictors in recurrent and metastatic head and neck squamous cell cancer (R/M-HNSCC) patients treated with chemotherapy (CT) plus cetuximab as first-line therapy. He concluded that in non-selected recurrent and metastatic HNSCC patients, a median PFS and OS of 7.4 and 16.9 months, superior to 5.6 and 10.1 months reported in Extreme trial (Vermorken et al. 2008). ECOG PS, larynx/hypopharynx location and skin toxicity related to Cetuximab could be used to define patient prognosis(41).

Pembrolizumab as a monotherapy agent in advanced stages of head and neck cancer

Prof Ezra E W Cohen MD et al conducted **a** randomised, open-label, phase 3 study at 97 medical centres in 20 countries. Patients with head and-neck squamous cell carcinoma that progressed during or after platinum-containing treatment for recurrent or metastatic disease (or both), or whose disease recurred or progressed within 3–6 months of previous multimodal therapy containing platinum for locally advanced disease, were recruited to receive Pembrolizumab 200 mg every 3 weeks intravenously or any of the standard doses of methotrexate, docetaxel, or cetuximab intravenously (standard-of-care group). This study showed that the median overall survival in the Pembrolizumab group was 8·4 compared to 6·9 months with standard of care group with fewer side effects. The most common treatment-related adverse event was hypothyroidism with Pembrolizumab(42) .

Pembrolizumab in advanced and metastatic HNSCC

Barbara Burtness et al in 2015 did a randomised ,open label, phase 3 study, which was called the KEYNOTE-048 in which she compared Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck. Pembrolizumab with chemotherapy improved overall

survival versus cetuximab with chemotherapy in the total population (13·0 months *versus* 10·7 months). Based on the observed efficacy and safety, Pembrolizumab alone or in combination with platinum and 5-fluorouracil is an appropriate first-line treatment for recurrent or metastatic HNSCC(6).

Nivolumab in advanced stage head and neck cancer

Robert L. Ferris et al conducted a randomized, open-label, phase 3 trial, with 361 patients with recurrent squamous-cell carcinoma of the head and neck whose disease had progressed within 6 months after platinum-based chemotherapy to receive nivolumab (at a dose of 3 mg per kilogram of body weight) every 2 weeks or standard, single-agent systemic therapy (methotrexate, docetaxel, or cetuximab).The median overall survival was 7.5 months in the nivolumab group versus 5.1 months in the standard therapy group. The estimates of the 1-year survival rate were approximately 19 percentage points higher with nivolumab than with standard therapy (36.0% vs. 16.6%). The median progression-free survival was 2.0 months with nivolumab versus 2.3 months with standard therapy. The rate of progression-free survival at 6 months was 19.7% with nivolumab versus 9.9% with standard therapy. The response rate was 13.3% in the nivolumab group versus 5.8% in the standard-therapy group. Treatment-related adverse events of grade 3 or 4 occurred in 13.1% of the patients in the nivolumab group versus 35.1% of those in the standard-therapy group. Physical, role, and social functioning was stable in the nivolumab group, whereas it was meaningfully worse in the standard-therapy group(7).

Palliative radiotherapy in head and neck cancers

Mohanti et al did another retrospective study in 505 patients of stage IVA, IVB head and neck cancer with a palliative radiation regimen of 20 Gy/5 fractions in 1 wk. More than 1/3 rd. of the patients showed partial response with more than 50 % showing symptomatic relief. Median overall survival was 6.7 months .All the patients had patchy mucositis at 1-mo follow-up(43).

Ghoshal et al did a prospective study in 25 patients with stage IV head and neck cancer. His palliative radiotherapy regimen was 30 Gy/10 fractions over 2 weeks. This resulted in a

response rate of 100% with >50% patient reported pain relief at 4 weeks and was associated with G2 mucositis in 1/3rd of the study group(44).

Agarwal et al did a Retrospective study in 110 patients with T4 disease with a palliative radiotherapy regimen of 40 Gy/16 fraction .Results showed that 10% of the patients showed complete response and 63% of the patients showed partial response with median overall survival of 12 months. However 14% of the patients had G3 dermatitis and 3% had G4 and 63% had G3 mucositis(10).

Amardeep S Grewal et al in a review paper mentioned about the need for palliative radiotherapy in incurable head and neck cancers. He concluded that palliative radiation therapy, along with other systemic and surgical measures, has the potential to significantly improve the QOL in advanced and metastatic head and neck cancers. However there is little high-level evidence and a lack of consensus to direct the selection of an optimal palliative radiation regimen. An ideal palliative radiation regimen should alleviate symptoms secondary to the cancer with minimal treatment toxicity and side effects while improving a patient's quality of life(12).

Paris et al did a Prospective study in 37 patients with advanced stage head and neck cancer with 3 cycles of palliative radiation with 14.8 Gy/4fractions, bid over 2 d, with a 3- to 4-wk break. The results were 28% CR; 49% PR; 85% subjective palliative response with a median overall survival of 3 months with this regimen(45).

June Corry et al conducted a study in previously untreated patients with incurable squamous cell carcinoma of the head and neck with the primary objective to estimate the rate of tumour response to a cyclical hypofractionated palliative radiotherapy regimen(14 Gy in four fractions, given twice a day and at least 6h apart, for 2 consecutive days called QUAD SHOT repeated at 4 weekly intervals for a further two courses if there was no tumour progression) .Secondary objectives to prospectively evaluate toxicity, quality of life (QOL) using EORTC QLQ-C30 and survival in these patients. The study concluded that the QUAD SHOT regimen is an effective palliative treatment with minimal toxicity and a good response rate, which impacts positively on patients' QOL(11).

METRONOMIC CHEMOTHERAPY IN HEAD AND NECK

Lee et al conducted a prospective phase II single arm open label study of metronomic oral cyclophosphamide(50 mg to 150 mg) in 56 patients with loco regionally advanced, recurrent, inoperable or metastatic nasopharyngeal carcinoma with good general condition (PS 1-2) and have progressed on at least 2 lines of palliative systemic chemotherapy. After a median follow up of 9.95 months, the ORR was 8.9% and the DCR was 57.1%. The median PFS and OS were 4.47 months and 9.20 months respectively. Besides those who had loco regionally recurrent disease had better PFS compared to those who had distant metastasis(46).

Vivek Agarwala et al did a match pair analysis between with weekly Paclitaxel (80 mg/m2) and cetuximab in 60 patients with metastatic/recurrent head and neck squamous cell cancer. The median OS was 191 days in metronomic cohort and 256 days in cetuximab cohort. Cetuximab based chemotherapy leads to significant improvement in OS as compared to metronomic chemotherapy in palliative chemotherapy of head and neck cancers(47).

Vijay Patil et al did an open-label randomised phase 3 trial comparing, oral metronomic chemotherapy versus intravenous cisplatin in patients with recurrent, metastatic, inoperable head and neck carcinoma, the results showed that Oral metronomic chemotherapy is non-inferior to intravenous cisplatin with comparable overall survival in head and neck cancer in the palliative setting. It is also associated with fewer adverse events. This study thus proved that metronomic chemotherapy is an alternative option in palliative head and neck cancer patients who are not eligible or not tolerating or affording palliative systemic or targeted therapy(13).

Kamlesh kumar harsh et al in a single-arm, retrospective study of Metronomic palliative chemotherapy in locally advanced, recurrent and metastatic head-and-neck cancer showed that Oral metronomic chemotherapy using celecoxib and methotrexate is an effective, economical, and well-tolerated regimen with good pain control and low toxicity profile in patients with locally advanced, recurrent and metastatic head-and-neck cancer(48).

Geetha M et al published the results of a triplet metronomic chemotherapy regimen incorporating a tyrosine kinase inhibitor(erlotinib) in recurrent/metastatic head and neck cancers patients showing that the addition of erlotinib to a metronomic chemotherapy schedule of methotrexate and celecoxib resulted in an improved PFS(47).

Vinin nv et al did a retrospective review in 106 patients with head and neck cancer in palliative setting where 80 patients received oral metronomic chemotherapy (methotrexate and erlotinib). Patients who underwent palliative oral MCT had a median PFS of 134 days which is considered as promising treatment method. Results confirmed more than 50% response rate with lower Grade 3-4 toxicities(47)

Vijay M. Patil, et al conducted a Phase I/II Study of Palliative Triple Metronomic Chemotherapy with erlotinib 150 mg once per day, celecoxib 200 mg twice per day, and methotrexate 9 mg/m^2 per week in Platinum-Refractory/Early-Failure Oral Cancer. In phase I study 9 mg/m^2 methotrexate was identified as the OBD. The study showed improved 3 month PFS and 6 month OS and an improvement in the mean Functional Assessment of Cancer Therapy-Head and Neck Trial Outcome Index score (6.1 units at day 8). This study showed that the quality of life associated with head and neck cancer was improved with oral metronomic chemotherapy(49).

VM Patil et al conducted a Retrospective analysis of palliative metronomic chemotherapy in head and neck cancer. The study results show that the median time to failure was 3.5 months. The overall median survival was 155 days (95% confidence interval 140.2–169.8 days). Failure within 6 months of previous treatment was the most important factor influencing OS. There was a trend toward lower OS in patients with oral cancers. Among the various oral cancer sub sites, oral tongue primary had a lower OS.

From this study he concluded that Oral metronomic chemotherapy has promising results when used in a selected cohort of patients but has dismal results in patients who failed within 6 months of previous treatment(50).

Noronha V et al did a prospective randomized phase II study comparing metronomic chemotherapy with chemotherapy (single agent cisplatin), in 110 patients with metastatic, relapsed or inoperable squamous cell carcinoma of head and neck. Patients in the MCT arm had significantly longer PFS (median 101 days) compared to the IP arm (median 66 days) .The overall survival (OS) was also increased significantly in the MCT arm (median 249 days) compared to the IP arm (median 152 days). There were fewer grade 3/4 adverse effects with MCT, which was not significant(51).

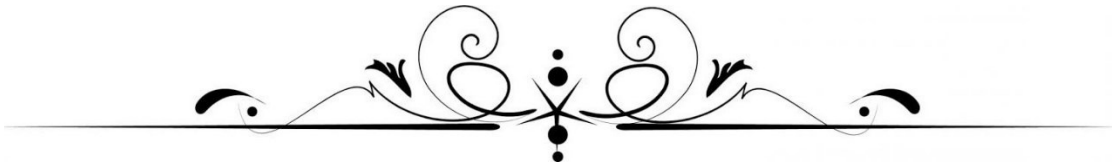
Metronomic chemotherapy and improvement in QOL

Shilpa Kandipalli et al conducted a study with Oral Metronomic Chemotherapy with Methotrexate and Capecitabine. Quality of Life assessment was done at month 0, month 3 and month 6.The predominant problematic domains identified by QOL H&N-35 scale were pain, difficulty in swallowing, dry mouth, mouth opening, sticky saliva, social eating, social contact and less sexuality. There is a significant improvement in QOL of most of the survivors in the study at the end of 6 months. But there was no significance as far as illness, senses, coughing; feeding tube and weight gain are concerned(52)

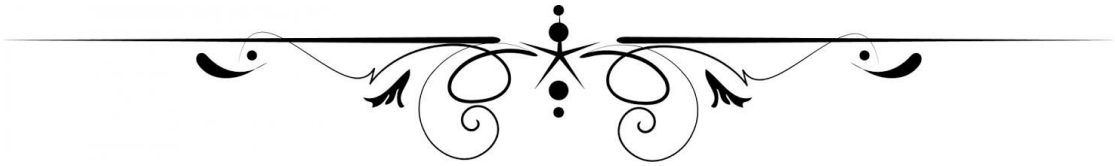
Vijay Patil et al evaluated the Quality of life and quality-adjusted time without toxicity in palliative treated head-and-neck cancer patients. There was an improvement in the social well-being, emotional well-being, functional well-being, H and N cancer subscale, FACT H and N trial outcome index .FACT G-total score and FACT H and N total score with palliative chemotherapy. The QTWiST value for a utility score of 0.25 for toxicity and relapse state was 145.93 days. He concluded that metronomic chemotherapy is associated with improvement in QOL and has a low duration of time spent in toxicity state(53).

Vipul nautiyal et al evaluated the Quality of Life in recurrent and metastatic HNSCC after oral metronomic chemotherapy in 175 patients. Results showed that there was statistically significant improvement in overall EORTC QLQ-C30 score from baseline in methotrexate and celecoxib arm compared with Capecitabine and with placebo(54).

K S Senthil Kumar et al in a study evaluated the Impact of Oral Metronomic Therapy on Quality of Life in 50 patients of Advanced/Recurrent Head and Neck Squamous Cell Carcinoma. $3/4^{th}$ of the patients became pain-free at the end of 6 months. A decreased pain grade was observed in another $1/4^{th}$ patients. Mean QLQ-C 30 score at the time of presentation was 68.67, 75.35 at 2 months, 81.26 at 4 months, and 85.38 at the end of 6 months. Mean QLQ-H&N 35 score at the time of presentation was 61.53, 72.16 at 2 months, 76.43 at 4 months, and 81.69 at the end of 6 months. In subgroup analysis, both QLQ-C30 and QLQ-H&N 35 significantly correlated with disease progression and based on the results he came to the conclusion that the use of oral metronomic therapy with methotrexate and celecoxib significantly improves the QOL and improves pain control in patients with advanced/recurrent HNSCC(55).



MATERIALS & METHODS



MATERIALS AND METHODS

Study Setting: Study was conducted in the Department of Radiation Oncology, AIIMS Jodhpur

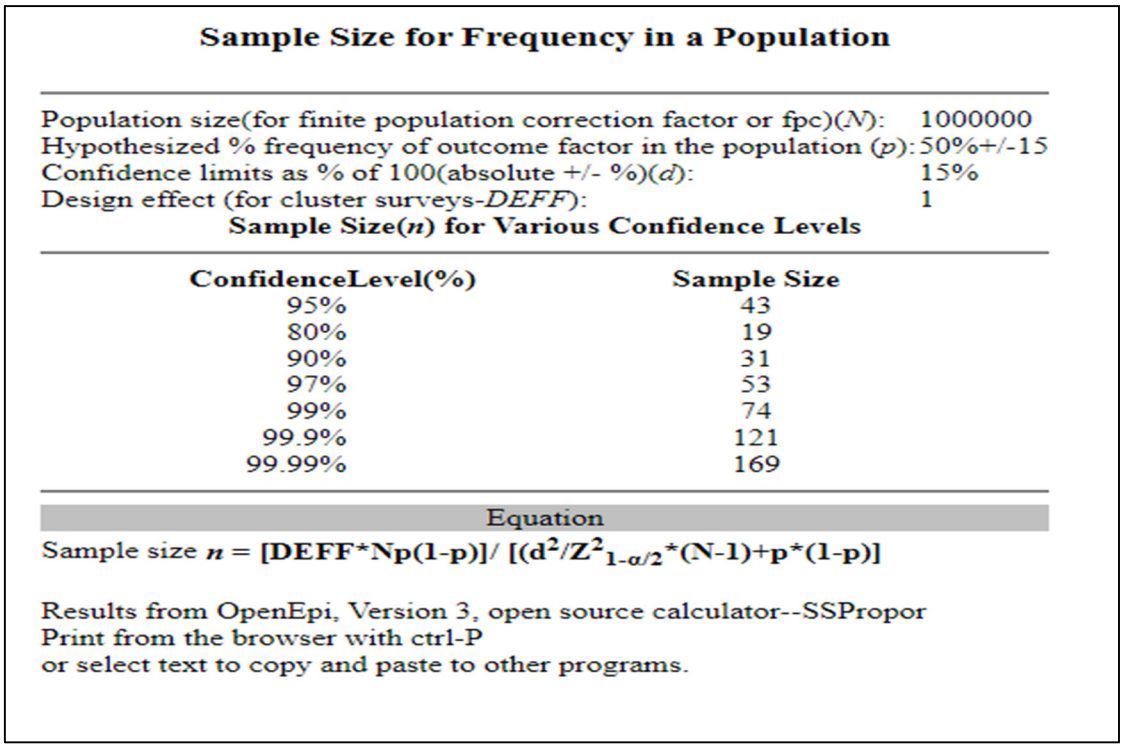
Study design: Single Arm prospective study

Study participants: Locally advanced, recurrent and metastatic squamous cell carcinoma of head and neck cancer region, clinically suitable for metronomic methotrexate and celecoxib based chemotherapy

Study Period: 2 years

Sample Size Calculations: **Sample Size (n): 43**

Open EPI software from the internet was used for the sample size calculation(56). Based on literature review it was estimated that at least 50% of patients will have events during the study period affecting the quality of life and progression free survival(13).



Sample Size for Frequency in a Population

Population size(for finite population correction factor or fpc)(*N*): 1000000
Hypothesized % frequency of outcome factor in the population (*p*): 50%+/-15
Confidence limits as % of 100(absolute +/- %)(*d*): 15%
Design effect (for cluster surveys-*DEFF*): 1

Sample Size(*n*) for Various Confidence Levels

ConfidenceLevel(%)	Sample Size
95%	43
80%	19
90%	31
97%	53
99%	74
99.9%	121
99.99%	169

Equation

Sample size $n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]$

Results from OpenEpi, Version 3, open source calculator--SSPropor
Print from the browser with ctrl-P
or select text to copy and paste to other programs.

Figure 3 : Sample size calculation using open epi(56)

The inclusion and exclusion criteria were as follows-

Inclusion criteria

1. Age >18 years
2. Pathologically proven squamous cell /other pathology of head and neck cancer planned for palliative treatment.
3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-3
4. Clinically judged suitable for starting metronomic methotrexate –celecoxib based palliative chemotherapy.

Exclusion Criteria

1. Patients who are eligible for radical treatment
2. Patients with hematological malignancies like Non-Hodgkin's Lymphoma etc.
3. Patients not willing for close follow-up
4. Patients with any medical condition prohibiting use of Methotrexate or Celecoxib (Severely deranged LFTs / Myelo-suprerssion etc.)
5. Patients who are unfit for radical treatment but not willing for metronomic chemotherapy

THE PATIENT

The patients underwent standard medical history and clinical evaluation which was captured in the Institute's Computerised Patient Management System (CPMS). Details of Performance status, comorbidities, smoking history and habits, height, weight, X Ray Chest PA view, CECT Face-Neck- Chest – Abdomen etc. was acquired and saved in the CPMS and study digital repository both. Informed consent was served, explained and signed before accrual in study. Radiological investigations were done and repeated only if there was clear clinical advantage. In view of palliative intent of the treatment, the study avoided any injudicious use of investigations or treatment modalities.

THE TREATMENT

The patient accrual

After the approval from the Institute Ethics Committee (IEC) (copy of approval letter annexed) patients with diagnosis of locally advanced, recurrent and metastatic head and neck squamous cell cancer attending the outpatient department (OPD) of the Institute were screened. Those patients who fulfilled the inclusion and exclusion criteria were explained and offered accrual in the study.

The laboratory investigations

All patients had confirmed histopathological report of head and neck squamous cell carcinoma. Patients underwent standard haematological investigations as complete blood count (CBC), liver function test (LFT) and kidney function test (KFT) at the baseline and 4 weekly basis during the study period. X-Ray chest and CECT of Head and Neck and Thorax region was acquired or repeated only if clear clinical advantage was there. In view of palliative intent of the treatment, the study avoided any injudicious use of investigations or treatment modalities.

The study protocol- metronomic methotrexate and celecoxib

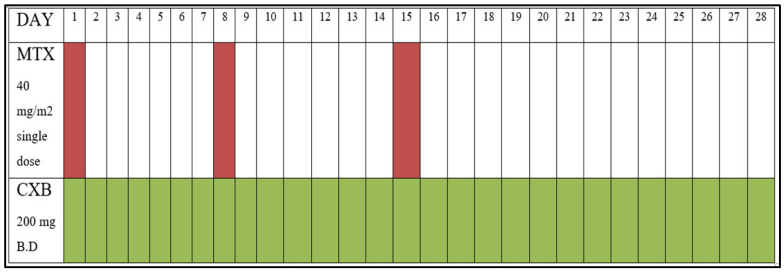


Figure 4: Dose and schedule of metronomic chemotherapy as per study protocol

After informed consent and counselling, patients underwent routine blood investigations and based on the eligibility criteria was subjected to QOL assessment using European Organisation for Research and Treatment of cancer Head and neck 35 (EORTC H&N 35) questionnaire(57) and photographs started on Tab Methotrexate 40 mg /m2 D1 ,D8 and D15, along with Tab Celecoxib 200 mg BD for 28 days. After 28 days of a cycle patients were

called back for clinical assessment of response to metronomic chemotherapy using EORTC H&N 35 questionnaire and photographs along with clinical examination**.**

Treatment after progression on the study protocol

All the patients on the study protocol were on under close monitoring using direct visits and repeat of blood investigations on 4 weekly basis. In between, the patients were monitored telephonically and photographs obtained through Whatsapp. Any suspicion of progressive disease (PD) during interim telemedicine monitoring was confirmed by direct physical examination of the patient. Once there was any evidence of PD, clinical evaluation and decision was taken for further options of treatment while also considering the patients' and their families' wishes. Broadly following further treatment options were available:

a) Best supportive care

   Patients with poor performance status or who were not fit for any oncological intervention like radiation therapy or systemic palliative chemotherapy were advised for best supportive care with pain medications, nutritional support, proper counselling and symptomatic care.

b) Palliative radiation therapy

   Patients who were radiation naïve and progressed on metronomic chemotherapy or who received radiation therapy long back (>1year) in radical setting were advised to receive palliative radiation therapy (30Gy/10 fraction or 20Gy/5 fraction regimens and in hemostatic setting even single fraction regimens were used)

c) Platinum based palliative chemotherapy

   Patients who progressed on metronomic chemotherapy and who either received palliative radiation therapy after progression or who were unfit for radiation therapy were continued on platinum based (cisplatin or carboplatin) palliative chemotherapy based on their performance status.

The Quality of Life (QOL) measurements using EORTC H&N 35

For each patient enrolled in the study we obtained the QOL scores by using EORTC H&N 35 questionnaire which consisted of 35 questions (Figure 5: EORTC H&N 35 symptom scales and scoring) and 4 options under each question scored from 1-4. Option 1 was designated as 'not at all', option 2 as 'A little bit', option 3 as 'quite a bit' and option 4 as 'very much'. For

e.g.: for question no 31, "*Have you had pain in your mouth?"* a patient with little bit of pain may mark the option 2 in the questionnaire. And similarly based on the severity of the symptoms patients will be allowed to mark the suitable options for all the 35 question sin the questionnaire. This option number is taken as the score from which a Raw score and a linear transformation score is derived with the help of the EORTC H&N 35 scoring manual as given in figure (Figure 6: EORTC H&N 35 Principles for scoring and linear transformation (57)).

	Scale	Number of items (n)	Item range*	QLQ-H&N35 item numbers ($I_1, I_2, \ldots, I_n$)
Symptom scales / items				
Pain	PA	4	3	31 – 34
Swallowing	SW	4	3	35 – 38
Teeth	TE	1	3	39
Opening mouth	OM	1	3	40
Dry mouth	DR	1	3	41
Sticky saliva	SS	1	3	42
Senses	SE	2	3	43, 44
Coughing	CO	1	3	45
Felt ill	FI	1	3	47
Speech	SP	3	3	46, 53, 54
Social eating	SO	4	3	49 – 52
Social contact	SC	5	3	48, 55 – 58
Sexuality	SX	2	3	59, 60
Pain killers	PK	1	1	61
Nutritional supplements	NU	1	1	62
Feeding tube	FE	1	1	63
Weight loss	WL	1	1	64
Weight gain	WG	1	1	65

* "Item range" is the difference between the possible maximum and the minimum response to individual items. Most items are scored 1 to 4, giving range = 3.

Figure 5: EORTC H&N 35 symptom scales and scoring

Principle for scoring

1) **Raw score**

For each multi-item scale, calculate the average of the corresponding items.

$$Raw\ Score = RS = \left\{\frac{(I_1 + I_2 + \dots + I_n)}{n}\right\}$$

For each single-item measure, the score of the concerning item corresponds to the raw score.

There are no reverse scoring items.

2) **Linear Transformation**

To obtain the Score S, standardize the raw score to a 0 – 100 range using the following transformation:

$$\text{Symptom scales: } S = \left\{\frac{(RS-1)}{range}\right\} \times 100$$

Figure 6: EORTC H&N 35 Principles for scoring and linear transformation (57)

Once Raw score and Linear Transformation scores (Figure 6: EORTC H&N 35 Principles for scoring and linear transformation (57)) were obtained at the beginning and end of each cycle, the data was compared for any statistically significant change in QOL in each of the 18 domains given in the scoring manual between the following groups:

The comparison was done between baseline QOL and QOL obtained after 1 month of metronomic chemotherapy.

Similarly, comparison was done between baseline QOL and QOL after 3 cycles of metronomic chemotherapy.

Subgroup analysis was done in terms of age, gender, sub site, stage at the time of recruitment, state of disease at recruitment, performance status and prior alternative therapy.

The measurement of toxicities

Toxicity assessment was done using clinical examination and blood investigations (CBC, LFT, KFT) monthly and graded using Common Terminology Criteria for Adverse Events 5.0 (CTCAE 5.0)(58)

CTCAE has a common schema to grade toxicity with grade 0 as none and grade 5 as death. Grade 1 and 2 are considered mostly as mild and are frequently encountered while grade 3 and 4 are considered severe and better avoided. For e.g.:

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the oral mucosal. **Navigational Note:** -					

Figure 7: CTCAE 5.0 Oral mucositis

Common toxicities associated with methotrexate and celecoxib which were evaluated were mucositis, nausea, constipation, dysphagia, anemia, neutropenia, thrombocytopenia, liver dysfunction and kidney dysfunction.

All toxicities were managed symptomatically and dose reduction done whenever required.

Clinical photographs

Patients' clinical photographs were acquired during each visit to the hospital as well as via Whatsapp on weekly basis for closely monitoring the visible tumour (especially oral cavity lesions) so as to promptly identify any sign of disease progression as well as mucositis at the earliest. Clinical photographs were used as a reference for comparison of the tumour during physical visit by the patient to the hospital.

The List of variables and Statistical Analysis:

Independent variables: Age, Gender, Prior substance use, clinical stage, tumour size, nodal status, prior treatment, histology of the tumour, number of chemo cycles, post metronomic chemotherapy treatment are main independent variables.

Outcome variables: Serial QOL measurements, Serial photographs to evaluate visible tumour volume are the main outcome variables and progression free survival and overall survival was also studied.

Data Analysis: The Various variables measured were analysed using descriptive and inferential statistics. Distribution of data of categorical variables such as, gender, clinical characteristics, histopathology, clinical stage, type of prior treatment was expressed as frequency and percentages. The continuous data such as age, QOL, overall survival and

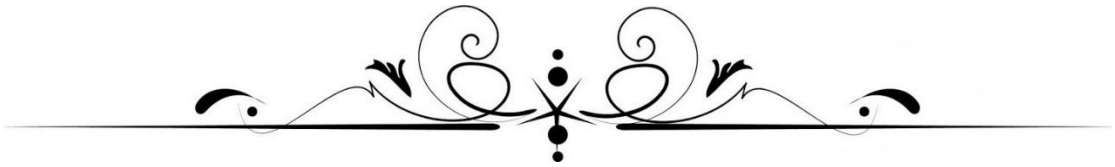
progression free survival on metronomic chemotherapy were expressed as mean or median. The change in QOL before and after each cycle of metronomic chemotherapy was compared using t test and Mann-Whitney u test for parametric and non-parametric data respectively. Survival analysis was done by Kaplan Meier plots and median follow up by reverse Kaplan Meier. All statistical analysis was carried out at 5% level of significance and 95% confidence interval and p value < 0.05 was considered statistically significance. The statistical analysis was done using Python and its libraries pandas, matplotlib, plotly, scipy, scikit learn and python stats module(59).

Statistical tests used in this study are as follows:

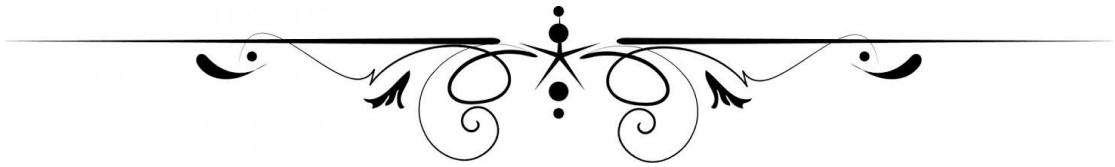
Sr. No	Statistical analysis
The data was checked for normal distribution using Shapiro Wilk Test wherever applicable	
1	**Comparison of QOL before and after each cycle**
	t test
	Mann-Whitney u test
2	**Change in QOL with age groups before and after each cycle of metronomic chemotherapy**
	t test
	Mann-Whitney u test
3	**Change in QOL with gender before and after each cycle of metronomic chemotherapy**
	t-test
	Mann-Whitney u test
4	**Change in QOL with site before and after each cycle of metronomic chemotherapy**

	t-test
	Mann-Whitney u test
5	**change in QOL with stage before and after each cycle of metronomic chemotherapy**
	t-test
	Mann-Whitney u test
6	**Change in QOL with type of disease before and after each cycle of metronomic chemotherapy**
	t-test
	Mann-Whitney u test
7	**Change in QOL with performance status before and after each cycle of metronomic chemotherapy**
	t-test
	Mann-Whitney u test
8	**Change in QOL with prior treatment before and after each cycle of metronomic chemotherapy**
	t-test
	Mann-Whitney u test
9	**Survival analysis**
	Kaplan-Meier survival analysis

Table 1: STATISTICAL TESTS USED IN THE STUDY



RESULTS



RESULTS

DEMOGRAPHIC DATA

TOTAL NUMBER OF PATIENTS: 43

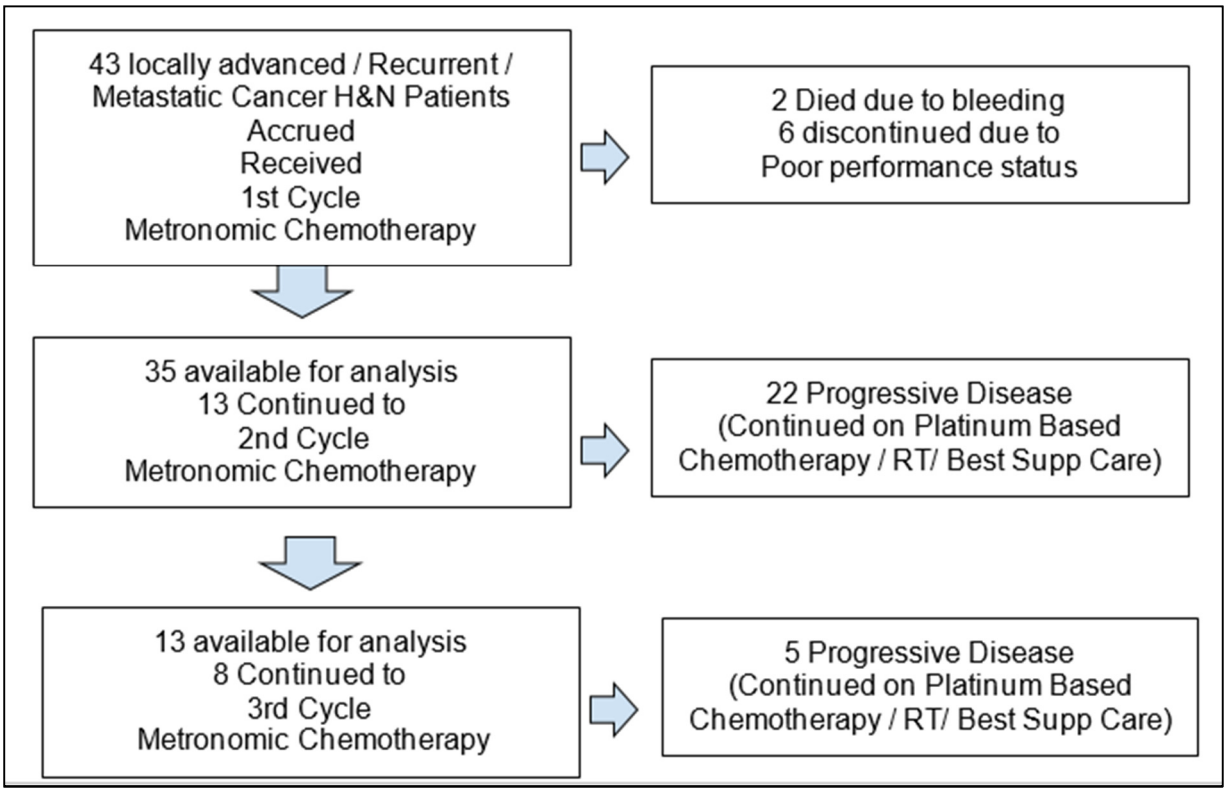


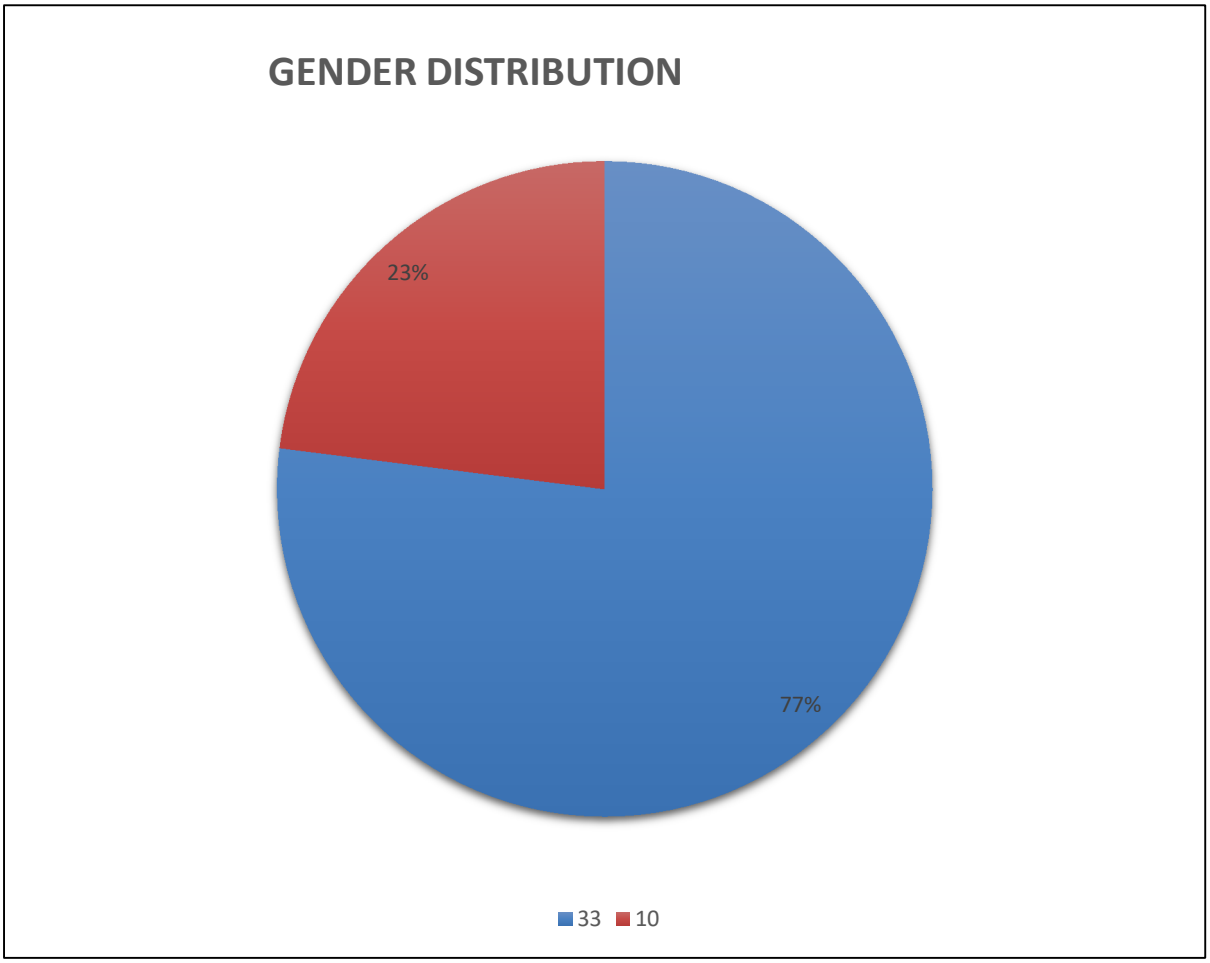
Figure 8: Flowchart representing patient accrual and number of patients available for analysis throughout the study

Total 43 number of patients were accrued in the study and started on study protocol. 2 patients died due to tumour bleed within a month. Many patients were eligible only for best supportive care at different time points. Ultimately only 13 patients were available for 2nd cycle and 8 for the 3rd cycle. At the time of analysis 26 (60.4%) patients have died and 16 (37.2%) patients are still alive and 1 patient has been lost to follow up.

GENDER DISTRIBUTION

SEX	NUMBER	PERCENTAGE
M	33	77%
F	10	23%

Table 2:GENDER DISTRIBUTION



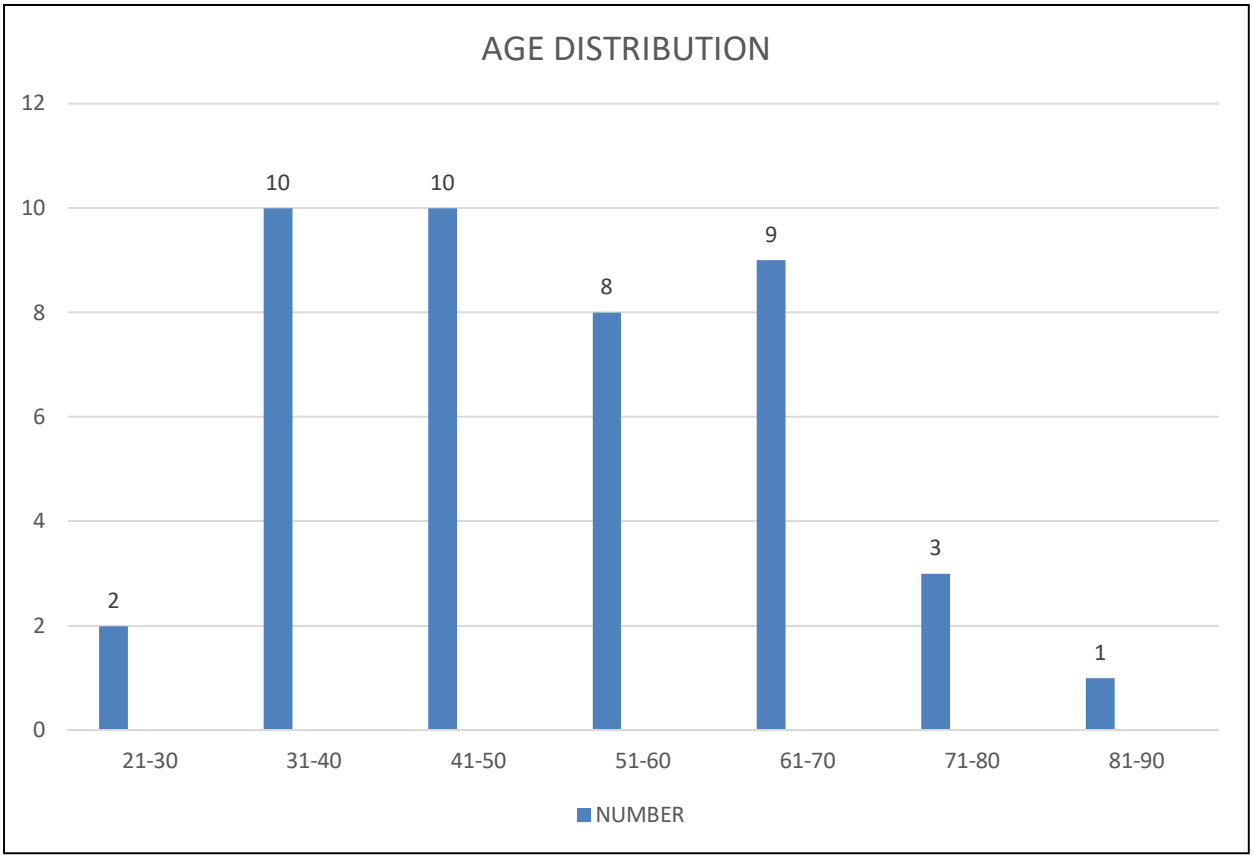
PLOT 1:GENDER DISTRIBUTION

Gender distribution: Majority of the patients in the study were of male gender (77%).

AGE DISTRIBUTION

AGE GROUP	NUMBER
21-30	2
31-40	10
41-50	10
51-60	8
61-70	9
71-80	3
81-90	1

Table 3: AGE DISTRIBUTION



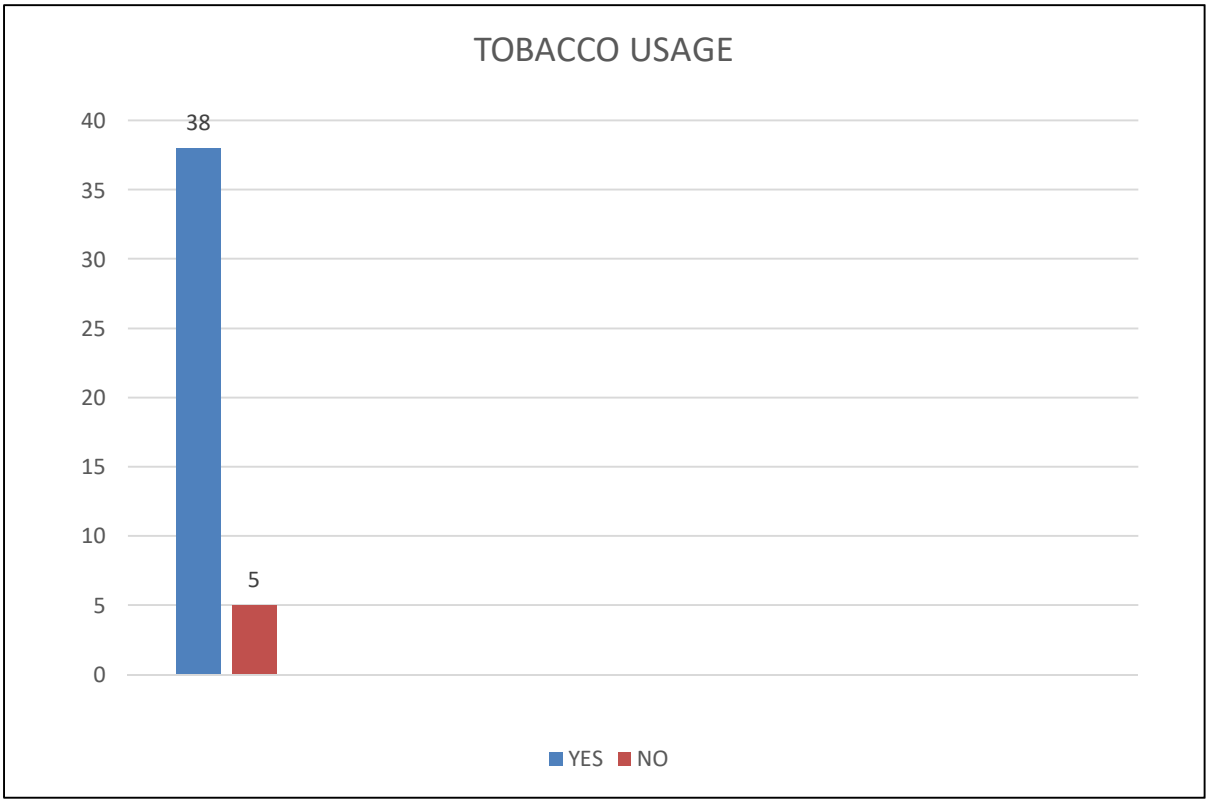
PLOT 2: AGE DISTRIBUTION

Age Groups: Majority of the patients were of age 31-50 years (46.5%).

TOBACCO USAGE

TOBACCO USAGE	YES	NO
	38	5

Table 4: TOBACCO USAGE



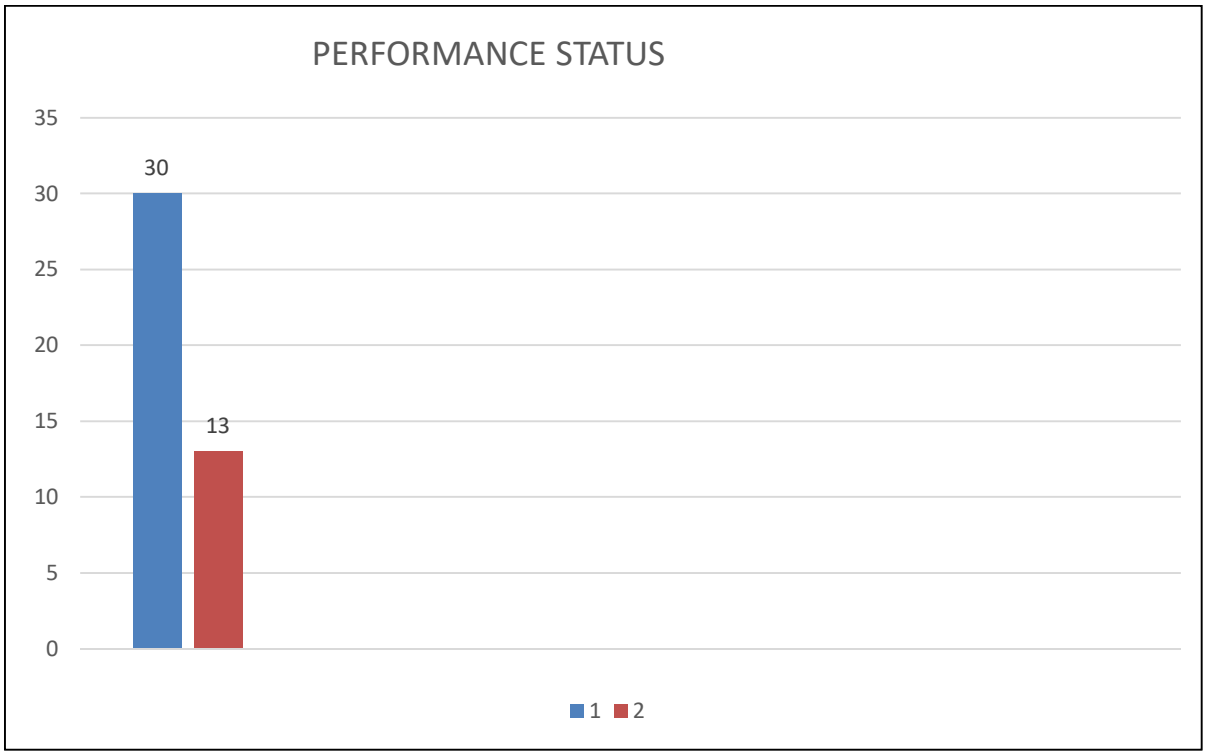
PLOT 3: TOBACCO USAGE

Tobacco usage: Majority of the patients were tobacco users (88.3%).

INITIAL PERFORMANCE STATUS

INITIAL PERFORMANCE STATUS	1	2
	30	13

Table 5: INITIAL PERFORMANCE STATUS



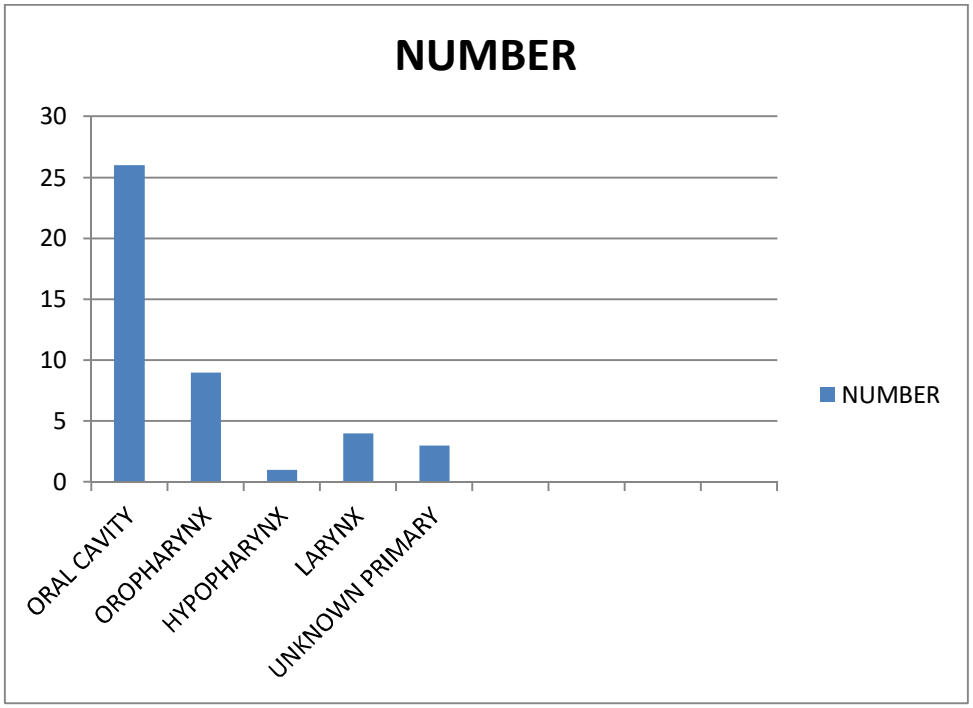
PLOT 4: INITIAL PERFORMANCE STATUS

Performance status: Majority of the patients were having a performance status of ECOG: 1 (69.7%)

PRIMARY SITE OF DISEASE

SITE	NUMBER
ORAL CAVITY	26
OROPHARYNX	9
HYPOPHARYNX	1
LARYNX	4
UNKNOWN PRIMARY	3

Table 6: PRIMARY SITE OF DISEASE



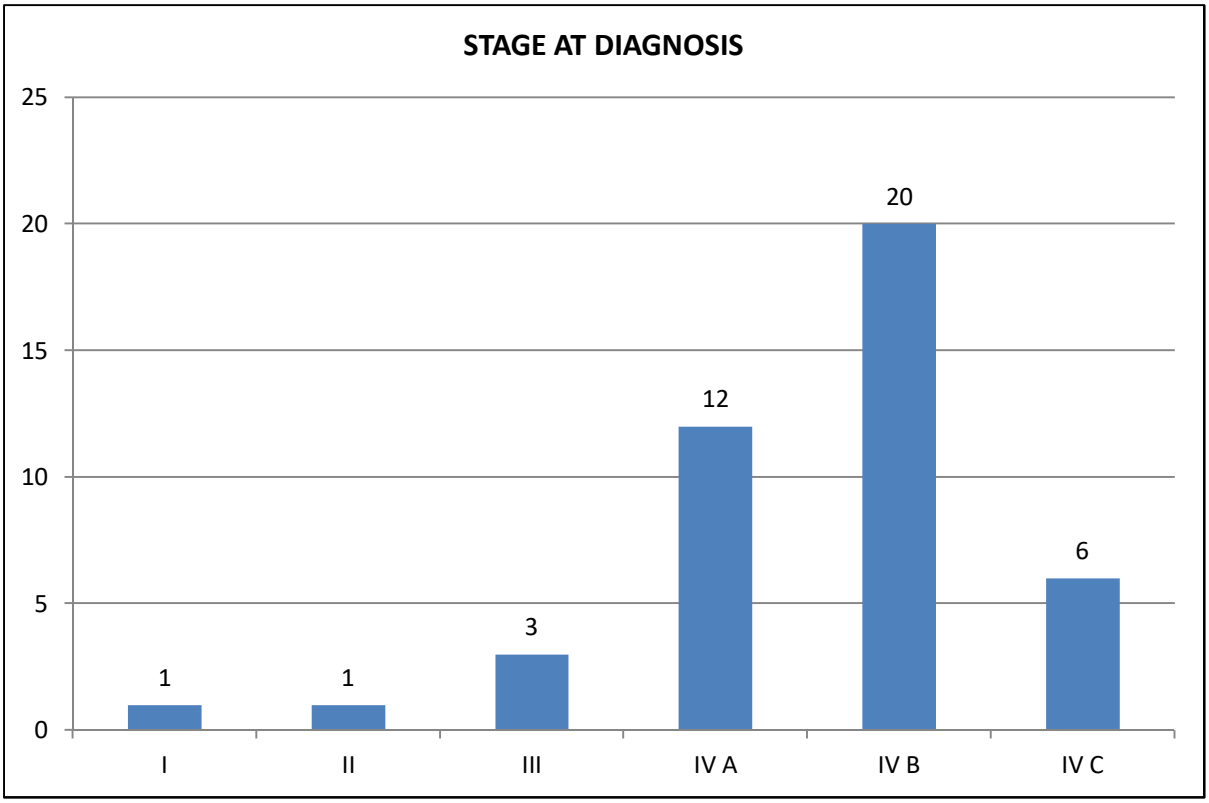
PLOT 5: PRIMARY SITE OF DISEASE

Primary site of disease: Most of the patients in the study group had oral cavity as the primary site of involvement (60.4%)

STAGE AT THE TIME OF DIAGNOSIS

STAGE AT DIAGNOSIS	NUMBER OF PATIENTS
I	1
II	1
III	3
IV A	12
IV B	20
IV C	6

Table 7: STAGE AT THE TIME OF DIAGNOSIS



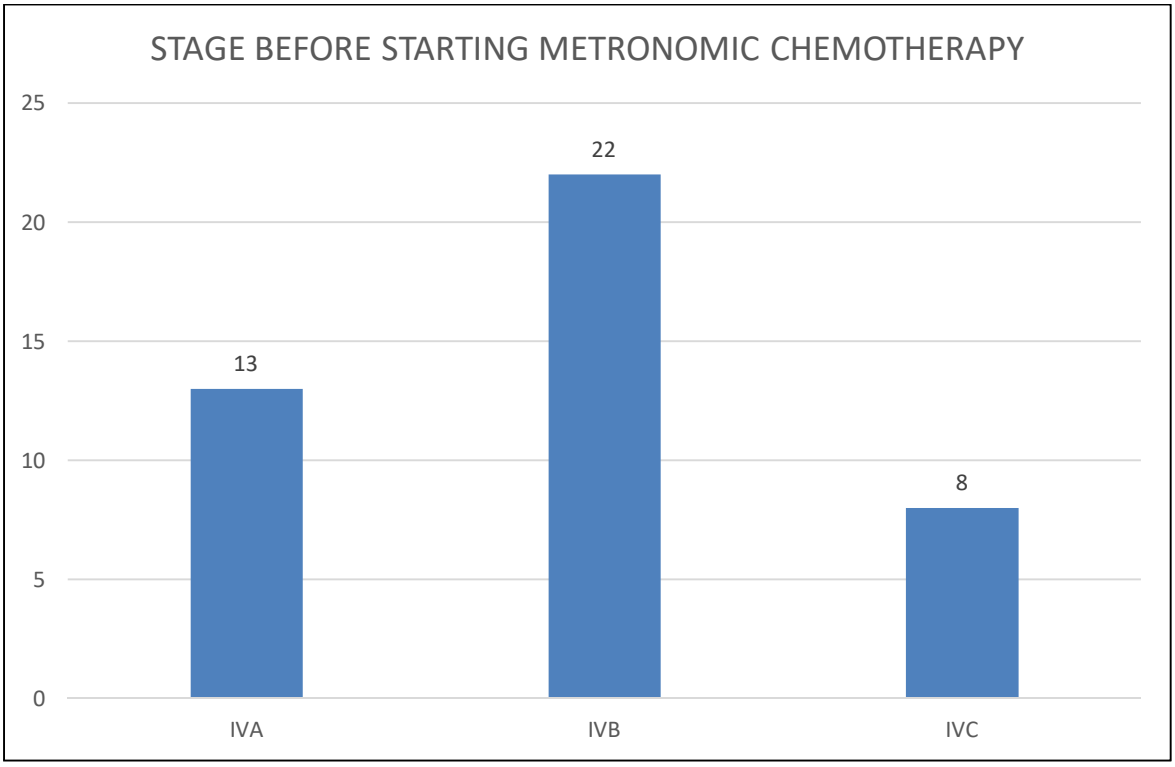
PLOT 6: STAGE AT THE TIME OF DIAGNOSIS

Stage at diagnosis: Most of the patients were in stage IVB (46.5%) at the time of diagnosis.

STAGE BEFORE STARTING METRONOMIC CHEMOTHERAPY

STAGE	NO : OF PATIENTS
IVA	13
IVB	22
IVC	8

Table 8: STAGE BEFORE STARTING METRONOMIC CHEMOTHERAPY



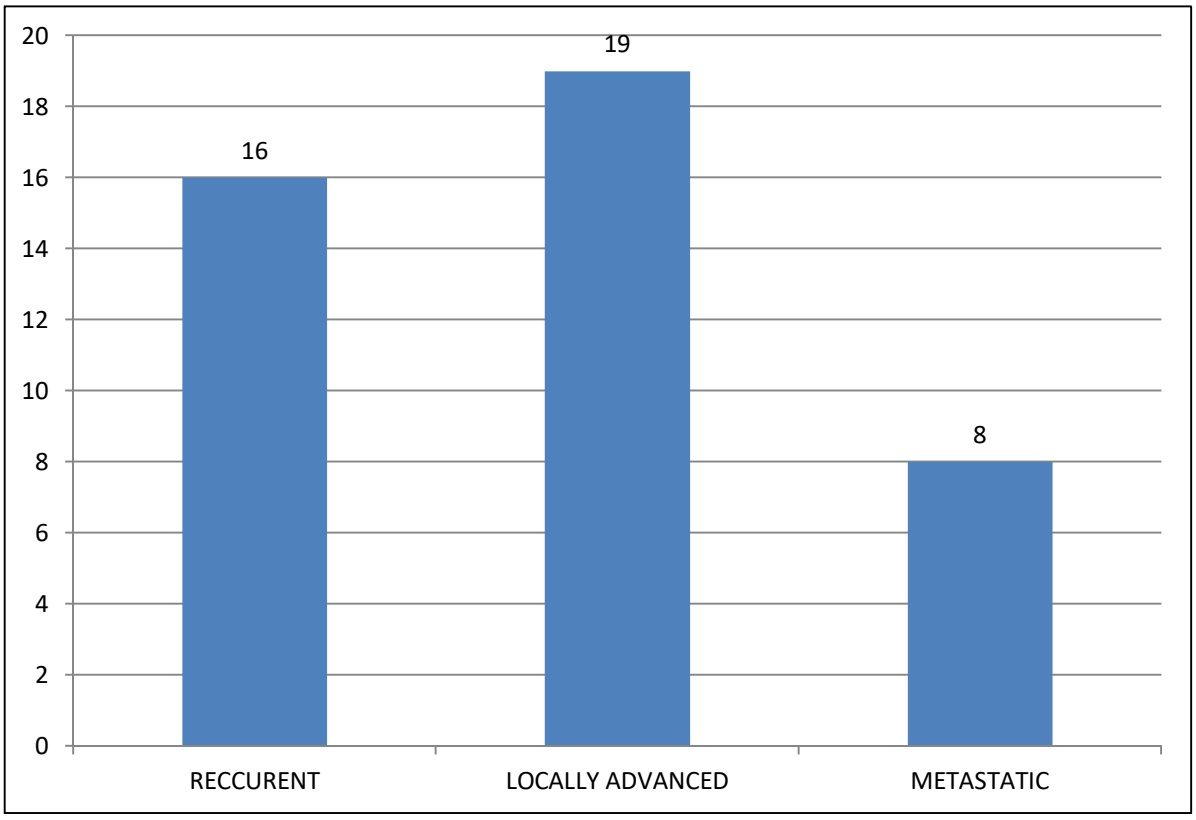
PLOT 7: STAGE BEFORE STARTING METRONOMIC CHEMOTHERAPY

Stage at accrual into study: Most of the patients were of stage IVB (51.1%) at the time of accrual

TYPE OF DISEASE

DISEASE TYPE	NO : OF PATIENTS
RECCURENT	16
LOCALLY ADVANCED	19
METASTATIC	8

Table 9: TYPE OF DISEASE



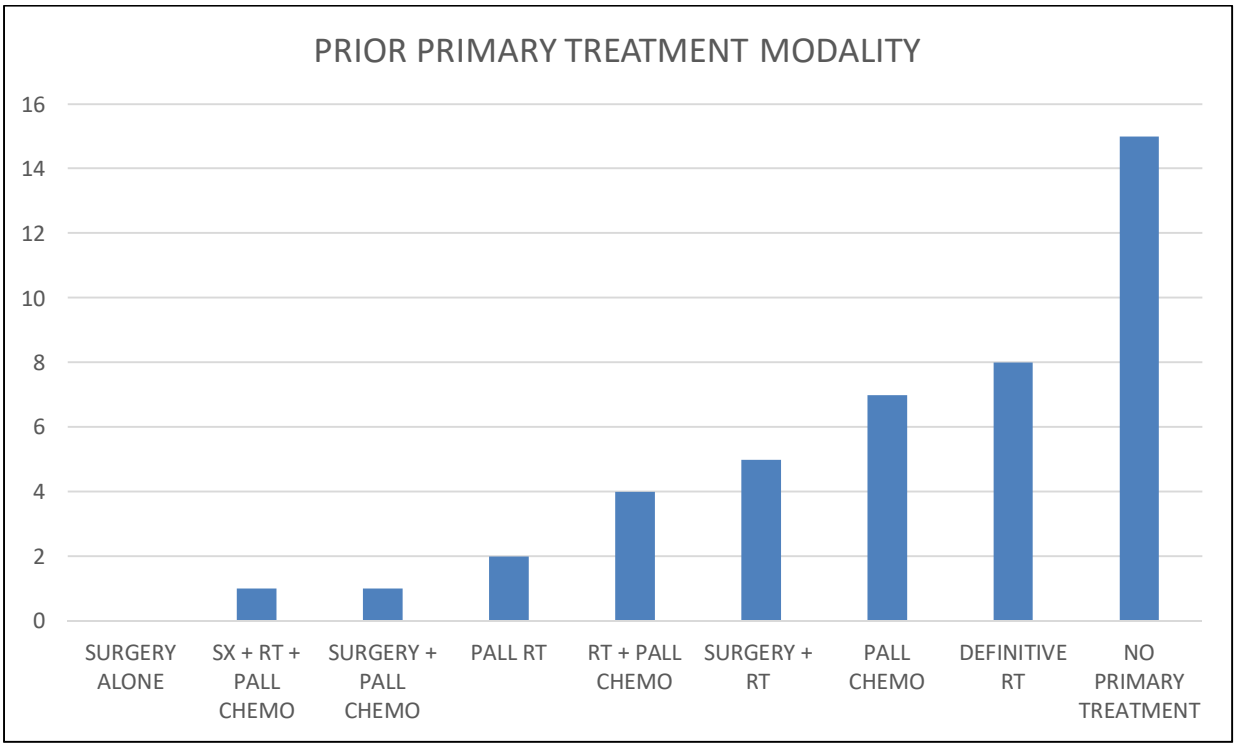
PLOT 8: TYPE OF DISEASE

Type of disease: majority of patients were having locally advanced disease (44.2%) followed by recurrent disease (37.2%).

PRIOR PRIMARY TREATMENT MODALITY

MODALITY	NO: OF PATIENTS
SURGERY ALONE	0
SURGERY + RT + PALL CHEMO	1
SURGERY + PALL CHEMO	1
PALL RT	2
RT + PALL CHEMO	4
SURGERY + RT	5
PALL CHEMO	7
DEFINITIVE RT	8
NO PRIMARY TREATMENT	15

Table 10: PRIOR PRIMARY TREATMENT MODALITY



PLOT 9: PRIOR PRIMARY TREATMENT MODALITY

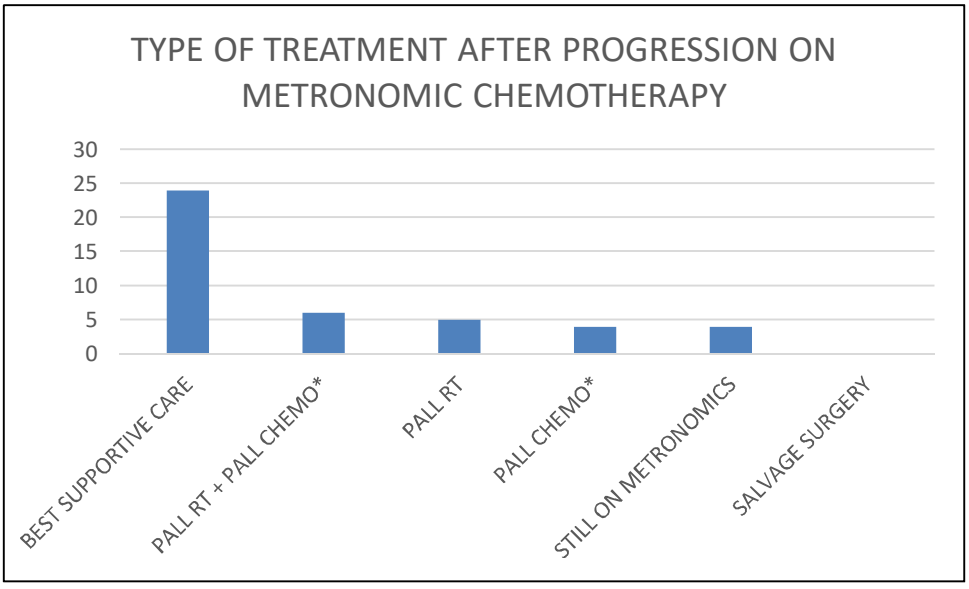
Prior primary treatment received: Most of the patients were treatment naïve (35%) at the time of accrual into the study and definitive radiation therapy was the most common modality received by 18.6% of patients as their primary modality of treatment.

TYPE OF TREATMENT AFTER PROGRESSION ON METRONOMIC CHEMOTHERAPY

MODALITY	NO: OF PATIENTS
BEST SUPPORTIVE CARE	24
PALL RT + PALL CHEMO*	6
PALL RT	5
PALL CHEMO*	4
STILL ON METRONOMICS	4
SALVAGE SURGERY	0

*Palliative chemotherapy: paclitaxel combined with cisplatin or carboplatin

Table 11: TYPE OF TREATMENT AFTER PROGRESSION ON METRONOMIC CHEMOTHERAPY



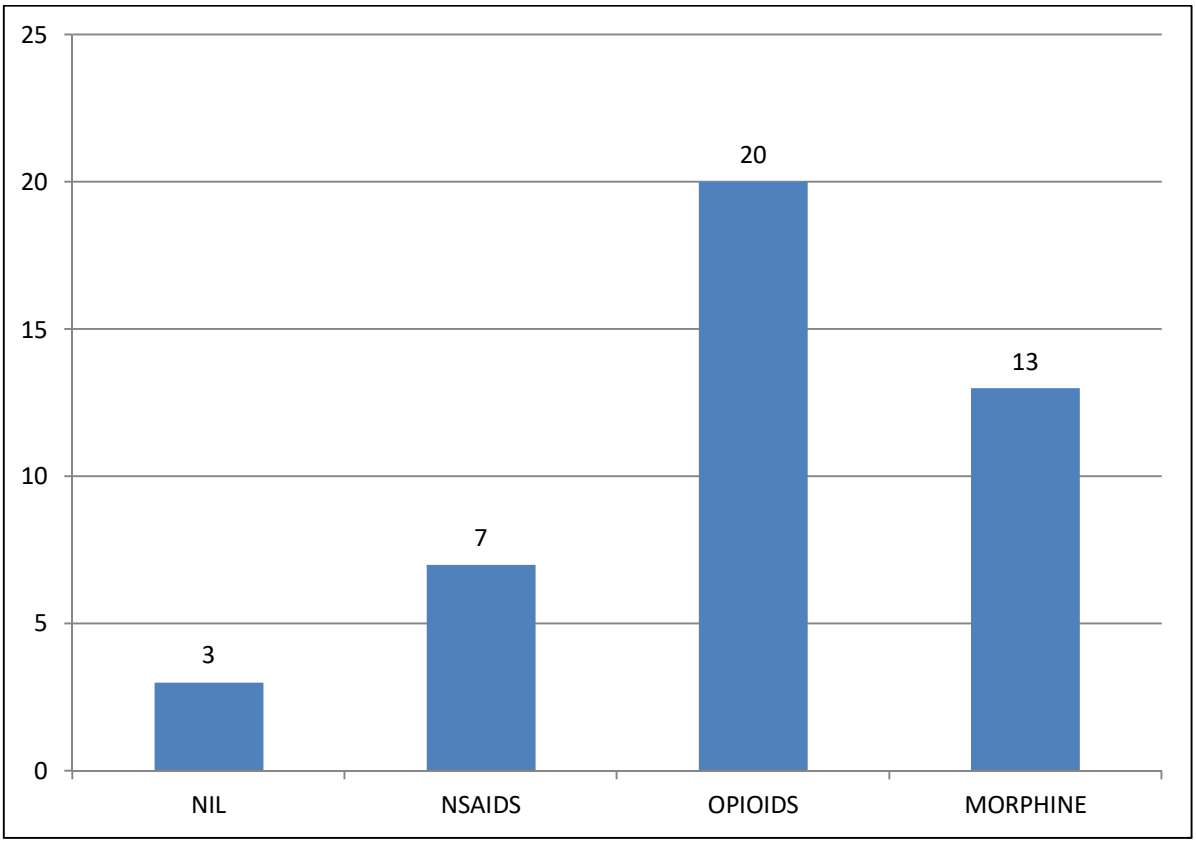
PLOT 10: TYPE OF TREATMENT AFTER PROGRESSION ON METRONOMIC CHEMOTHERAPY

Treatment received on progression on metronomic chemotherapy: Majority of the patients received Best Supportive Care (55.8%) on progression on metronomic chemotherapy.

PAIN MEDICATIONS

PAIN MEDS	NO : OF PATIENTS
NIL	3
NSAIDS	7
OPIOIDS(TRAMADOL)	20
MORPHINE	13

Table 12: PAIN MEDICATIONS

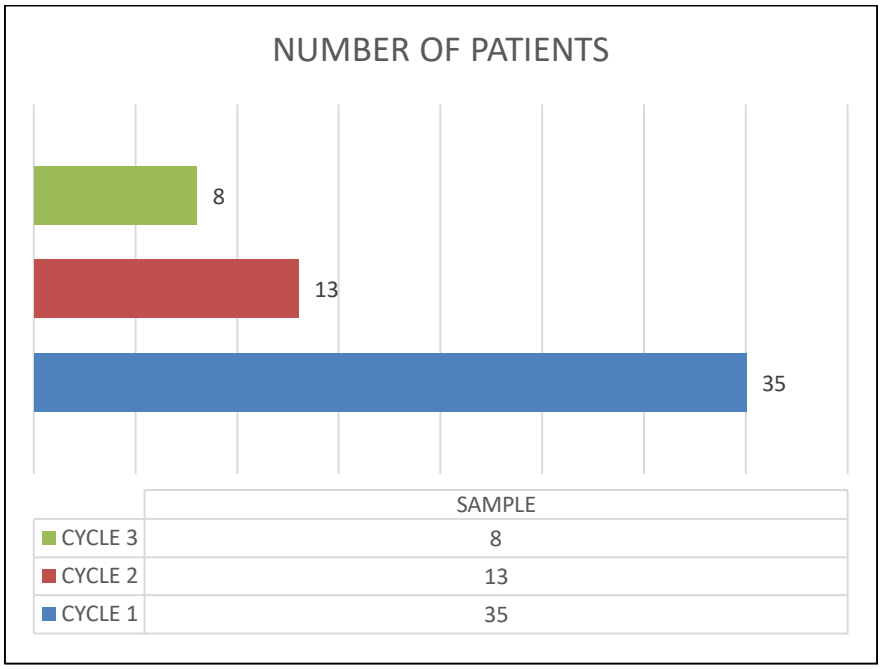


PLOT 11: PAIN MEDICATIONS

Out of 43 patients 3 were not on any pain medications except Celecoxib (part of study protocol) and the rest who received pain medications majority had pain control on opioids other than morphine (46.5%).

RESULTS OF QOL

NUMBER OF PATIENTS AT EACH CYCLE

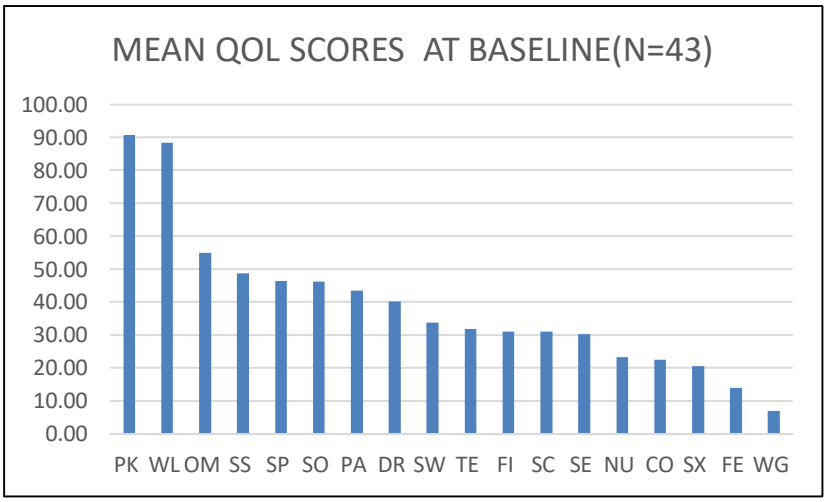


PLOT 12: NUMBER OF PATIENTS AT EACH CYCLE

MEAN QOL SCORES AT BASELINE

SYMPTOM SCALE	NO: OF PATIENTS(N)	MEAN QOL SCORE
PAIN KILLERS (PK)	43	90.70
WEIGHT LOSS(WL)	43	88.37
MOUTH OPENING(OM)	43	55.04
STICKY SALIVA(SS)	43	48.84
SPEECH(SP)	43	46.51
SOCIAL EATING(SO)	43	46.32
PAIN(PA)	43	43.60
DRY MOUTH(DR)	43	40.31
SWALLOWING(SW)	43	33.91
TEETH(TE)	43	31.78
FELT ILL(FI)	43	31.01
SOCIAL CONTACT(SC)	43	31.01
SENSES(SE)	43	30.23
NUTRITIONAL SUPPLEMENTS(NU)	43	23.26
COUGH(CO)	43	22.48
SEXUALITY(SX)	30	20.56
FEEDING TUBE(FE)	43	13.95
WEIGHT GAIN(WG)	43	6.98

Table 13: MEAN QOL SCORES AT BASELINE

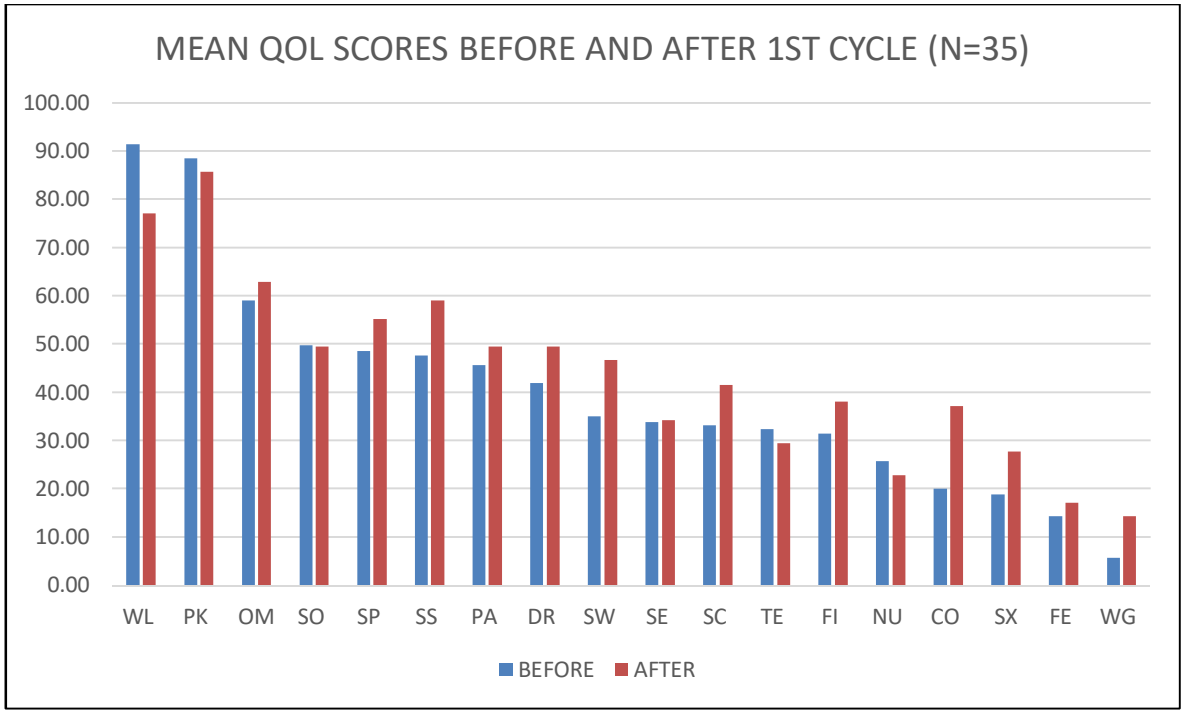


PLOT 13: MEAN QOL SCORES AT BASELINE

MEAN QOL SCORES BEFORE AND AFTER 1ST CYCLE OF METRONOMIC CHEMOTHERAPY (N=35)

SYMPTOM SCALE	MEAN SCORES AT BASELINE	MEAN SCORES AFTER 1ST CYCLE
WL	91.43	77.14
PK	88.57	85.71
OM	59.05	62.86
SO	49.76	49.52
SP	48.57	55.24
SS	47.62	59.05
PA	45.71	49.52
DR	41.90	49.52
SW	35.00	46.67
SE	33.81	34.29
SC	33.14	41.52
TE	32.38	29.52
FI	31.43	38.10
NU	25.71	22.86
CO	20.00	37.14
SX	18.84	27.78
FE	14.29	17.14
WG	5.71	14.29

Table 14: MEAN QOL SCORES BEFORE AND AFTER 1ST CYCLE OF METRONOMIC CHEMOTHERAPY

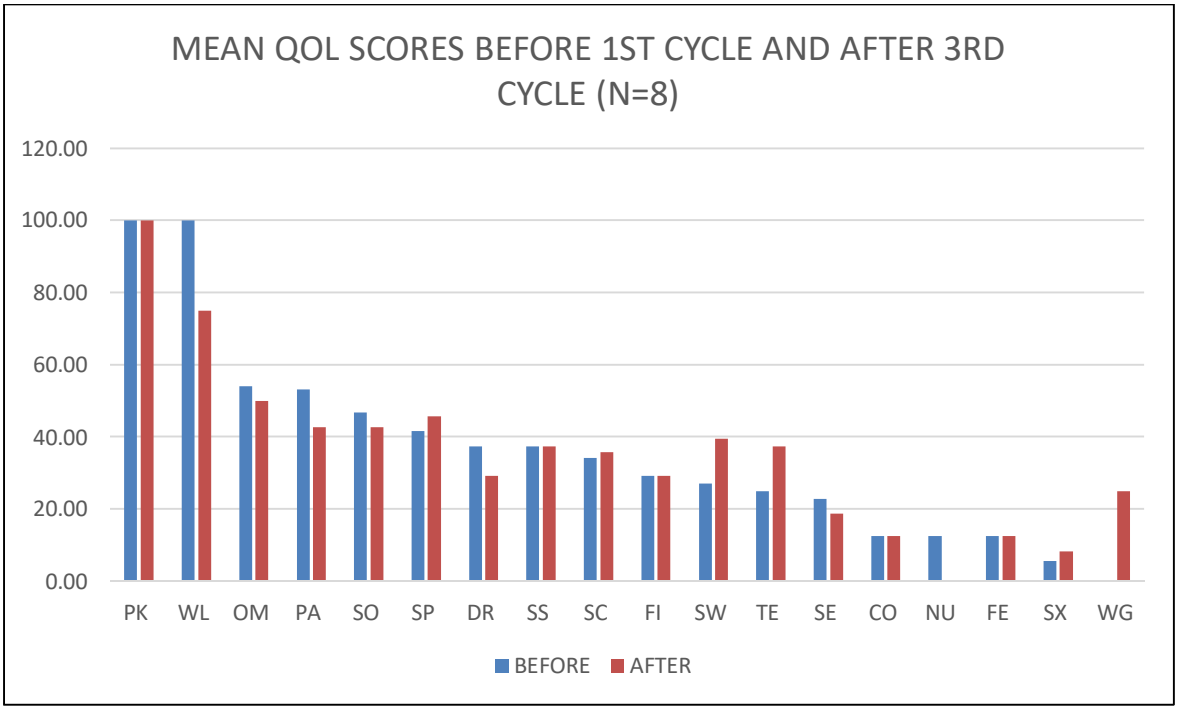


PLOT 14: MEAN QOL SCORES BEFORE AND AFTER 1ST CYCLE OF METRONOMIC CHEMOTHERAPY

MEAN QOL SCORES BEFORE 1ST CYCLE AND AFTER 3RD CYCLE OF METRONOMIC CHEMOTHERAPY (N=8)

SYMPTOM SCALE	MEAN SCORES AT BASELINE	MEAN SCORES AFTER 3RD CYCLE
PK	100.00	100.00
WL	100.00	75.00
OM	54.17	50.00
PA	53.13	42.71
SO	46.88	42.71
SP	41.67	45.83
DR	37.50	29.17
SS	37.50	37.50
SC	34.17	35.83
FI	29.17	29.17
SW	27.08	39.58
TE	25.00	37.50
SE	22.92	18.75
CO	12.50	12.50
NU	12.50	0.00
FE	12.50	12.50
SX	5.56	8.33
WG	0.00	25.00

Table 15: MEAN QOL SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

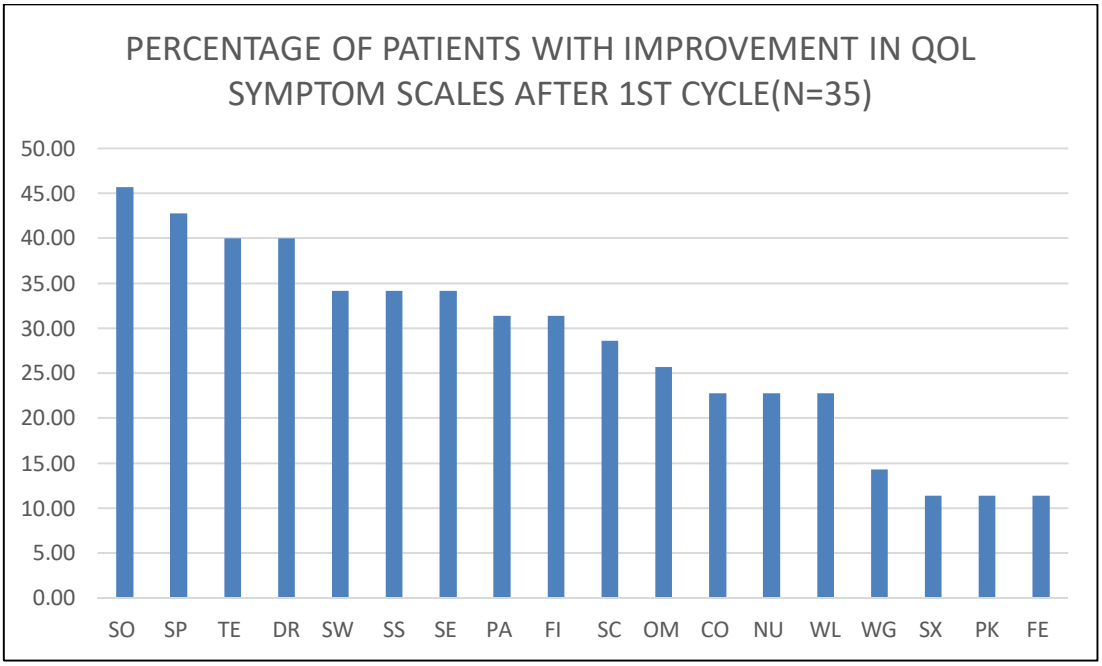


PLOT 15: MEAN QOL SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

PERCENTAGE OF PATIENTS WITH IMPROVEMENT IN QOL SYMPTOM SCALES AFTER FIRST CYCLE

QOL SYMPTOM SCALE	PERCENTAGE OF PATIENTS SHOWING IMPROVEMENT
SO	45.70
SP	42.80
TE	40.00
DR	40.00
SW	34.20
SS	34.20
SE	34.20
PA	31.40
FI	31.40
SC	28.6
OM	25.70
CO	22.80
NU	22.80
WL	22.80
WG	14.3
SX	11.40
PK	11.40
FE	11.40

Table 16: PERCENTAGE OF PATIENTS WITH IMPROVEMENT IN QOL SYMPTOM SCALES AFTER FIRST CYCLE

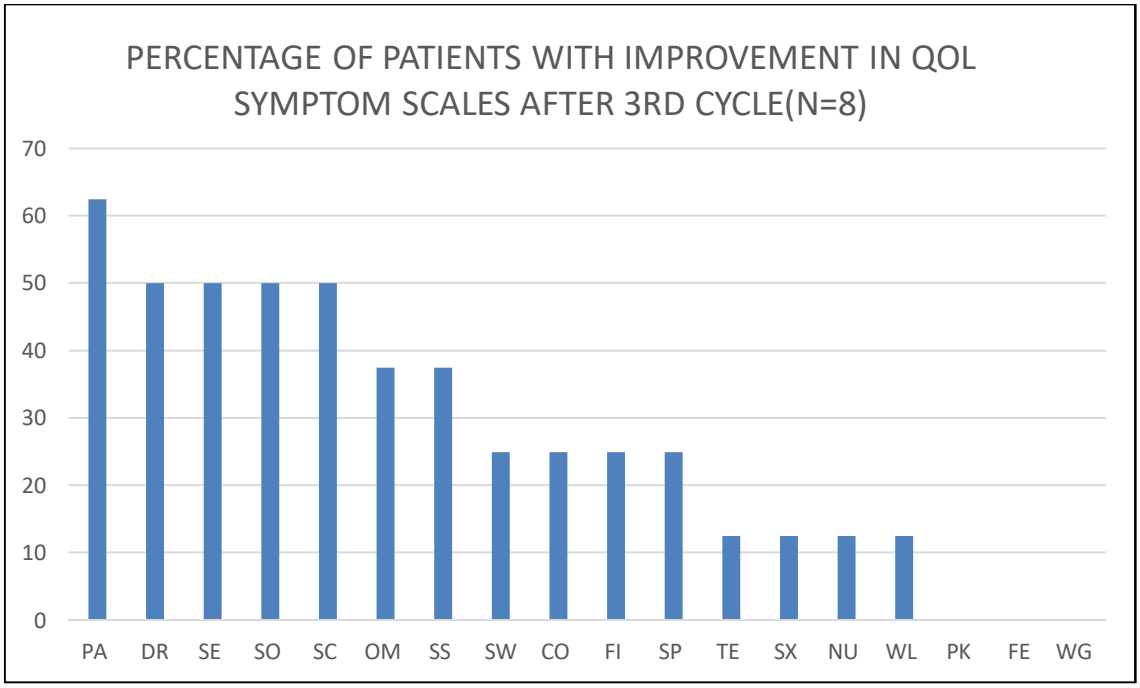


PLOT 16: PERCENTAGE OF PATIENTS WITH IMPROVEMENT IN QOL SYMPTOM SCALES AFTER FIRST CYCLE

PERCENTAGE OF PATIENTS WITH IMPROVEMENT IN QOL SYMPTOM SCALES AFTER 3RD CYCLE

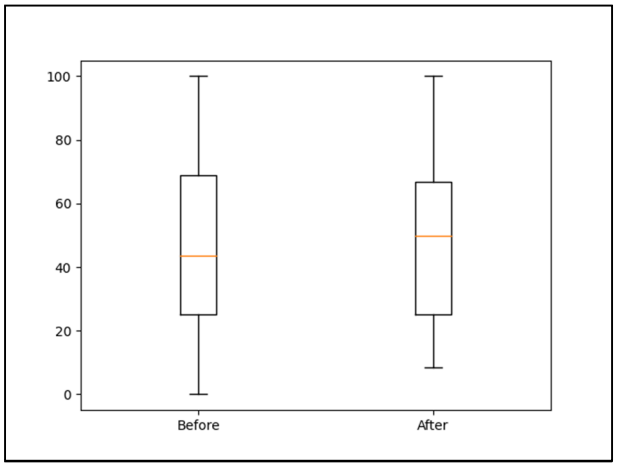
QOL SYMPTOM SCALE	PERCENTAGE OF PATIENTS SHOWING IMPROVEMENT
PA	62.5
DR	50
SE	50
SO	50
SC	50
OM	37.5
SS	37.5
SW	25
CO	25
FI	25
SP	25
TE	12.5
SX	12.5
NU	12.5
WL	12.5
PK	0
FE	0
WG	0

Table 17: PERCENTAGE OF PATIENTS WITH IMPROVEMENT IN QOL SYMPTOM SCALES AFTER THIRD CYCLE



PLOT 17: PERCENTAGE OF PATIENTS WITH IMPROVEMENT IN QOL SYMPTOM SCALES AFTER THIRD CYCLE

COMPARISON OF PAIN SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY



PLOT 18: COMPARISON OF PAIN SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

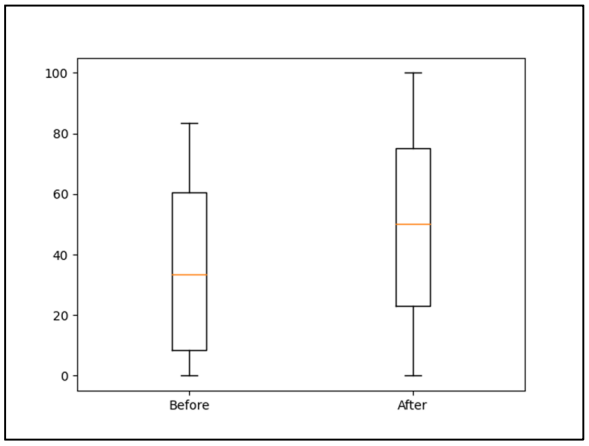
The above plot shows Box and Whisker plot between before and after values of pain scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is -8.33 with a p value =0.56.

Thus there was no worsening in pain scores with metronomic chemotherapy at the end of first cycle.

Most of these patients were having average pain score of 2 out of 4 and were on pain medications like additional NSAIDS (besides celecoxib) or tramadol or morphine as indicated and needed by the patients. The requirement for pain medications thus did not reduced significantly with a month of metronomic chemotherapy.

There was no statistically significant change in pain scores related QOL between age groups, genders, sub sites, stages, and state of disease, performance status and prior treatment groups at the end of first cycle.

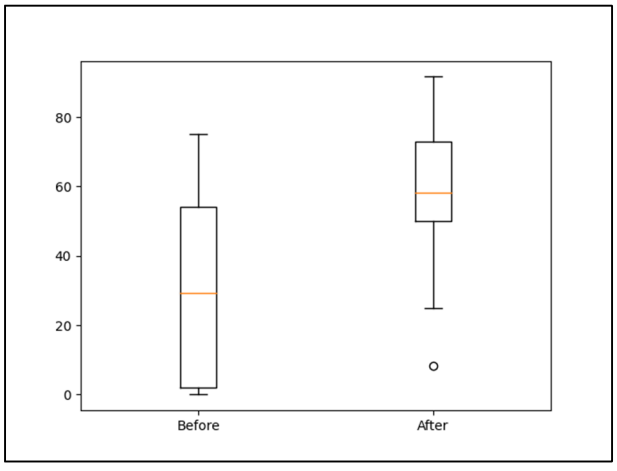
COMPARISON OF SWALLOWING SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY



PLOT 19: COMPARISON OF SWALLOWING SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of swallowing scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is -16.67 with a p value =0.09. Thus there was no significant worsening in swallowing scores with metronomic chemotherapy at the end of first cycle.

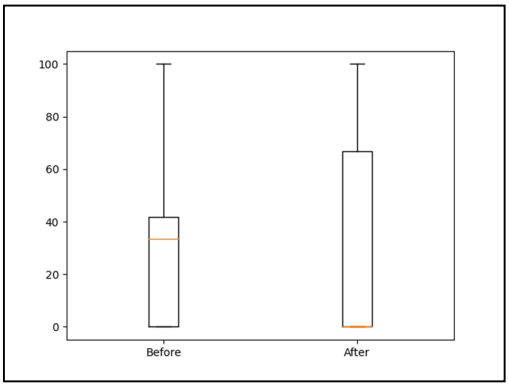
There was no statistically significant change in swallowing scores between age groups, genders, sub sites, stages, performance status and prior treatment groups. However, there was a statistically significant change in swallowing scores after 1st cycle in stage IV A with a p value of 0.04.



PLOT 20: COMPARISON OF SWALLOWING SCORES IN STAGE IVA PATIENTS BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

There was no statistically significant change in swallowing scores in stage IV B and IV C.

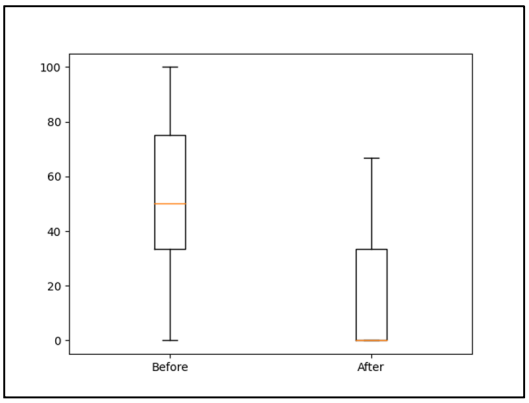
COMPARISON OF TOOTH SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY



PLOT 21: COMPARISON OF TOOTH SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of tooth scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is 33.33 with a p value =0.74. Thus there was no significant worsening in tooth scores with metronomic chemotherapy at the end of first Cycle.

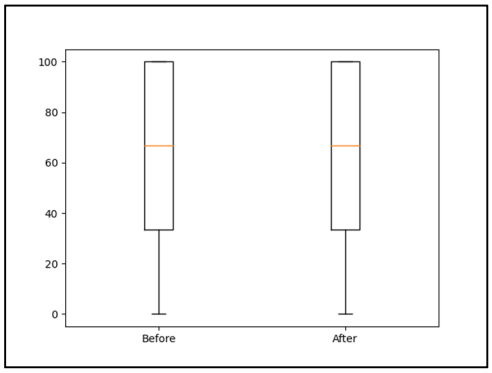
There was no statistically significant change in tooth scores between age groups, genders, sub sites, stages, and state of disease and performance Status. However, there was statistically significant improvement in tooth scores of previously untreated patients at the end of first cycle with a p value of 0.01.



PLOT 22: COMPARISON OF TOOTH SCORES IN PREVIOUSLY UNTREATED PATIENTS BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

However, there was no statistically significant change in tooth scores in other prior treatment groups.

COMPARISON OF MOUTH OPENING SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY



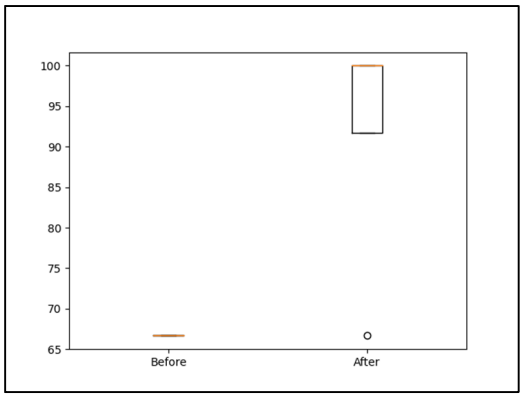
PLOT 23:COMPARISON OF MOUTH OPENING SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of mouth opening scores after 1st cycle of metronomic chemotherapy. The median values before and after 1st cycle is 0 with a p value =0.67

Thus there was no significant worsening in mouth opening scores with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in mouth opening scores between age groups, genders, sub sites, and state of disease, performance status and prior treatment groups.

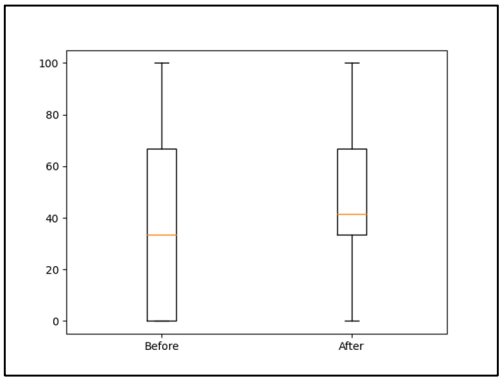
There was a statistically significant worsening in mouth opening scores in stage IVC after 1st cycle of metronomic chemotherapy with a p value of 0.02.



PLOT 24: COMPARISON OF MOUTH OPENING SCORES IN STAGE IVC GROUP OF PATIENTS BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

However there was no statistically significant change in mouth opening scores in stage IVA and IV B.

COMPARISON OF DRY MOUTH SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

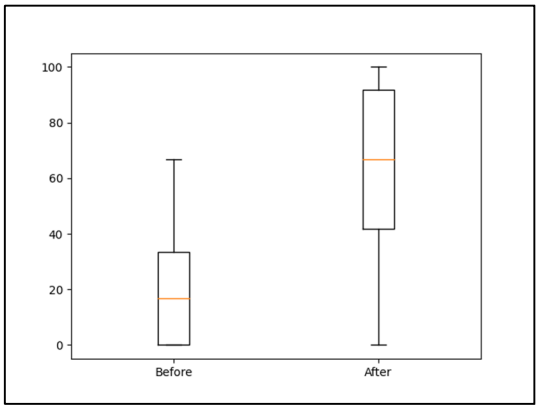


PLOT 25: COMPARISON OF DRY MOUTH SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of dry mouth scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is 0 with a p value =0.34. Thus there was no significant worsening in dry mouth scores with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in dry mouth scores between age groups, genders, sub sites, and state of disease, performance status and prior treatment groups.

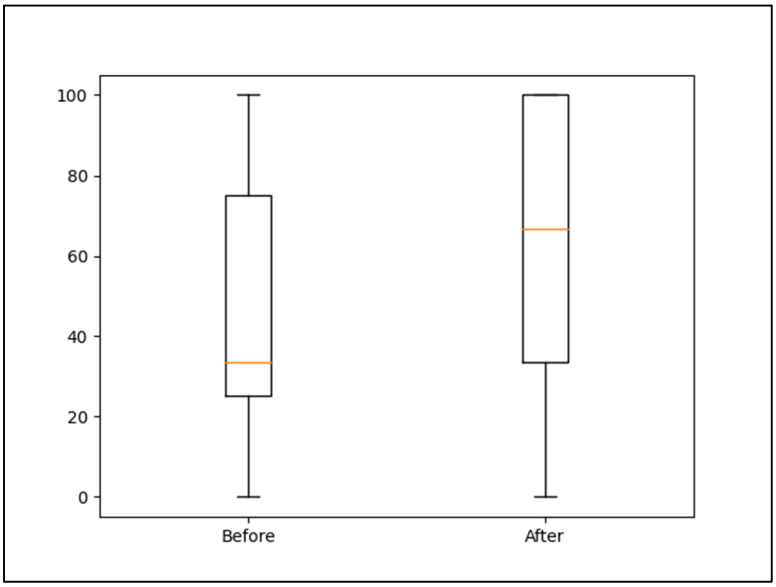
There was a statistically significant worsening in dry mouth scores in stage IVA after 1st cycle of metronomic chemotherapy with a p value of 0.01.



PLOT 26: COMPARISON OF DRY MOUTH SCORES IN STAGE IVA GROUP OF PATIENTS BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

However there was no statistically significant change in dry mouth scores in stage IVB and IVC.

COMPARISON OF STICKY SALIVA SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

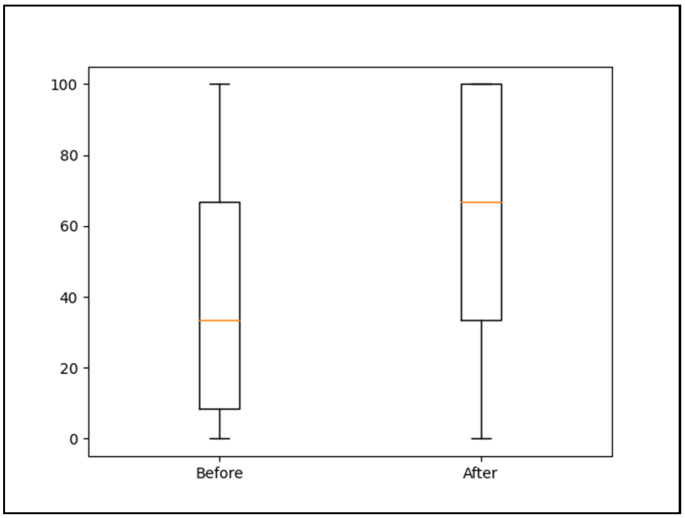


PLOT 27: COMPARISON OF STICKY SALIVA SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of sticky saliva scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is -33.33 with a p value =0.17. Thus there was no significant worsening in sticky saliva scores with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in sticky saliva scores between genders, sub sites, and state of disease, performance status and prior treatment groups.

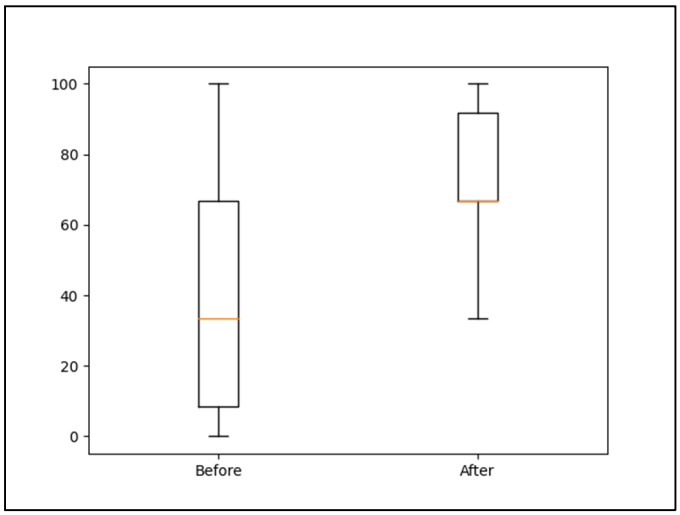
There was a statistically significant change in sticky saliva scores in age group >/= 40 years after 1st cycle of metronomic chemotherapy with a p value of 0.03.



PLOT 28: COMPARISON OF STICKY SALIVA SCORES IN AGE GROUP >/= 40 BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

However there was no statistically significant change in sticky saliva scores with age group <40 years.

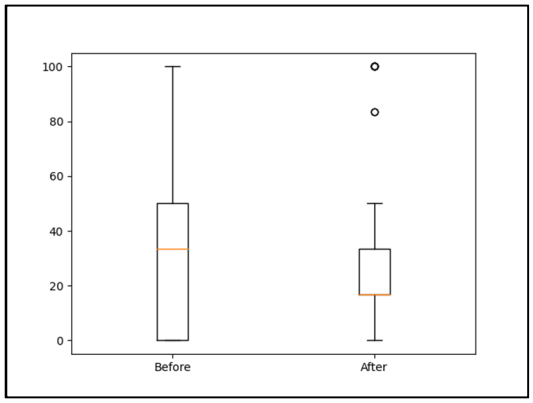
Also there was a statistically significant change in sticky saliva scores in stage IVA after 1st cycle of metronomic chemotherapy with a p value of 0.03.



PLOT 29: COMPARISON OF STICKY SALIVA SCORES IN STAGE IVA BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

However there was no statistically significant change in sticky saliva scores with stage IVB and IVC.

COMPARISON OF SENSES SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

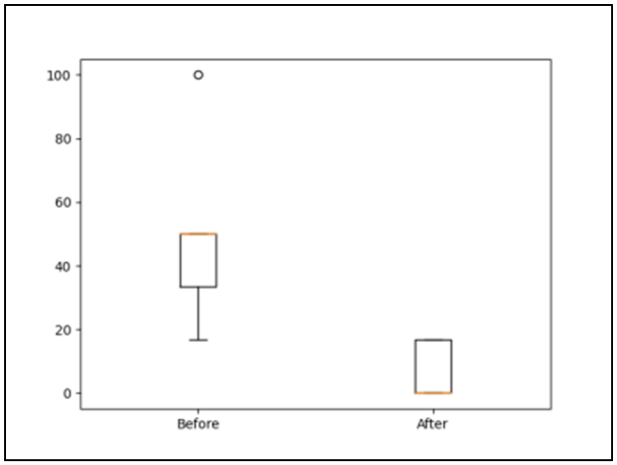


PLOT 30: COMPARISON OF SENSES SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of senses scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is 16.67 with a p value =0.95. Thus there was no significant worsening in senses scores with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in senses scores between age groups, genders, sub sites, stages, performance status and prior treatment groups.

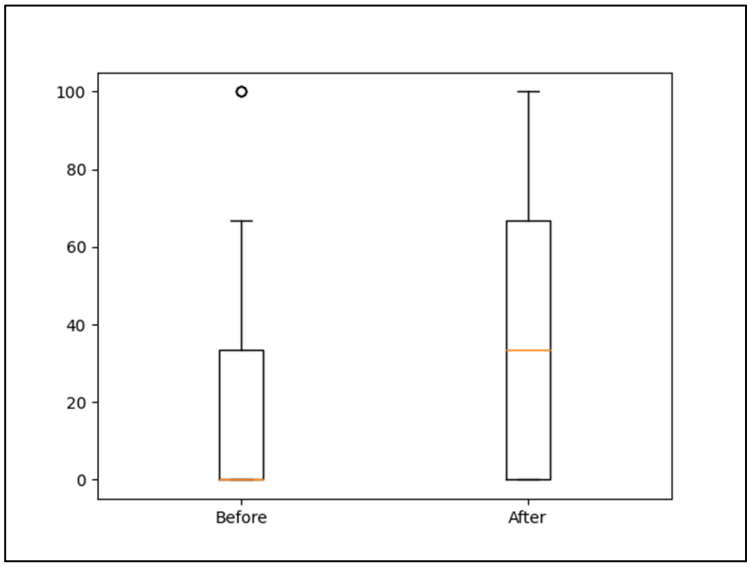
There was statistically significant change in senses scores with a p value of 0.01 in metastatic cases after 1st cycle of metronomic chemotherapy.



PLOT 31: COMPARISON OF SENSES SCORES IN METASTATIC PATIENTS BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

However there was no statistically significant change in senses scores in locally advanced or recurrent cases after 1st cycle.

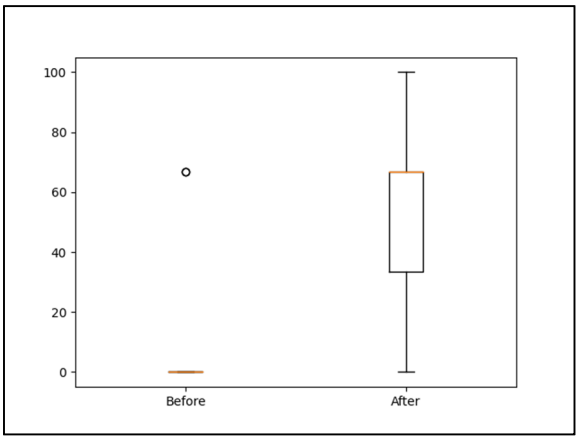
COMPARISON OF COUGHING SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY



PLOT 32: COMPARISON OF COUGHING SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of cough scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is -33.33 with a statistically significant p value =0.03. There was no statistically significant change in cough scores between genders, sub sites, and state of disease and prior treatment groups after 1st cycle of metronomic chemotherapy.

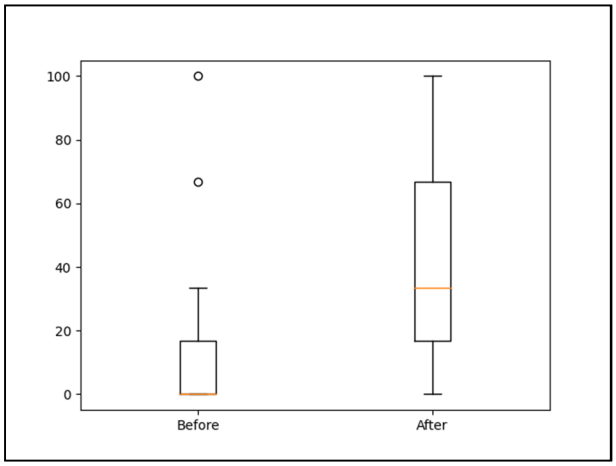
There was statistically significant change in cough scores in stage IVA with a p value of 0.006 after 1st cycle of metronomic chemotherapy.



PLOT 33: COMPARISON OF COUGHING SCORES IN STAGE IVA BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

However there was no statistically significant change in cough scores with stage IVB and IVC.

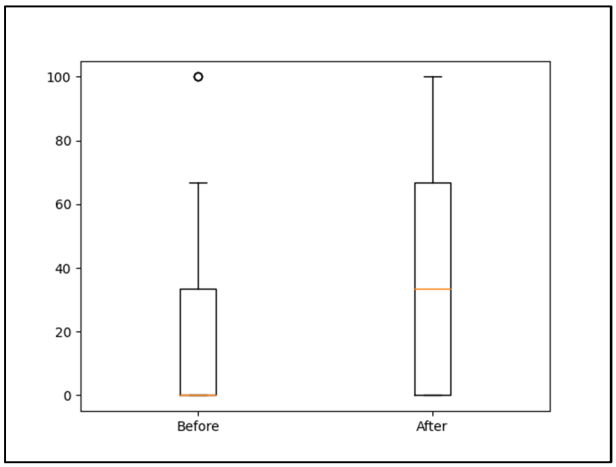
There was statistically significant change in cough scores in recurrent cases with a p value of 0.01 after 1st cycle of metronomic chemotherapy.



PLOT 34: COMPARISON OF COUGHING SCORES IN RECURRENT PATIENTS BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

However there was no statistically significant change in cough scores with locally advanced or metastatic cases.

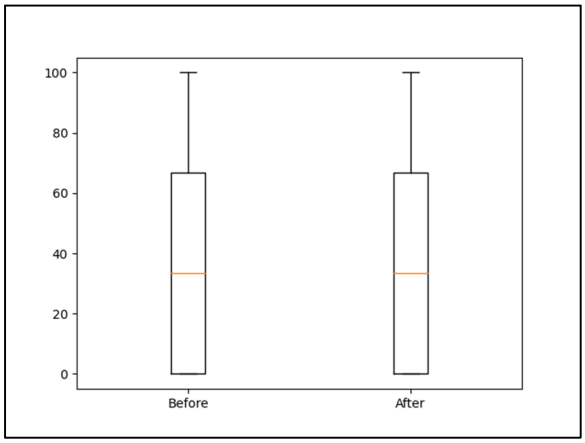
There was statistically significant change in cough scores in patients with performance status 1 with a p value of 0.006 after 1st cycle of metronomic chemotherapy.



PLOT 35: COMPARISON OF COUGHING SCORES IN PATIENTS WITH PS 1 BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

However there was no statistically significant change in cough scores in patients with performance status 2

COMPARISON OF FELT ILL SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

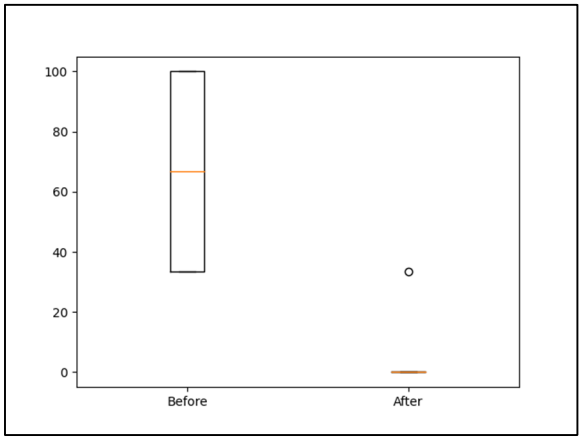


PLOT 36: COMPARISON OF FELT ILL SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of felt ill scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is 0 with a p value =0.41. Thus there was no significant worsening in felt ill scores with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in felt ill scores between age groups, genders, sub sites, stages, performance status and prior treatment groups.

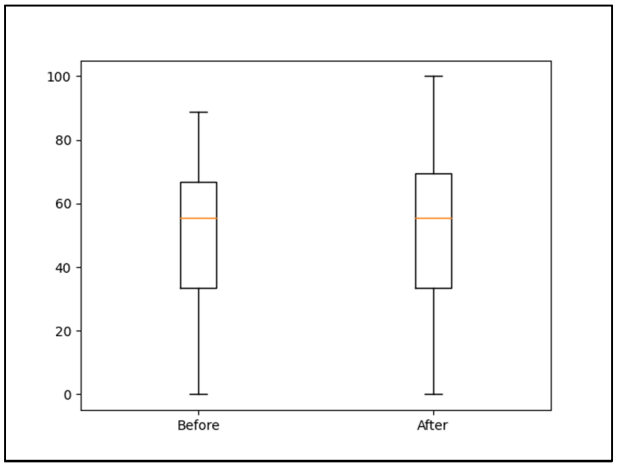
There was statistically significant change in felt ill scores in metastatic cases with a p value of 0.006 after 1st cycle of metronomic chemotherapy.



PLOT 37: COMPARISON OF FELT ILL SCORES IN METASTATIC PATIENTS BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

However there was no statistically significant change in felt ill scores with locally advanced and recurrent disease.

COMPARISON OF SPEECH SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

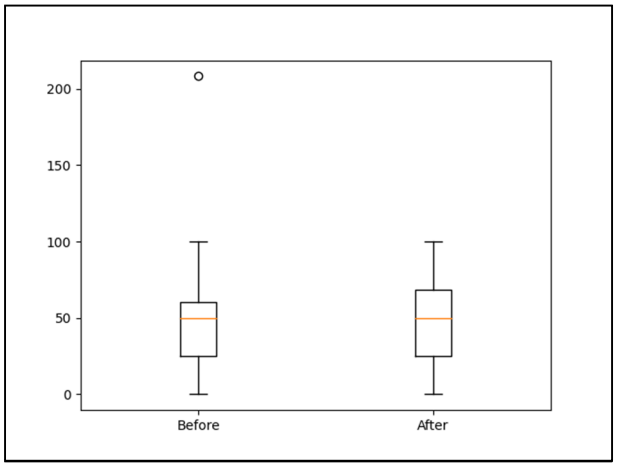


PLOT 38: COMPARISON OF SPEECH SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of speech scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is 0 with a p value =0.27.Thus there was no significant worsening in speech scores with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in speech scores between age groups, genders, sub sites, stages, and state of disease, performance status and prior treatment groups.

COMPARISON OF SOCIAL EATING SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

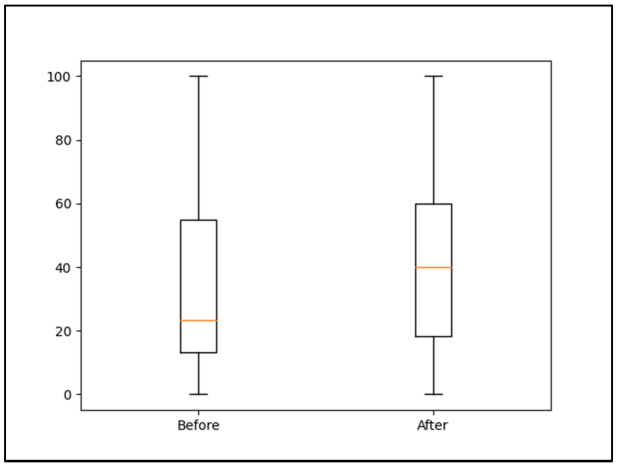


PLOT 39: COMPARISON OF SOCIAL EATING SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of social eating scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is 0 with a p value =0.97. Thus there was no significant worsening in social eating scores with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in social eating scores between age groups, genders, sub sites, stages, and state of disease, performance status and prior treatment groups.

COMPARISON OF SOCIAL CONTACT SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY



PLOT 40: COMPARISON OF SOCIAL CONTACT SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

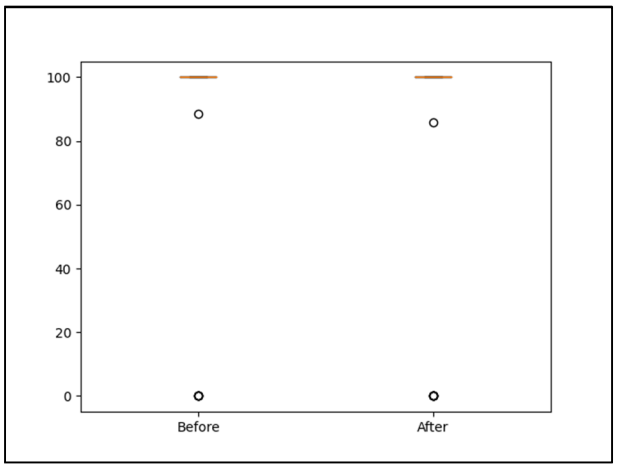
The above plot shows Box and Whisker plot between before and after values of social contact scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is -20 with a p value =0.20. Thus there was no significant worsening in difficulty in social contact scores with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in social contact scores between age groups, genders, sub sites, stages, and state of disease, performance status and prior treatment groups.

COMPARISON OF SEXUALITY SCORES BEFORE AND AFTER METRONOMIC CHEMOTHERAPY

A large number of patients were not ready to disclose their sexual behaviour to the investigator and in the remaining group who disclosed many were not sexually active and those who were sexually active had to abstain from sexual activity on disease progression and pain.

COMPARISON OF PAIN KILLERS SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

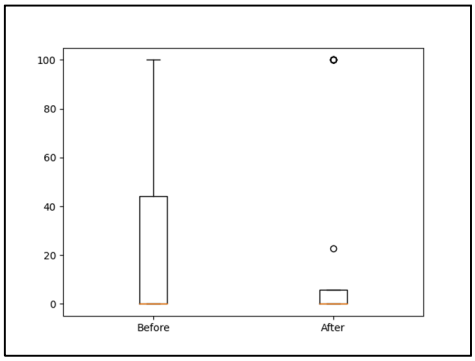


PLOT 41: COMPARISON OF PAIN KILLERS SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of pain killers score after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is 0 with a p value =0.71. Thus there was no significant change in pain killer score with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in pain killer score between age groups, genders, sub sites, stages, and state of disease, performance status and prior treatment groups.

COMPARISON OF NUTRITIONAL SUPPLEMENTS SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

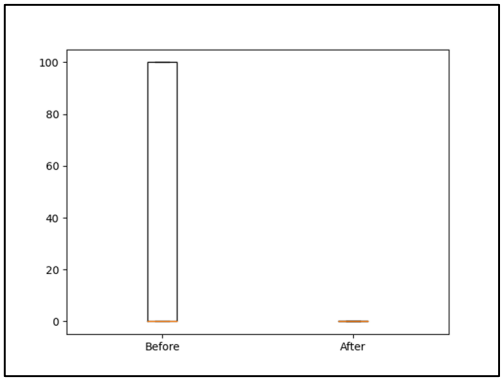


PLOT 42: COMPARISON OF NUTRITIONAL SUPPLEMENTS SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of nutritional supplements score after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is 0 with a p value =0.77. Thus there was no significant change in nutritional supplements score with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in nutritional supplements score between age groups, genders, sub sites, stages, and state of disease and prior treatment groups.

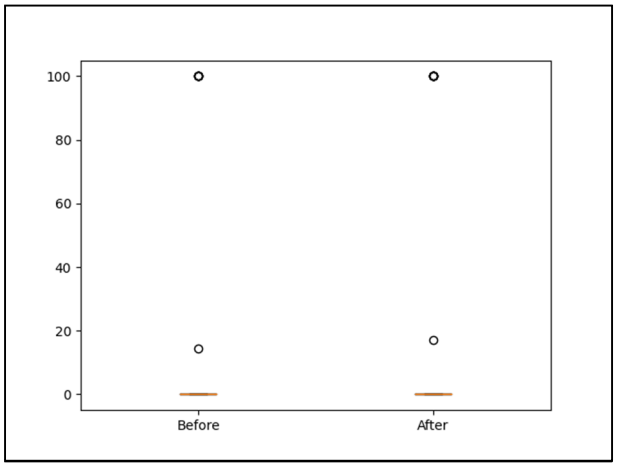
There was statistically significant change in nutritional supplements score in patients with performance status 2 with a p value of 0.03 after 1st cycle of metronomic chemotherapy.



PLOT 43: COMPARISON OF NUTRITIONAL SUPPLEMENTS SCORES IN PATIENTS WITH PS 2 BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

However no statistically significant change in QOL was present in performance status 1 patients.

COMPARISON OF FEEDING TUBE SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

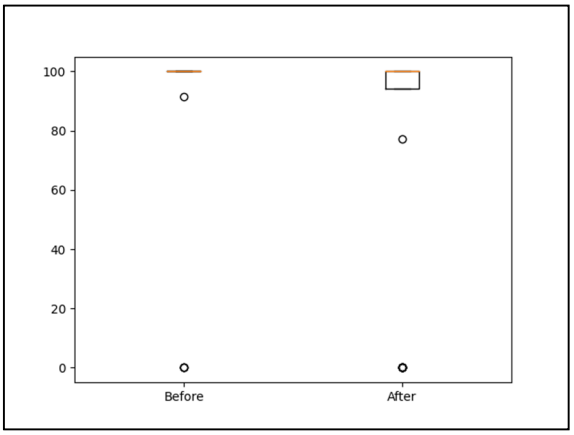


PLOT 44: COMPARISON OF FEEDING TUBE SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of feeding tube scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is 0 with a p value =0.73.Thus there was no significant change in feeding tube scores with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in feeding tube scores between age groups, genders, sub sites, stages, and state of disease, performance status and prior treatment groups.

COMPARISON OF WEIGHT LOSS SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

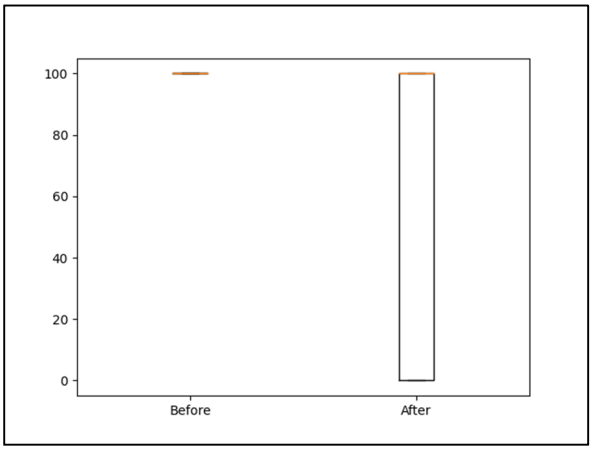


PLOT 45: COMPARISON OF WEIGHT LOSS SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of weight loss scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle 0 with a p value =0.09. Thus there was no significant change in weight loss scores with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in weight loss scores between age groups, genders, stages, and state of disease, performance status and prior treatment groups.

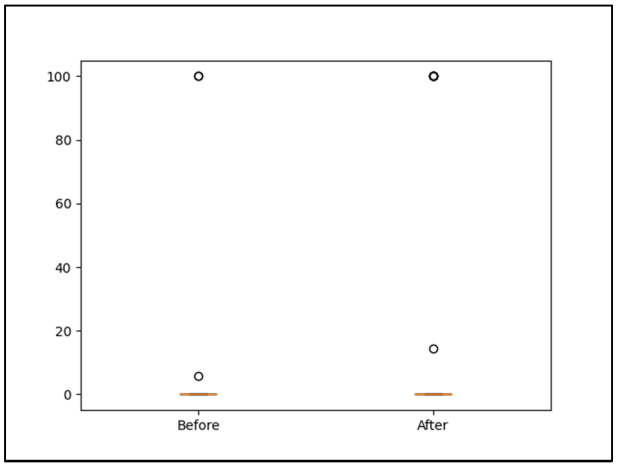
There was statistically significant change in weight loss scores in ca larynx patients with a p value of 0.02 after 1st cycle of metronomic chemotherapy.



PLOT 46: COMPARISON OF WEIGHT LOSS SCORES IN CA LARYNX PATIENTS BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

However there was no statistically significant change in weight loss scores with other sub sites of head and neck.

COMPARISON OF WEIGHT GAIN SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY



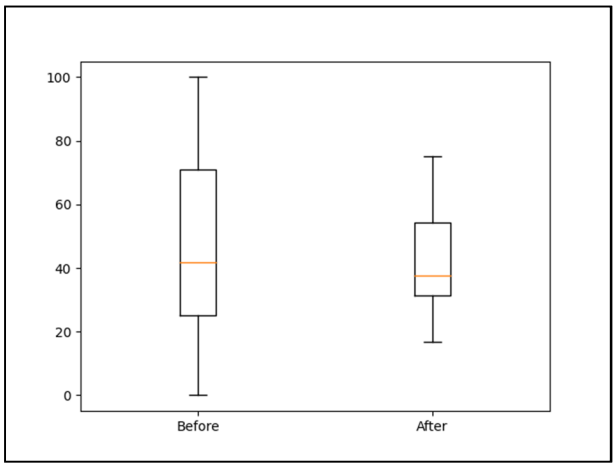
PLOT 47: COMPARISON OF WEIGHT GAIN SCORES BEFORE AND AFTER FIRST CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before and after values of weight gain scores after 1st cycle of metronomic chemotherapy. The median difference before and after 1st cycle is 0 with a p value =0.22. Thus there was no significant change in weight gain scores with metronomic chemotherapy at the end of first cycle.

There was no statistically significant change in weight gain scores between age groups, genders, sub sites, stages, and state of disease, performance status and prior treatment groups.

COMPARISON OF SCORES BEFORE FIRST AND AFTER THIRD CYCLE

COMPARISON OF PAIN SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY



PLOT 48: COMPARISON OF PAIN SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

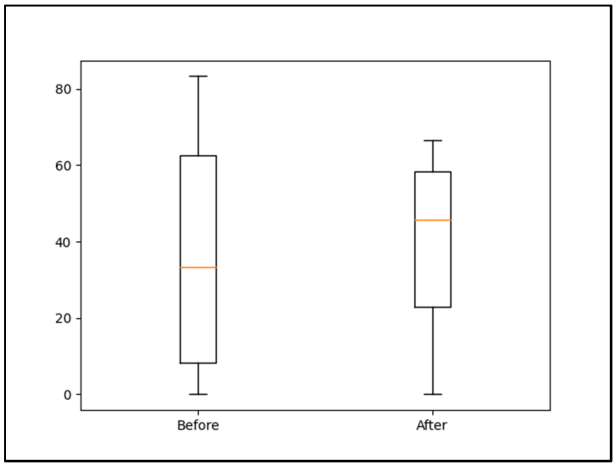
The above plot shows Box and Whisker plot between before first and after third cycle values of pain scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is -4.17 with a p value = 0.78

Thus there was no statistically significant deterioration in pain scores with metronomic chemotherapy at the end of 3 cycles.

Most of these patients were having average pain score of 2 out of 4 and were on pain medications like additional NSAIDS(besides celecoxib) or tramadol or morphine as indicated and needed by the patients. The requirement for pain medications thus did not reduced significantly with a month of metronomic chemotherapy.

There was no statistically significant change in pain related QOL between age groups, genders, sub sites, stages, and state of disease, performance status and prior treatment groups at the end of first cycle.

COMPARISON OF SWALLOWING SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

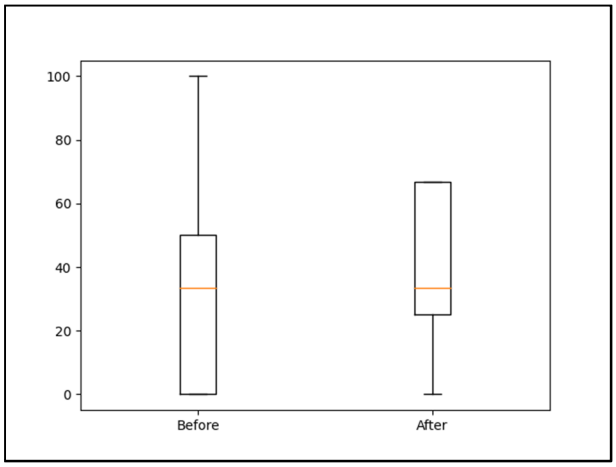


PLOT 49: COMPARISON OF SWALLOWING SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of swallowing scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is -12.5 with a p value = 0.71

Thus there was no statistically significant deterioration in swallowing scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF TOOTH SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

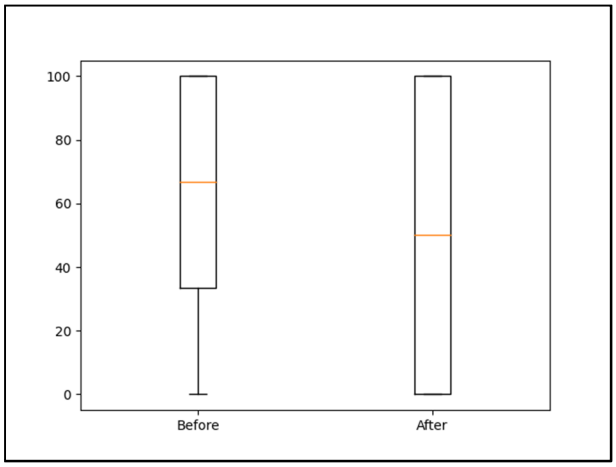


PLOT 50: COMPARISON OF TOOTH SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of tooth scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 0 with a p value = 0.51

Thus there was no statistically significant deterioration in tooth scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF MOUTH OPENING SCORES FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

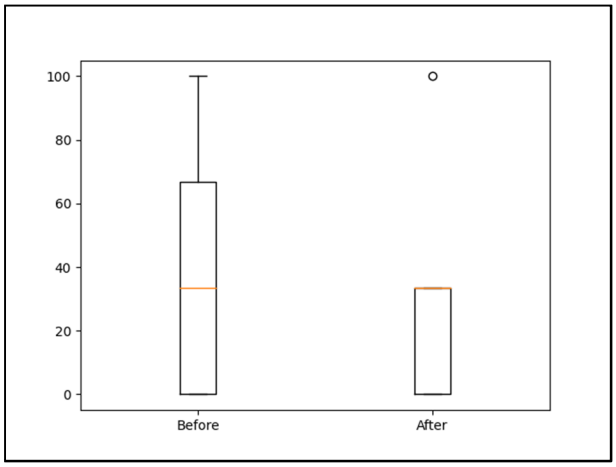


PLOT 51: COMPARISON OF MOUTH OPENING SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of mouth opening scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 16.67 with a p value = 0.67

Thus there was no statistically significant deterioration in mouth opening scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF DRY MOUTH SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

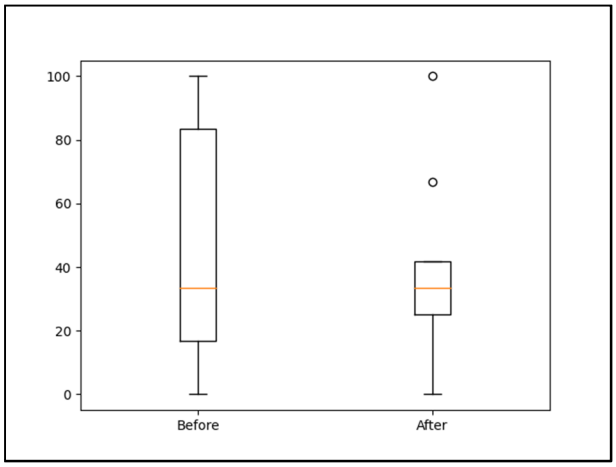


PLOT 52: COMPARISON OF DRY MOUTH SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of dry mouth scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 0 with a p value = 0.33

Thus there was no statistically significant deterioration in dry mouth scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF STICKY SALIVA SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

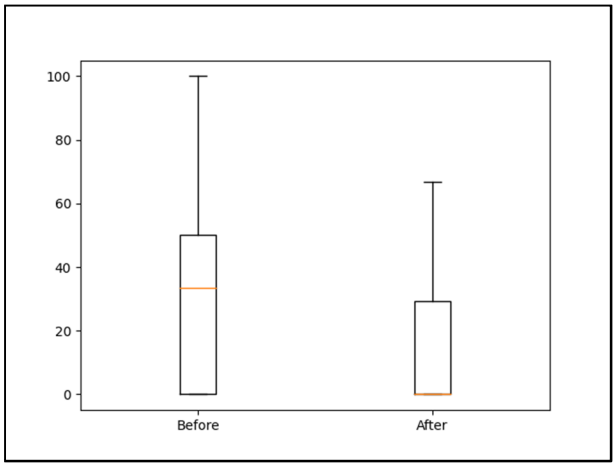


PLOT 53: COMPARISON OF STICKY SALIVA SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of stickiness of saliva scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 0 with a p value = 0.54

Thus there was no statistically significant deterioration in stickiness of saliva scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF SENSES SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

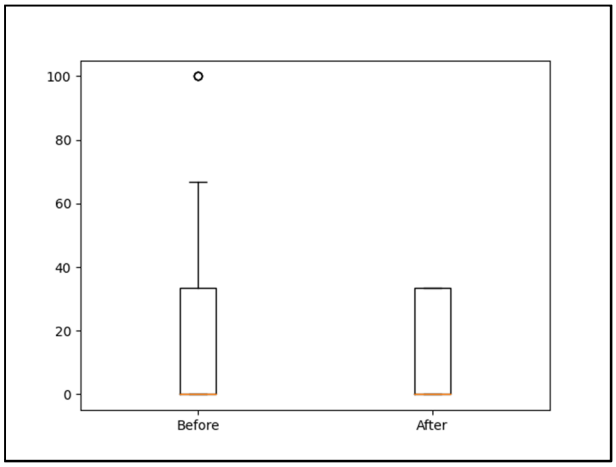


PLOT 54: COMPARISON OF SENSES SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of senses scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 33.33 with a p value = 0.22

Thus there was no statistically significant deterioration in senses scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF COUGH SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

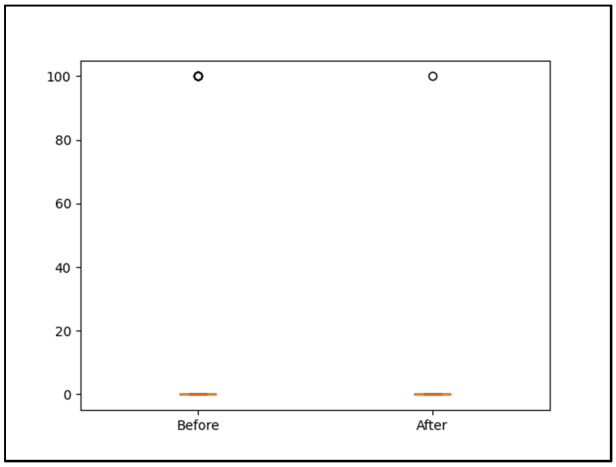


PLOT 55: COMPARISON OF COUGH SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of cough scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 0 with a p value = 0.88

Thus there was no statistically significant deterioration in cough scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF FELT ILL SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

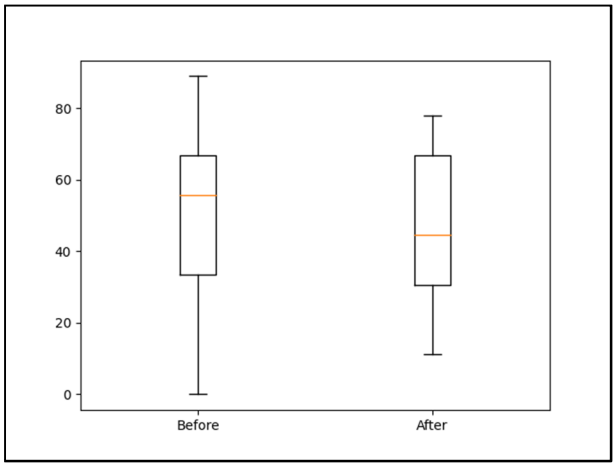


PLOT 56: COMPARISON OF FELT ILL SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of felt ill scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 0 with a p value = 0.83

Thus there was no statistically significant deterioration in felt ill scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF SPEECH SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

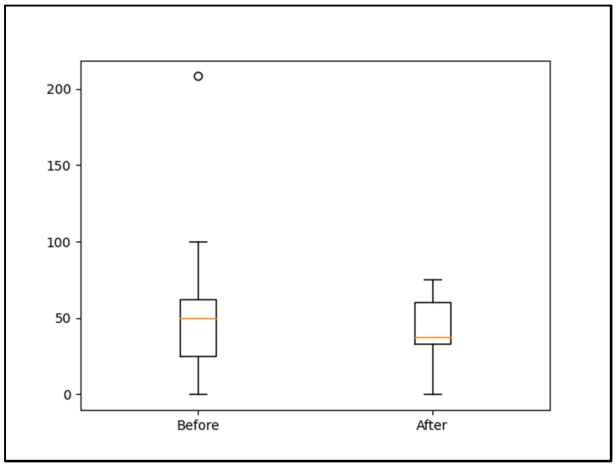


PLOT 57: COMPARISON OF SPEECH SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of speech scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 11.11 with a p value = 0.78

Thus there was no statistically significant deterioration in speech scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF SOCIAL EATING SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

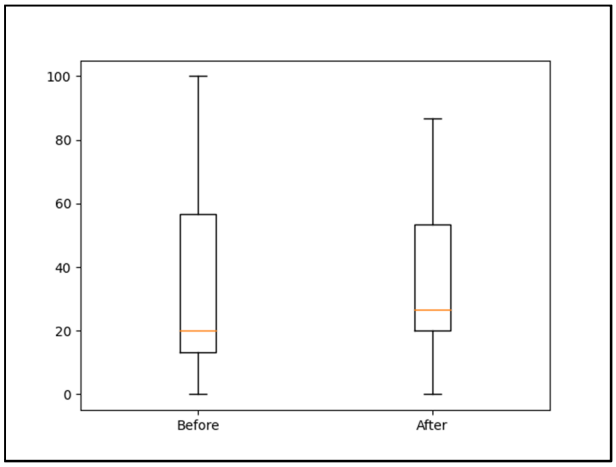


PLOT 58: COMPARISON OF SOCIAL EATING SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of social eating scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 12.5 with a p value = 0.76

Thus there was no statistically significant deterioration in social eating scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF SOCIAL CONTACT SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

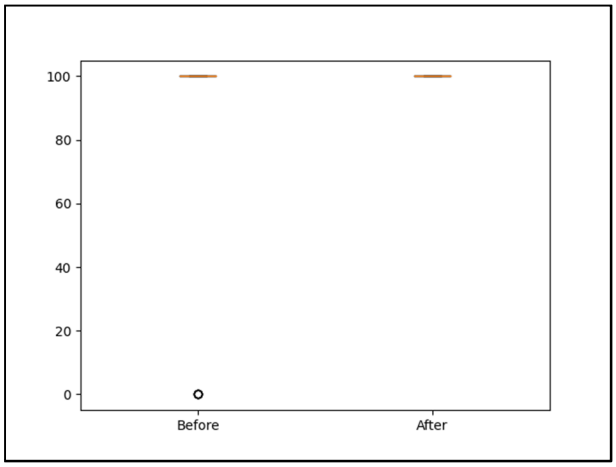


PLOT 59: COMPARISON OF SOCIAL CONTACT SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of social contact scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is -6.67 with a p value = 0.66

Thus there was no statistically significant deterioration in social contact scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF PAIN KILLERS SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

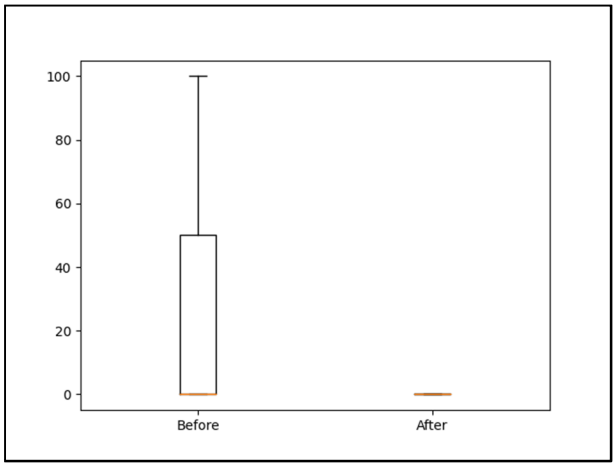


PLOT 60: COMPARISON OF PAIN KILLERS SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of pain killers scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 0 with a p value = 0.34

Thus there was no statistically significant deterioration in pain killers scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF NUTRITIONAL SUPPLEMENTS SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

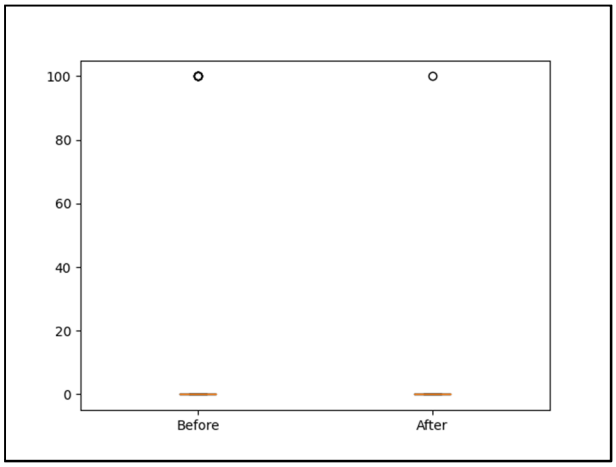


PLOT 61: COMPARISON OF NUTRITIONAL SUPPLEMENTS SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of nutritional supplements scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 0 with a p value = 0.11

Thus there was no statistically significant deterioration in nutritional supplements scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF FEEDING TUBE SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

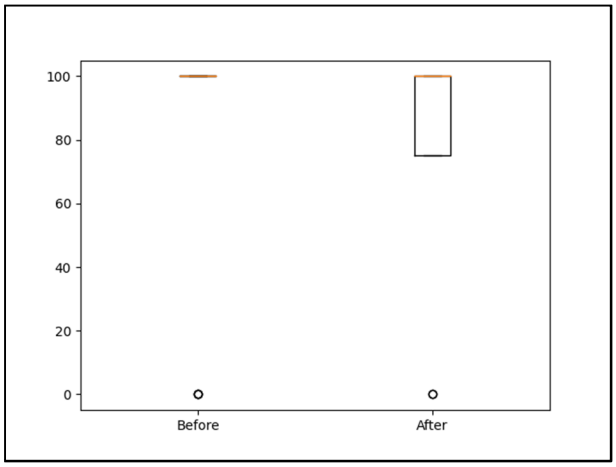


PLOT 62: COMPARISON OF FEEDING TUBE SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of feeding tube scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 0 with a p value = 0.92

Thus there was no statistically significant deterioration in feeding tube scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF WEIGHT LOSS SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

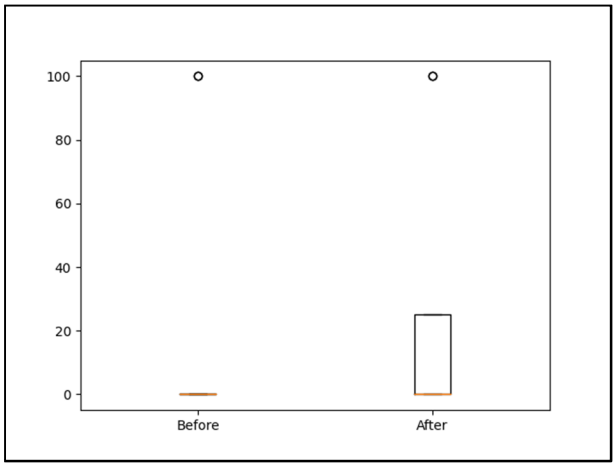


PLOT 63: COMPARISON OF WEIGHT LOSS SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of weight loss scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 0 with a p value = 0.21

Thus there was no statistically significant deterioration in weight loss scores with metronomic chemotherapy at the end of 3 cycles.

COMPARISON OF WEIGHT GAIN SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY



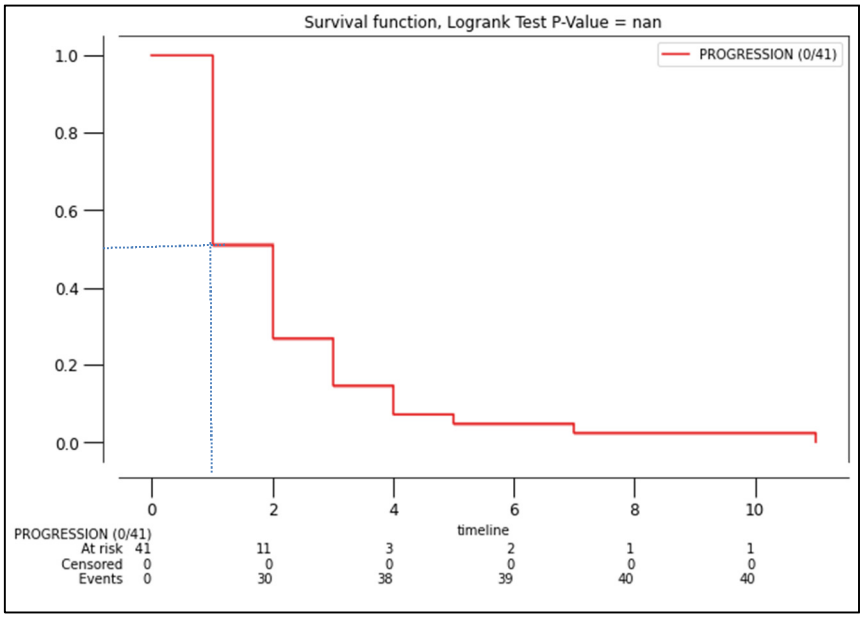
PLOT 64: COMPARISON OF WEIGHT GAIN SCORES BEFORE FIRST AND AFTER THIRD CYCLE OF METRONOMIC CHEMOTHERAPY

The above plot shows Box and Whisker plot between before first and after third cycle values of weight gain scores after 3 cycles of metronomic chemotherapy. The median difference before first and after third cycle of metronomic chemotherapy is 0 with a p value = 0.10

Thus there was no statistically significant deterioration in weight gain scores with metronomic chemotherapy at the end of 3 cycles.

SURVIVAL ANALYSIS

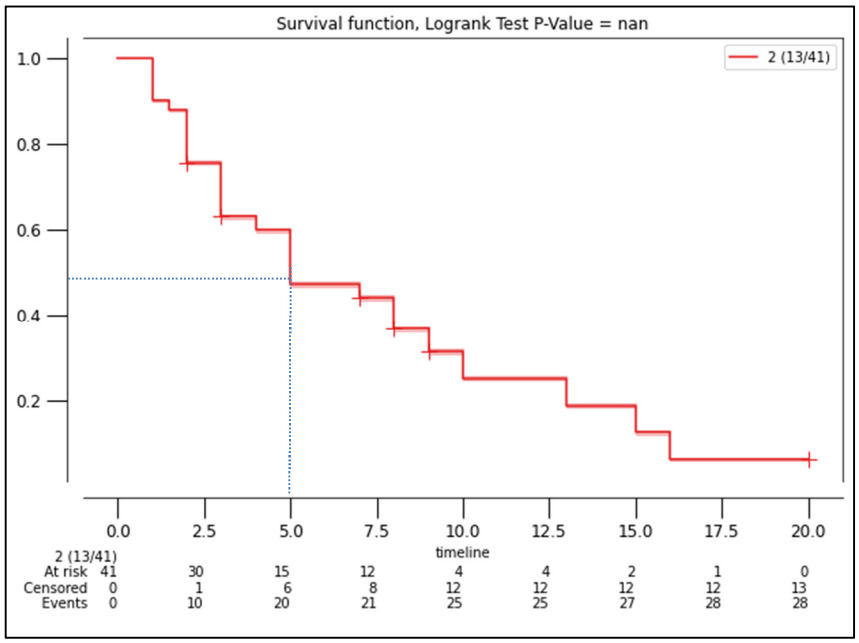
PROGRESSION FREE SURVIVAL ON METRONOMIC CHEMOTHERAPY



PLOT 65: PROGRESSION FREE SURVIVAL ON METRONOMIC CHEMOTHERAPY

The Kaplan Meier plot of the Progression Free Survival of patients on metronomic chemotherapy shows that the median Progression Free Survival (PFS) was 1 month. The median follow up period of the patients accrued in the study was 9 months.

OVERALL SURVIVAL OF ALL THE STUDY PATIENTS (N=43)

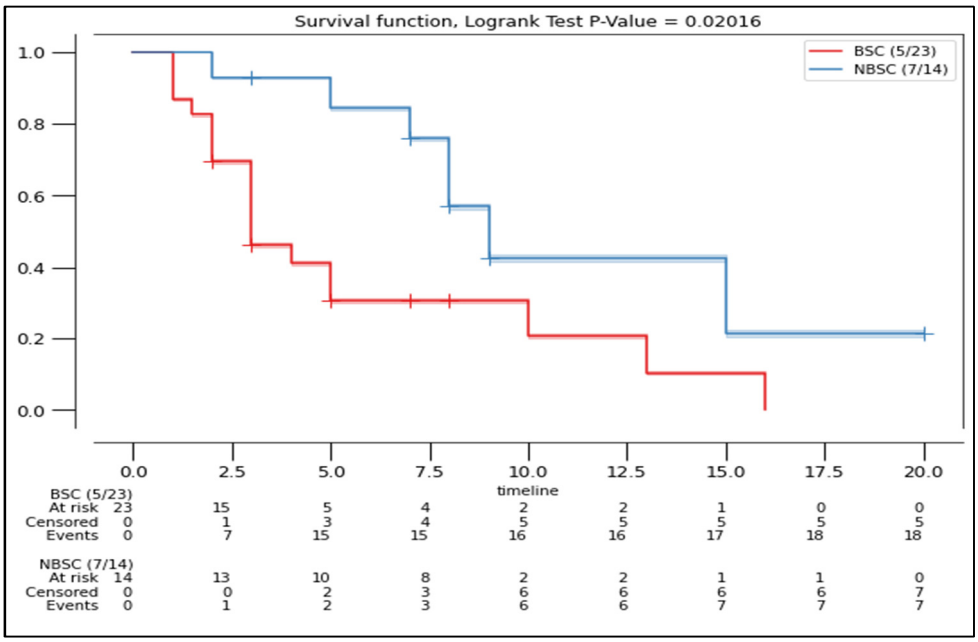


PLOT 66: OVERALL SURVIVAL OF PATIENTS ON METRONOMIC CHEMOTHERAPY

The Kaplan Meier plot of the Overall Survival (OS) of patients accrued in the study showed that the median Overall Survival was 5 months.

The median follow up period of the patients accrued in the study was 9 months.

COMPARISON OF OVERALL SURVIVAL BETWEEN PATIENTS ON THE BASIS OF FURTHER TREATMENT GIVEN AFTER PROGRESSION ON METRONOMIC CHEMOTHERAPY



PLOT 67: COMPARISON OF OVERALL SURVIVAL BETWEEN PATIENTS ON THE BASIS OF FURTHER TREATMENT GIVEN AFTER PROGRESSION ON METRONOMIC CHEMOTHERAPY

Group	Treatment Given After PD on Metronomic MTX-CXB based therapy	N	OS
BSC (Best Supportive Care)	Best Supportive Care – Palliative Care, Pain Medications, Counselling etc.	23	3
NBSC (Not Best Supportive Care)	Pall RT/ Pall RT followed by Platinum Based Chemotherapy / Only Platinum Based Chemotherapy	14	9

Table 18: TREATMENT AFTER PROGRESSIVE DISEASE ON METRONOMIC CHEMOTHERAPY

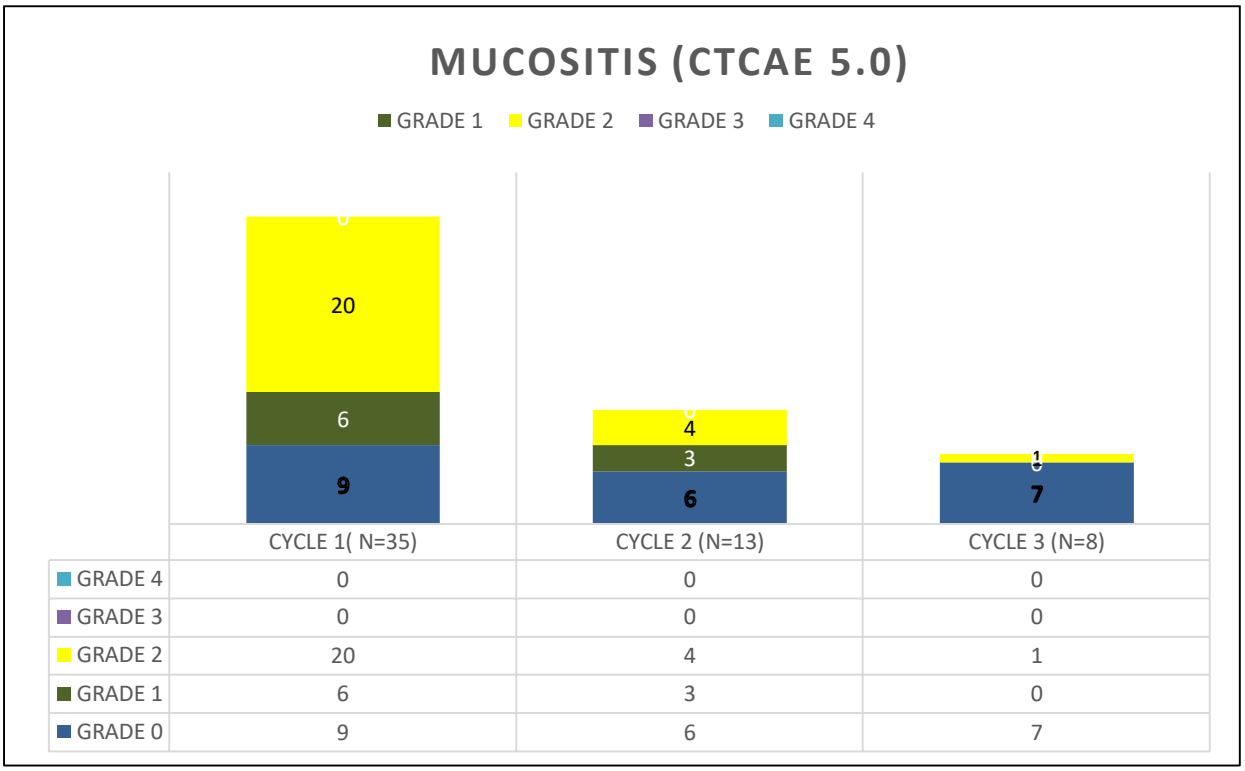
The median survival of patients who progressed on metronomic chemotherapy and further continued to receive other oncological treatments like palliative radiation therapy, palliative

chemotherapy or both was calculated from the Kaplan Meier plot and was found to be 9 months.

The patients who were unfit and could get only best supportive care after they progressed on metronomic chemotherapy had a median overall survival of 3 months. The difference of 6 months in the median OS is significant ($p = 0.02$)

RESULTS OF TOXICITY

MUCOSITIS

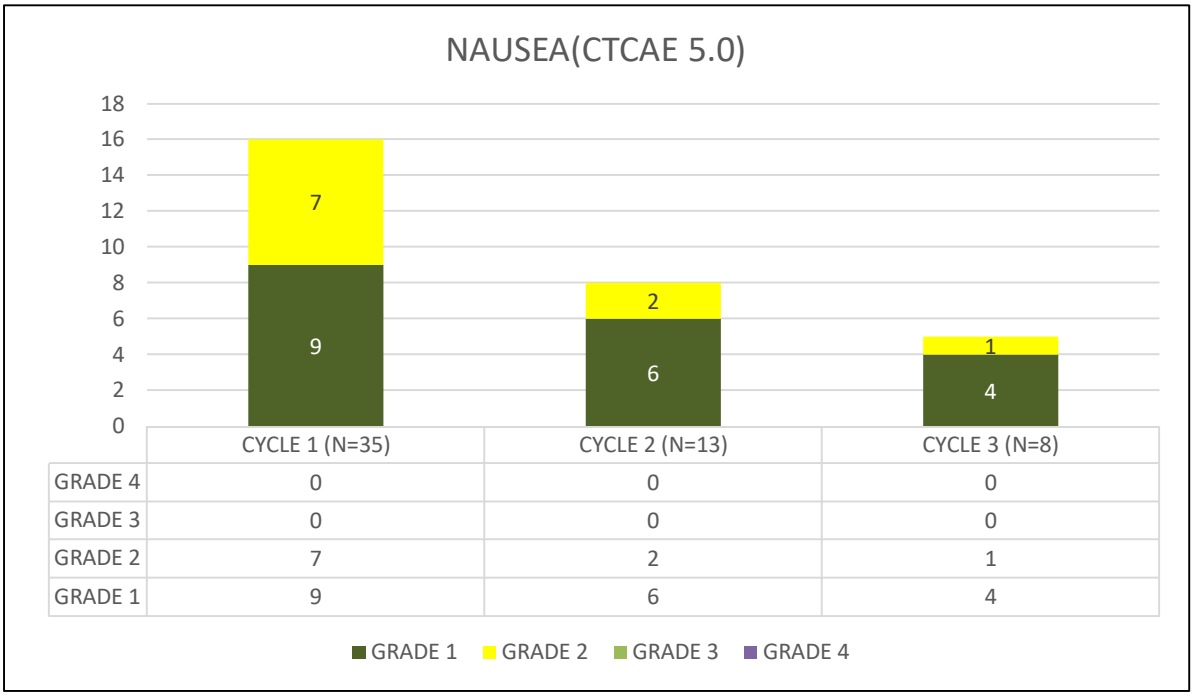


	CYCLE 1(N=35)	CYCLE 2 (N=13)	CYCLE 3 (N=8)
GRADE 4	0	0	0
GRADE 3	0	0	0
GRADE 2	20	4	1
GRADE 1	6	3	0
GRADE 0	9	6	7

PLOT 68: MUCOSITIS

In the study patients the most common toxicity encountered was mucositis but none of the patients had grade 3 or 4 mucositis.

NAUSEA

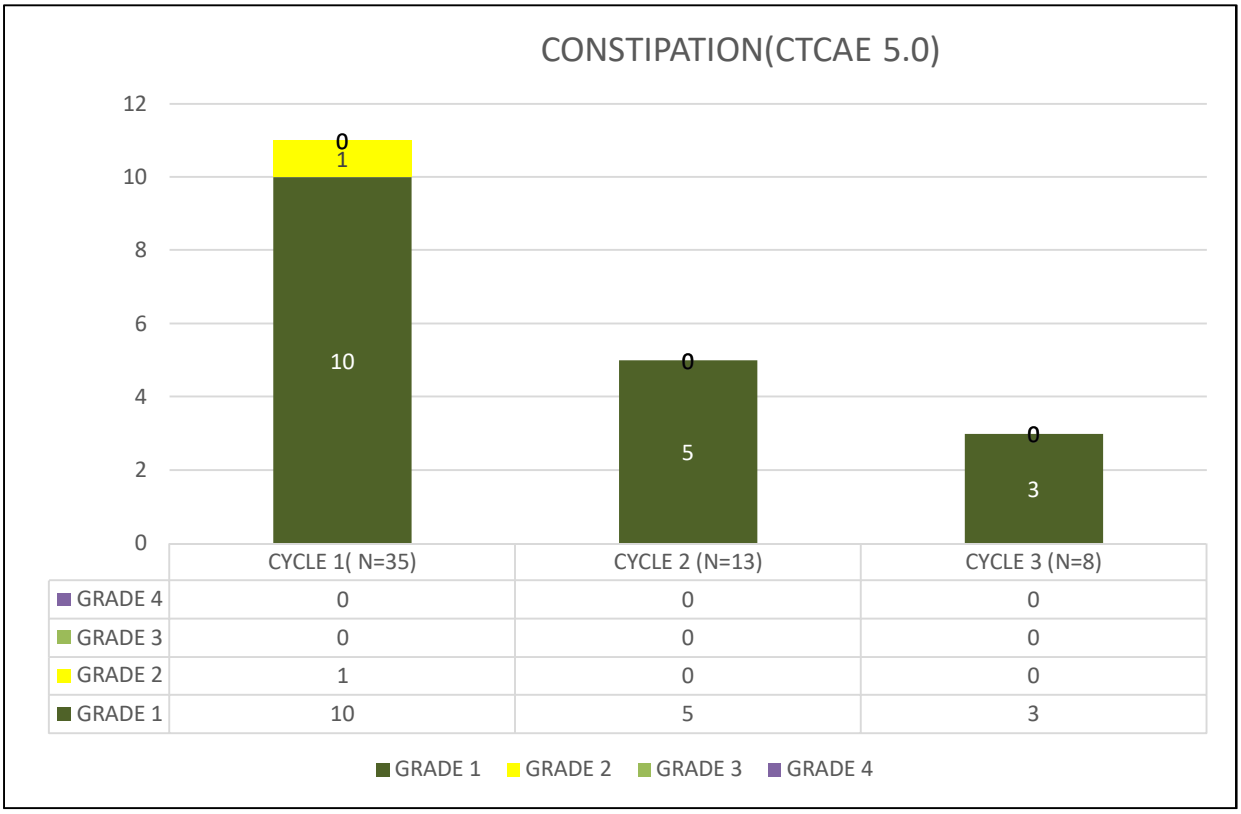


	CYCLE 1 (N=35)	CYCLE 2 (N=13)	CYCLE 3 (N=8)
GRADE 4	0	0	0
GRADE 3	0	0	0
GRADE 2	7	2	1
GRADE 1	9	6	4

PLOT 69: NAUSEA

Out of all the patients who experienced nausea none had grade 3 or 4 nausea or vomiting. Nausea may be contributed by the pain medications and supportive medications also.

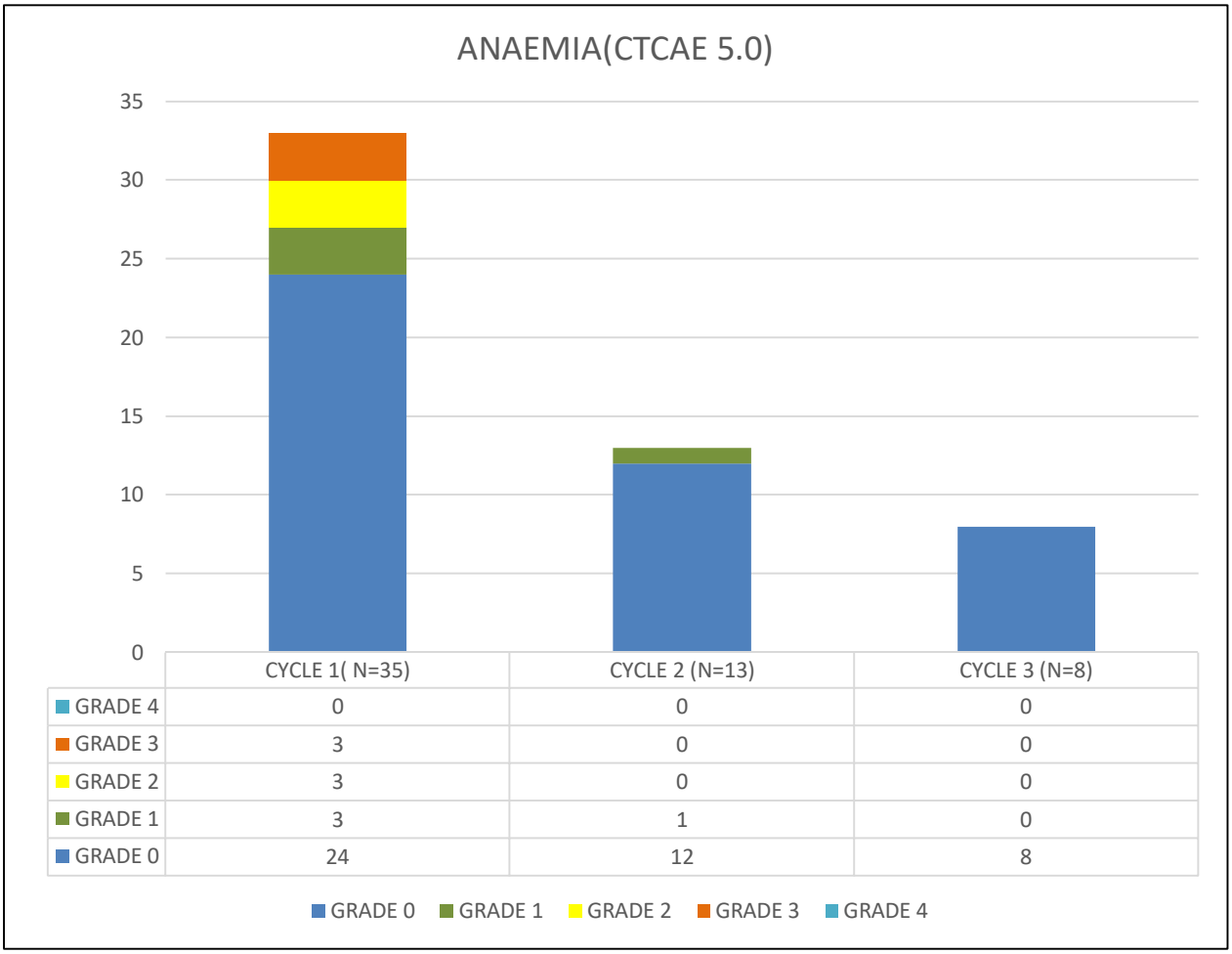
CONSTIPATION



PLOT 70: CONSTIPATION

Out of all the patients who had constipation none had grade 3 or 4 constipation. Constipation may be contributed by the eating habits of the patient along with pain meds like opioids and morphine also. Everyone who had constipation was managed with adequate medications and dietary advices.

ANAEMIA



PLOT 71: ANAEMIA

Patients were monitored for haematological toxicities during each cycle prior to starting methotrexate – celecoxib and also whenever seemed appropriate. Anaemia in these patients may be contributed by blood loss from the tumour, decreased nutritional intake by the patient and also by virtue of the tumour itself and anaemia of chronic disease. All patients who had any grades of anaemia were managed adequately with iron supplementation (oral and IV), nutritional counselling and blood transfusions *only* whenever it was uncompensated and necessary. Anaemia related to tumour bleed was corrected with blood transfusions and haemostatic radiation therapy as and when indicated.

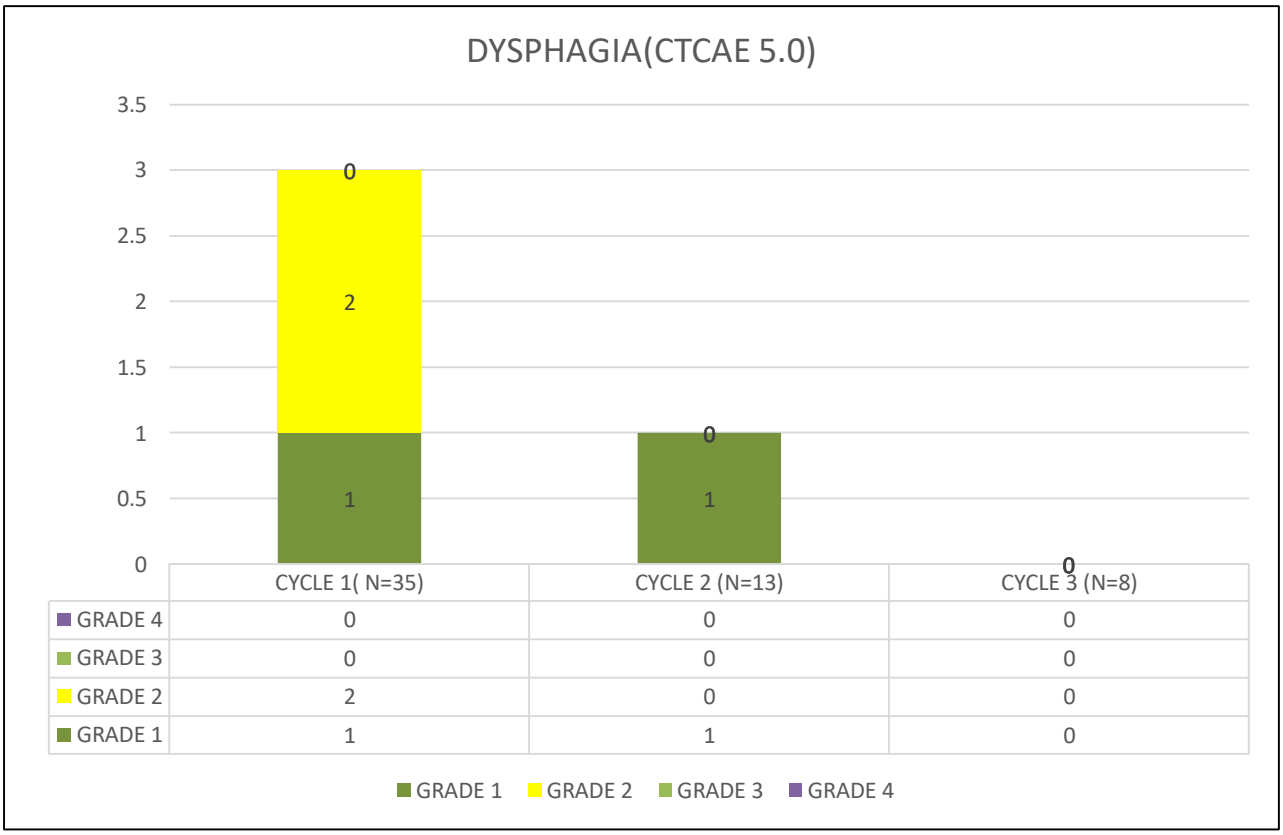
NEUTROPENIA

Out of all the patients treated with metronomic chemotherapy only one patient had neutropenia and the grade of neutropenia was 4. Same patient had thrombocytopenia.

THROMBOCYTOPENIA

Out of all the patients treated with metronomic chemotherapy only one patient had thrombocytopenia and the grade of thrombocytopenia was 3. Same patient had afebrile neutropenia.

DYSPHAGIA



PLOT 72: DYSPHAGIA

There were no patients with any grades of liver or kidney dysfunction throughout the course of study.

CLINICAL PHOTOGRAPHS

LIST OF PATIENTS

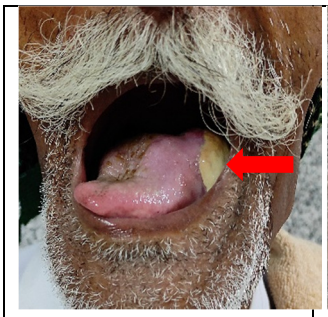
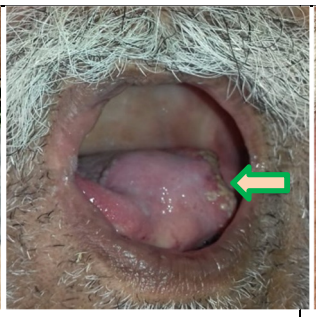
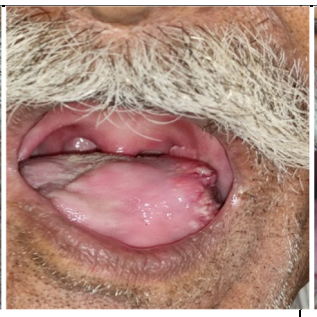
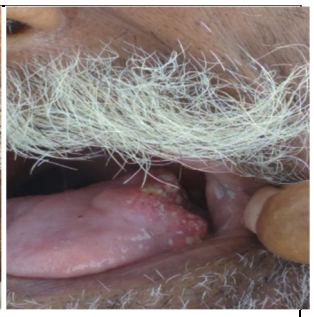
SI NO	PATIENT NAME	DIAGNOSIS
1	AR	Ca Left Lateral Border of Tongue with BOT involvement
2	ANDR	Secondary Neck with unknown primary
3	BR	Ca Left Buccal Mucosa with fistula
4	BS	Recurrent Ca Oropharynx
5	HS	Recurrent Ca Right Buccal Mucosa
6	N	Ca Right Buccal Mucosa
7	PS	Recurrent CA Base of Tongue with Neck Nodes
8	SK	Ca Lower GBS
9	S	Ca Buccal Mucosa
10	TD	Ca Left Buccal Mucosa
11	PD	Recurrent ca left buccal mucosa
12	AL	Recurrent ca left buccal mucosa
13	D	Secondary neck with unknown primary
14	HR	Ca Left Buccal Mucosa
15	KR	Ca oropharynx
16	M	Ca Left Buccal Mucosa
17	NB	Ca right Buccal Mucosa
18	PK	Recurrent ca left buccal mucosa
19	RC	Ca right Buccal Mucosa
20	RCH	Recurrent Ca Right Lower Alveolus & BM
21	SKA	Ca Right Buccal Mucosa
22	PRK	Ca Left Buccal Mucosa
23	TJR	Ca Left Buccal Mucosa
24	TAR	Sec Neck with Primary Unknown
25	BOR	Ca Base of Tongue with Lung Mets
26	NIA	Ca Left Buccal Mucosa
27	BAS	Ca Left Buccal Mucosa

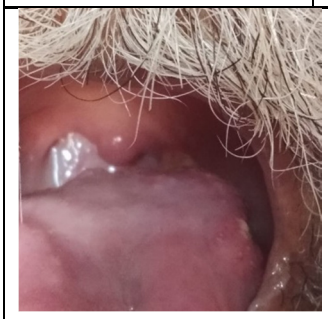
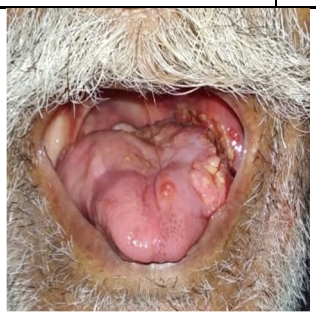
Table 19: LIST OF PATIENTS INCLUDED IN THE CLINICAL PHOTOGRAPH SECTION

Name	Mr. AR
Diagnosis	Ca Left Lateral Border of Tongue with BOT involvement
Stage at Accrual of Treatment	ycT4N0M0
Number of Cycles of Metronomic Chemotherapy Given	3
Partial Response	Starting from 3 weeks. Maximal > 80% at 10 weeks. Thereafter PD
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	5 Months

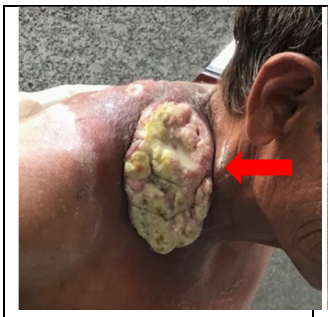
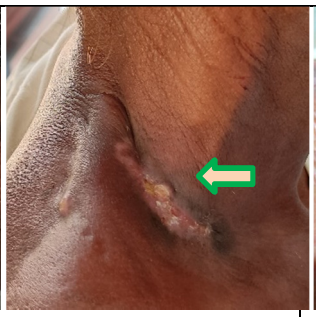
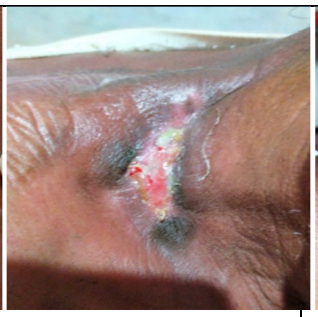
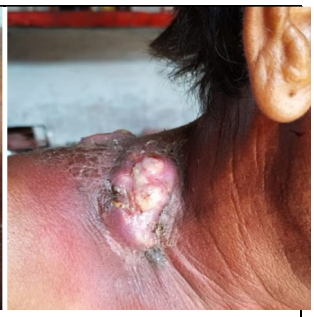
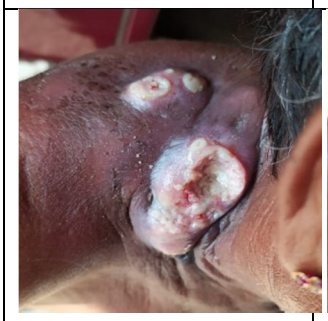
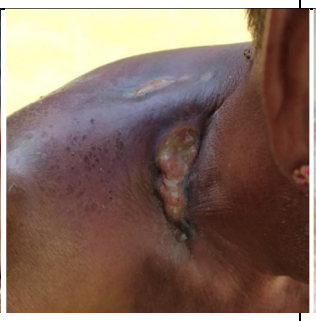
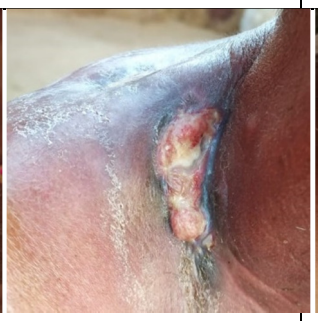
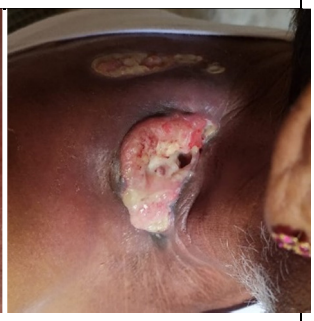
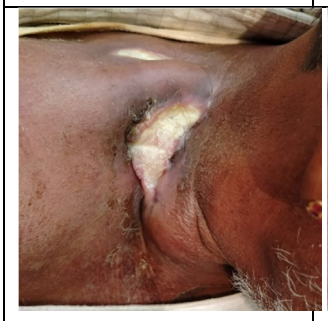
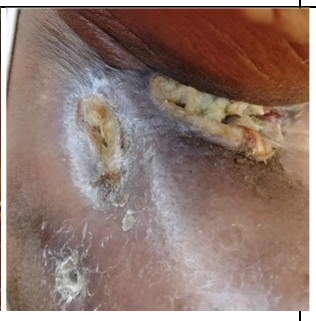
*Only visible disease included in the clinical photograph section

DISEASE BEFORE METRONOMICS
PARTIAL RESPONSE
DISEASE PROGRESSION

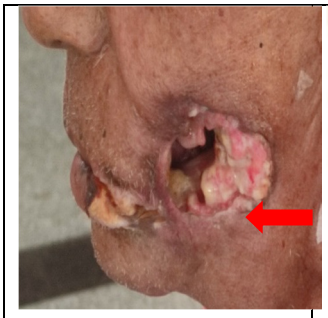
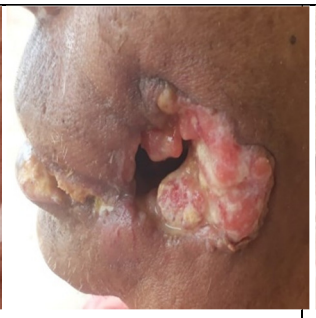
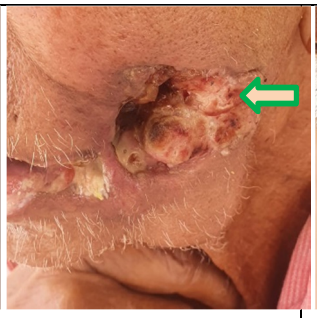
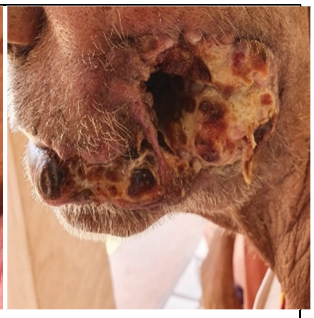
			
BEFORE MTX	AFTER 3 WEEKS	4 WEEKS	8 WEEKS

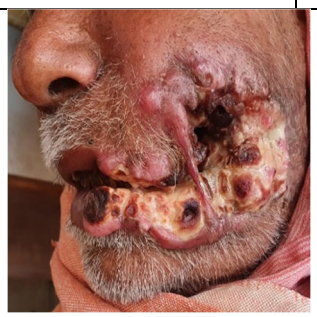
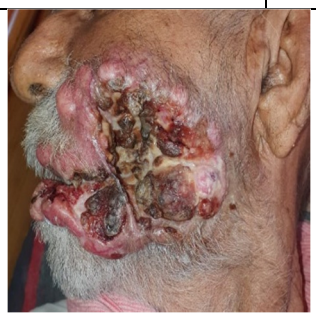
	
10 WEEKS	18 WEEKS

Name	Mr. ANDR
Diagnosis	Secondary Neck with unknown primary
Stage at Accrual of Treatment	cTxN3bcM0
Number of Cycles of Metronomic Chemotherapy Given	5
Partial Response	Starting from 4 weeks. Maximal > 80% at 4 weeks. Thereafter PD from 8 weeks onwards
Treatment after PD on Metronomic Chemotherapy	Palliative Radiation Therapy Followed by Platinum Based Palliative Chemotherapy
Survival in months	8 Months

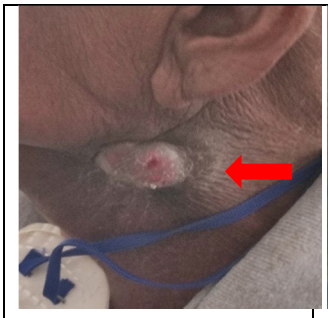
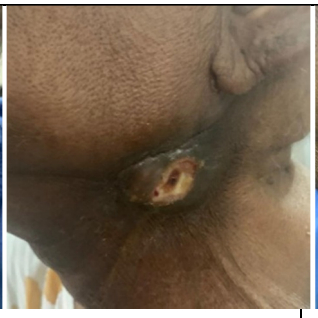
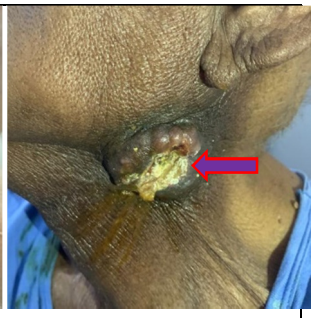
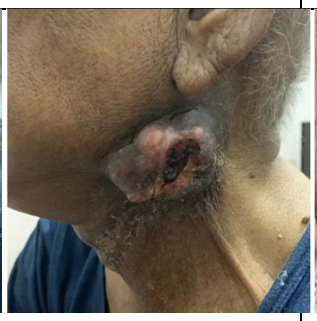
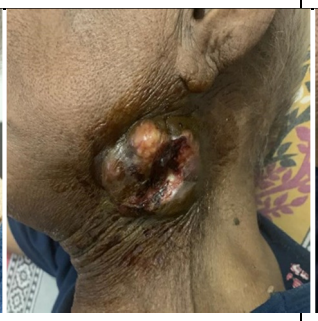
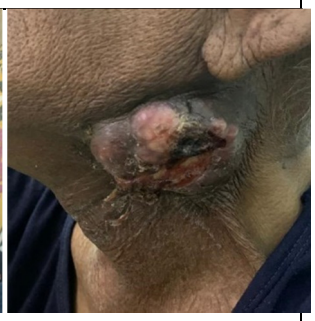
			
BEFORE MTX	4 WEEKS	6 WEEKS	8 WEEKS
			
10 WEEKS	12 WEEKS	14 WEEKS	16 WEEKS
			
20 WEEKS	24 WEEKS		

Name	Mr. BR
Diagnosis	Ca Left Buccal Mucosa with fistula
Stage at Accrual of Treatment	cT4N1M0
Number of Cycles of Metronomic Chemotherapy Given	1
Partial Response	At 3 weeks some PR. Thereafter rapid PD from week 4 onwards itself.
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	4 Months

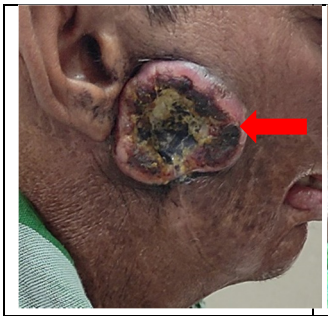
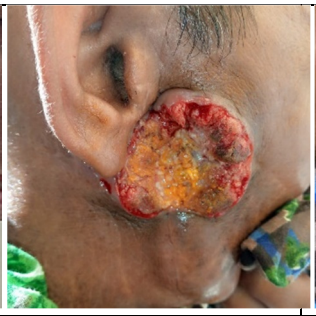
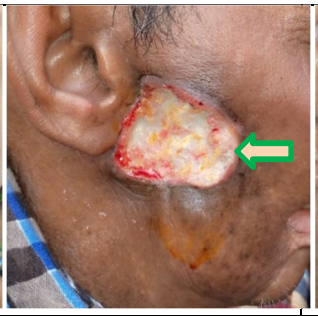
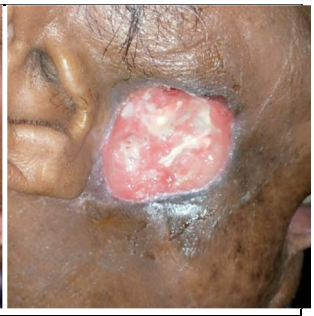
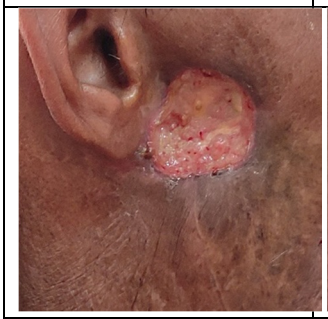
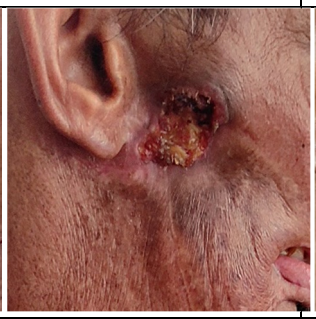
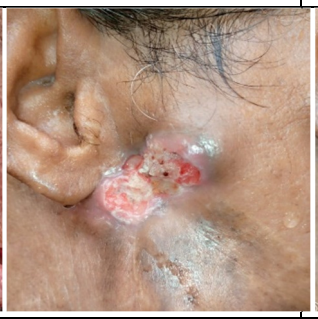
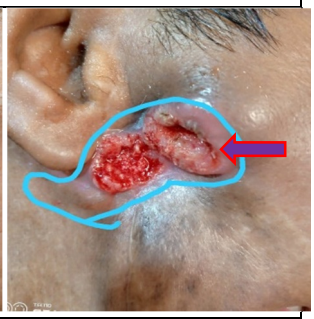
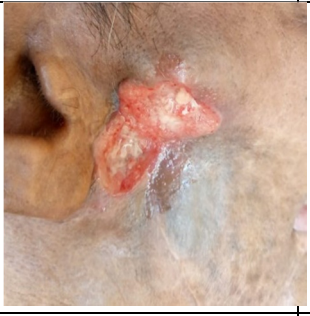
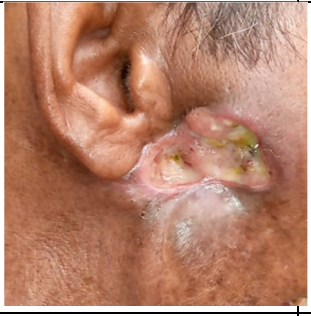
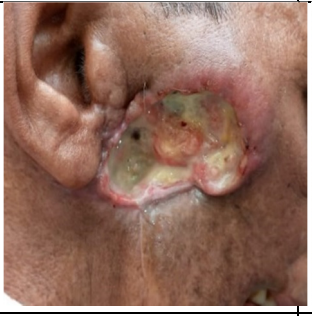
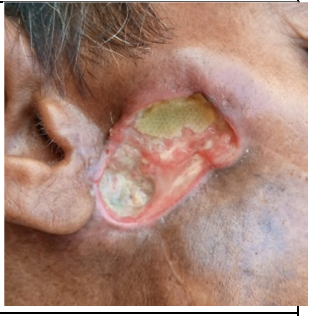
			
BEFORE MTX	1 WEEK	3 WEEKS	6 WEEKS

	
8 WEEKS	10 WEEKS

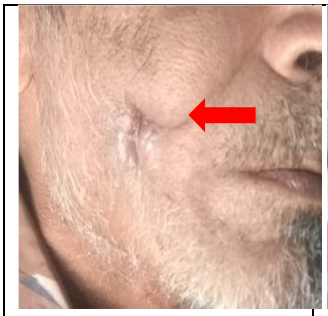
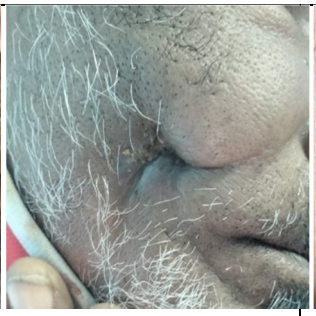
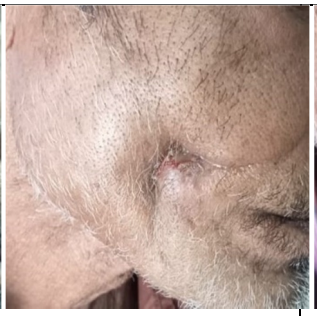
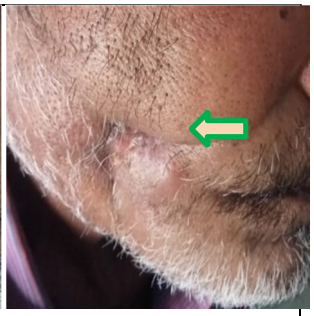
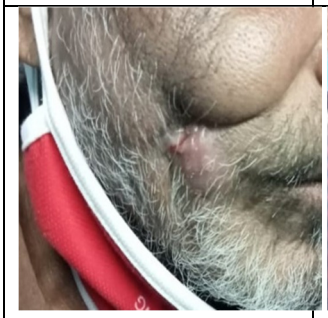
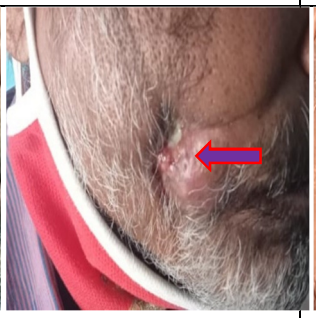
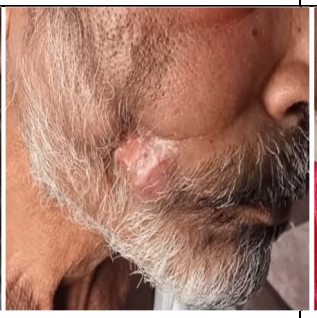
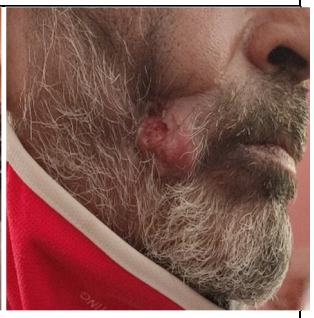
Name	Mr. BS
Diagnosis	Recurrent Ca Oropharynx
Stage at Accrual of Treatment	rcTxN3M0
Number of Cycles of Metronomic Chemotherapy Given	7
Partial Response	Starting from 2 weeks. Thereafter PD from 6 weeks only.
Treatment after PD on Metronomic Chemotherapy	Received palliative platinum based chemotherapy followed by best supportive care. Still alive at the time of analysis
Survival in months	7+ Months. Patient alive at the time of analysis

			
BEFORE MTX	2 WEEKS	4 WEEKS	6 WEEKS
			
10 WEEKS	12 WEEKS	13 WEEKS	15 WEEKS

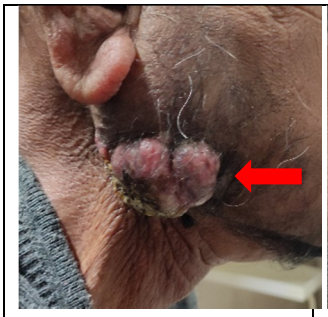
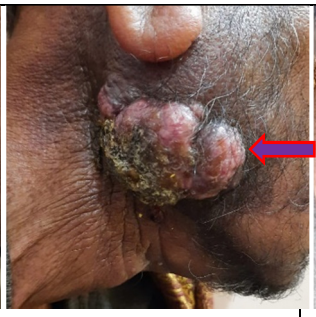
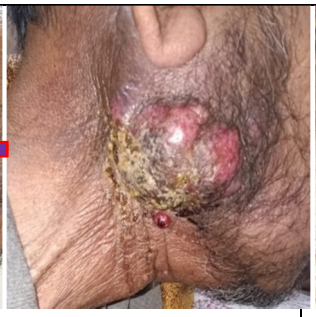
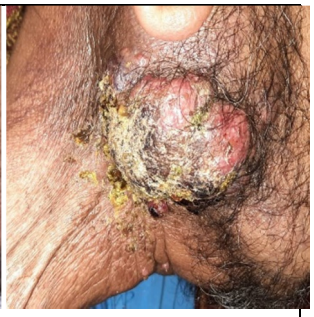
Name	Mr HS
Diagnosis	Recurrent Ca Right Buccal Mucosa (Post OP+ PORT recurrence)
Stage at Accrual of Treatment	rcT0N3bM0
Number of Cycles of Metronomic Chemotherapy Given	3
Partial Response	At 2 weeks. Ulcerated node started healing. Started PD at 12 weeks with swelling and ulceration of same node
Treatment after PD on Metronomic Chemotherapy	Palliative Radiation followed by Best Supportive Care
Survival in months	9+ Months. Alive at the time of analysis

			
BEFORE MTX	1 WEEK	2 WEEKS	4 WEEKS
			
5 WEEKS	8 WEEKS	10 WEEKS	12 WEEKS
			
13 WEEKS	14 WEEKS	18 WEEKS	20 WEEKS

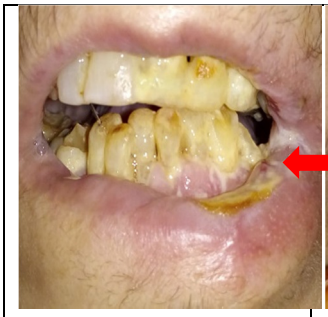
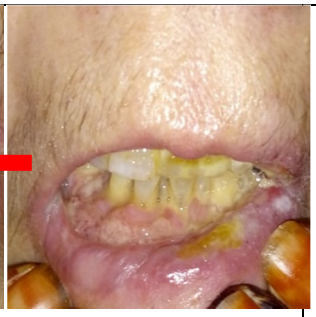
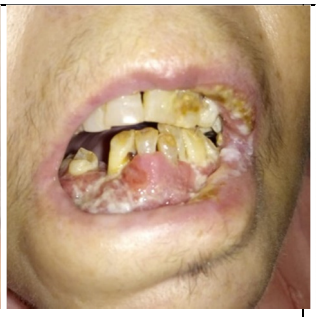
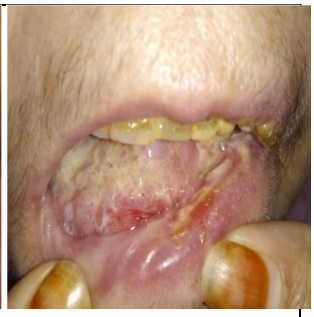
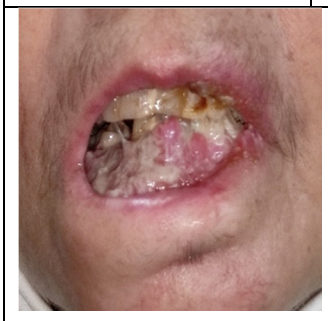
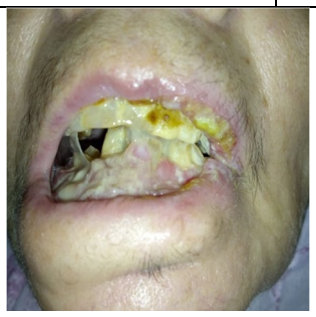
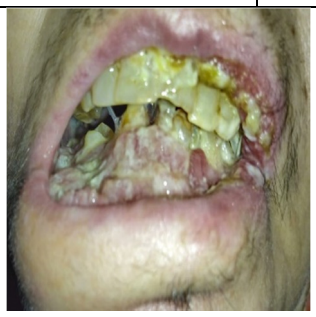
Name	Mr N
Diagnosis	Ca Right Buccal Mucosa
Stage at Accrual of Treatment	cT4bN1M0 (Patient had earlier refused for surgery or radical radiation therapy and was defaulter at multiple hospitals)
Number of Cycles of Metronomic Chemotherapy Given	3
Partial Response	At 3 weeks. PD at 5 weeks
Treatment after PD on Metronomic Chemotherapy	Palliative Radiation Therapy followed by Palliative Platinum Based Chemotherapy. Mandibular and masticator space involved.
Survival in months	8+ Months. Patient still alive with fistula and NG tube

			
BEFORE MTX	1 WEEK	2WEEKS	3 WEEKS
			
4 WEEKS	5 WEEKS	6 WEEKS	8 WEEKS

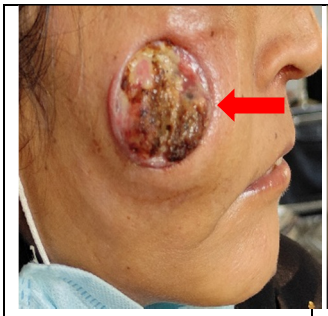
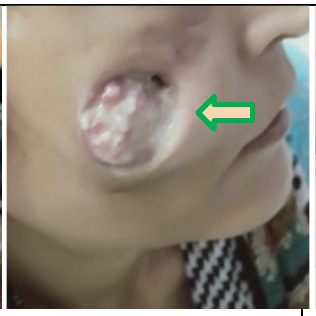
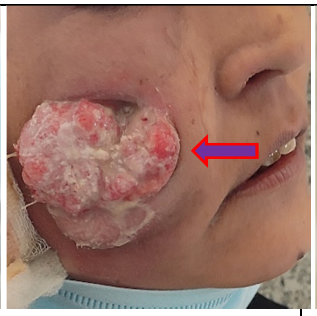
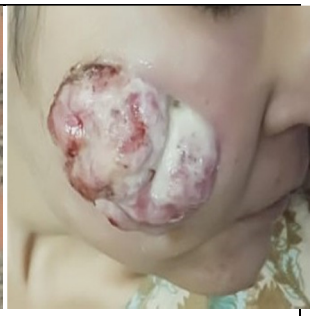
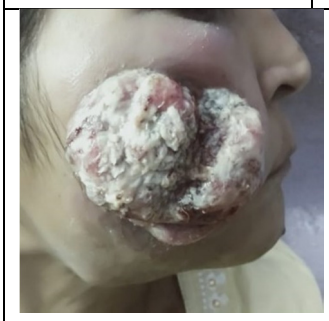
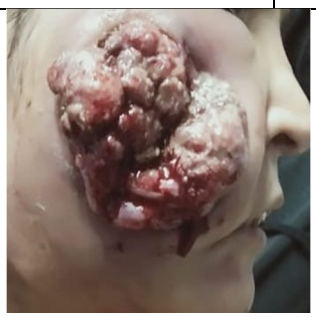
Name	Mr PS
Diagnosis	Recurrent CA Base of Tongue with Neck Nodes (Post CTRT recurrence)
Stage at Accrual of Treatment	rcT4N3bM0
Number of Cycles of Metronomic Chemotherapy Given	2
Partial Response	No PR. Patient progressed within a week and then lost to follow up ~1 month. Had presented in ER and was thereafter started only in best supportive care at home.
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	Lost to follow up – Not Known. Most likely demised at ~2 months.

			
BEFORE MTX	1 WEEK	2 WEEKS	4 WEEKS

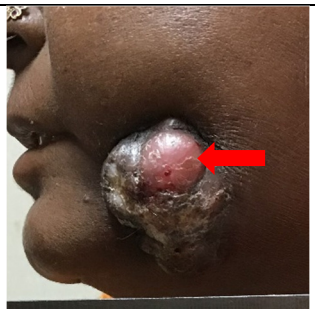
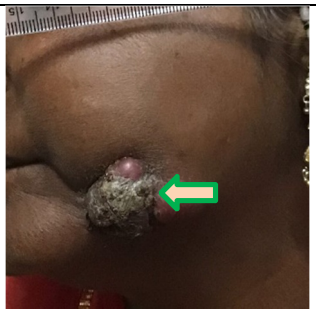
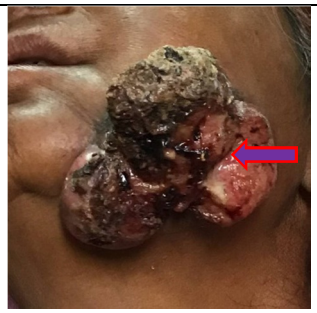
Name	Ms SK
Diagnosis	Ca Lower GBS
Stage at Accrual of Treatment	cT3N2M0 (Refused for Surgery)
Number of Cycles of Metronomic Chemotherapy Given	7
Partial Response	`No PR. Only Stable Disease (SD) for long and then PD
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care (Had refused for any radiation therapy)
Survival in months	16 Months

			
BEFORE MTX	4 WEEKS	8 WEEKS	12 WEEKS
			
14 WEEKS	18 WEEKS	20WEEKS	

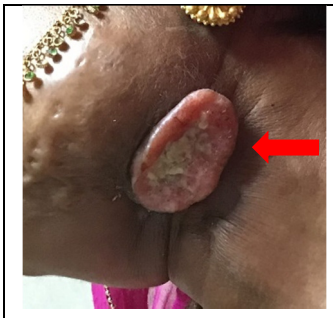
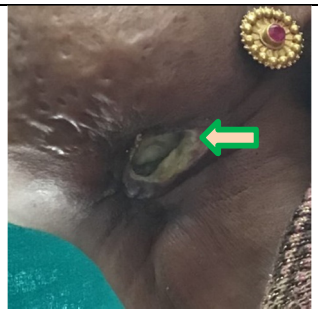
Name	Ms S
Diagnosis	Ca Buccal Mucosa
Stage at Accrual of Treatment	cT4bN2cM0
Number of Cycles of Metronomic Chemotherapy Given	3
Partial Response	At 2 weeks but PD at 4 weeks
Treatment after PD on Metronomic Chemotherapy	Palliative Radiation Therapy followed by Palliative Platinum Based Chemotherapy
Survival in months	7 Months

			
BEFORE MTX	2 WEEKS	4 WEEKS	6 WEEKS
			
8 WEEKS	10 WEEKS(Radiation)		

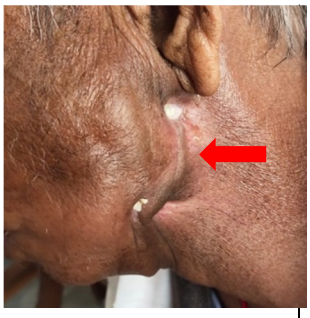
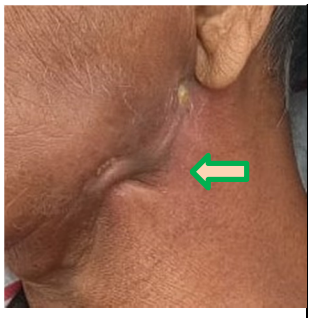
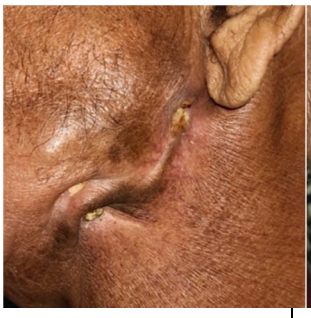
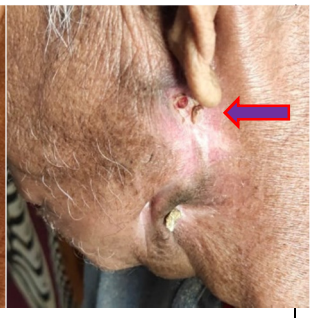
Name	Ms TD
Diagnosis	Ca Left Buccal Mucosa
Stage at Accrual of Treatment	cT4bN2bM0 (Defaulted and refused for radiation therapy)
Number of Cycles of Metronomic Chemotherapy Given	2
Partial Response	At 4 weeks but progressed after 8 weeks
Treatment after PD on Metronomic Chemotherapy	Palliative Radiation Therapy followed by platinum based palliative chemotherapy
Survival in months	Lost to follow up

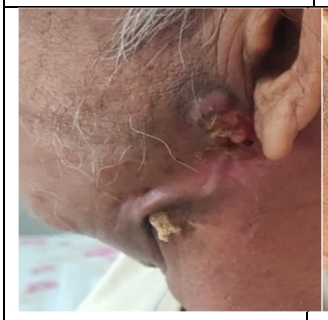
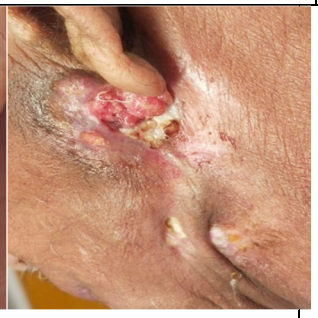
		
BEFORE MTX	4 WEEKS	8 WEEKS

Name	Ms PD
Diagnosis	Recurrent Ca Left Buccal Mucosa (~1 years Post Pall RT recurrence)
Stage at Accrual of Treatment	rcT0cN3bM0
Number of Cycles of Metronomic Chemotherapy Given	4
Partial Response	At 4 weeks.
Treatment after PD on Metronomic Chemotherapy	Re-radiation with Palliative Radiation followed by Platinum Based Chemotherapy
Survival in months	8 Months

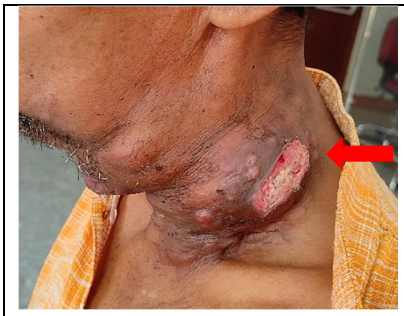
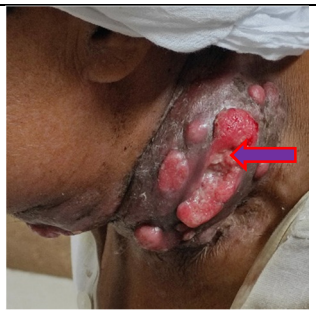
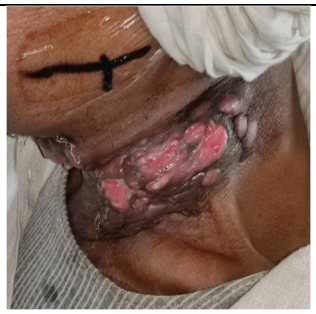
	
BEFORE MTX	4 WEEKS

Name	Mr AL
Diagnosis	Recurrent Ca Left Buccal Mucosa (Post CTRT recurrence)
Stage at Accrual of Treatment	cT4bN2bM0
Number of Cycles of Metronomic Chemotherapy Given	3
Partial Response	PR at 4 weeks. Ulcer and induration regressed. At 12 weeks the ulcer reappeared marking PD
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	8+ Months. Alive at the time of analysis

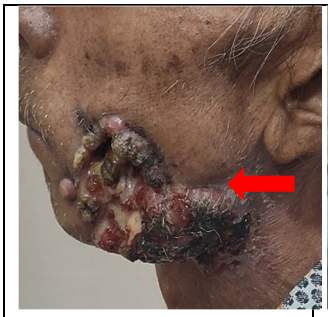
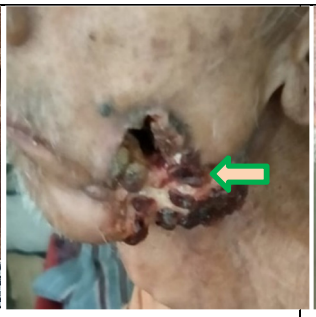
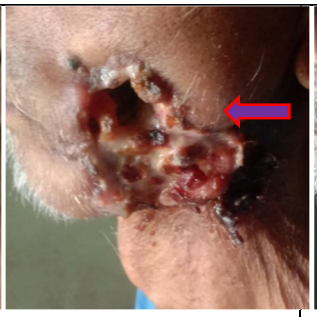
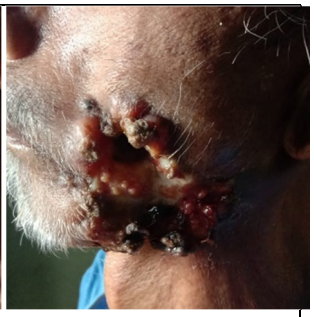
			
2 WEEKS	4 WEEKS	8 WEEKS	12 WEEKS

	
16 WEEKS	20 WEEKS

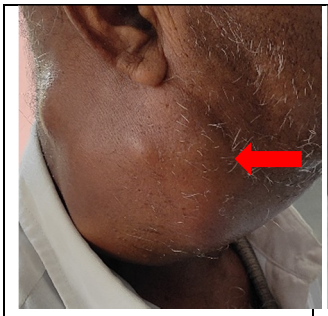
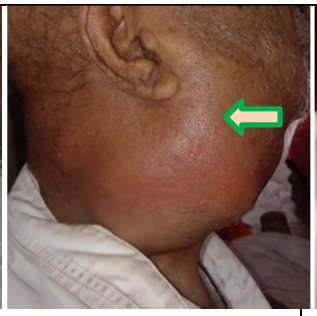
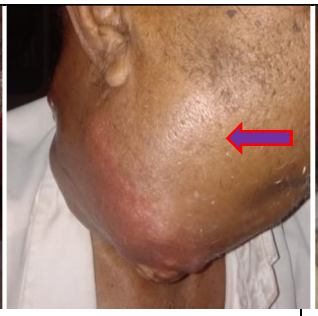
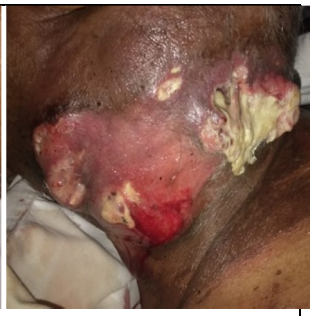
Name	Mr D
Diagnosis	Secondary Neck with unknown primary
Stage at Accrual of Treatment	cTxN3bM0
Number of Cycles of Metronomic Chemotherapy Given	1
Partial Response	No PR. Progressed (PD) at 4 weeks.
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care. Was planned for palliative radiation therapy but expired the next day he was planned for radiation therapy
Survival in months	3

		
BEFORE MTX	4 WEEKS	8 WEEKS

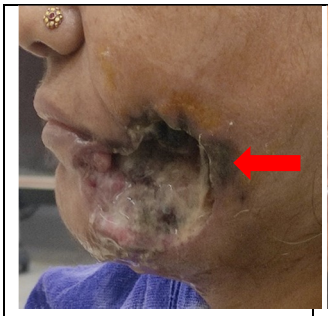
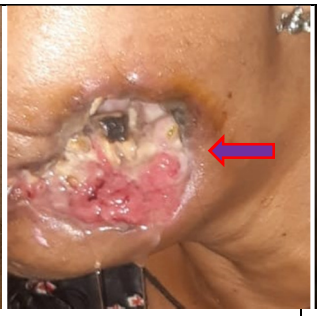
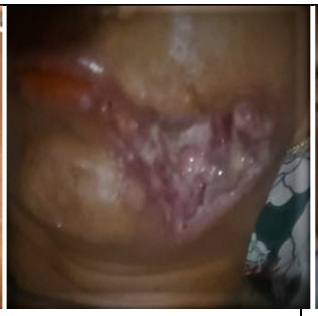
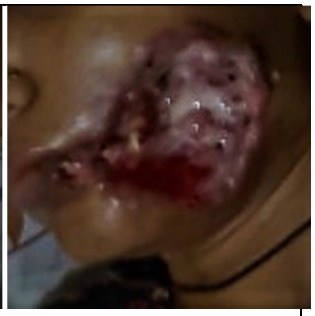
Name	Mr HR
Diagnosis	Ca Left Buccal Mucosa
Stage at Accrual of Treatment	cT4bN2cM0
Number of Cycles of Metronomic Chemotherapy Given	1
Partial Response	At 2 weeks but had PD at 4 weeks
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	2 Months

			
BEFORE MTX	2 WEEKS	4 WEEKS	6 WEEKS

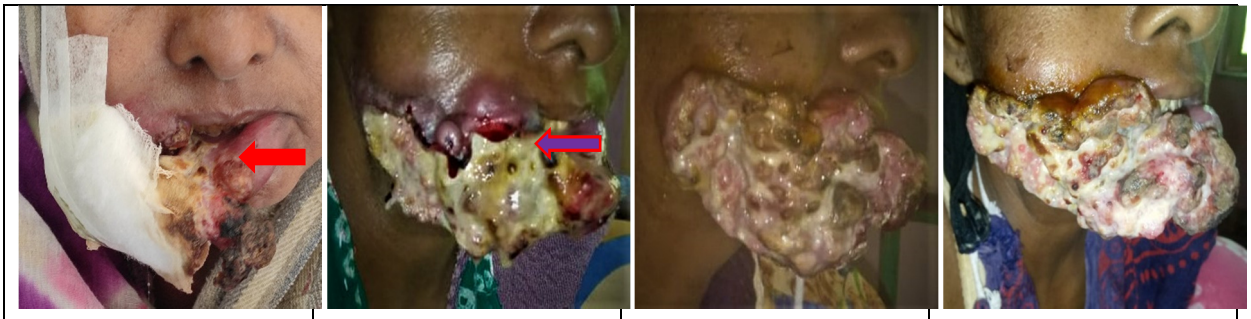
Name	Mr KR
Diagnosis	Ca Oropharynx
Stage at Accrual of Treatment	cT4aN3bM0
Number of Cycles of Metronomic Chemotherapy Given	1
Partial Response	At 2 weeks some regression of node and reduction in edema. Progressed at 6 weeks
Treatment after PD on Metronomic Chemotherapy	Bets supportive care
Survival in months	5 Months

			
BEFORE MTX	2 WEEKS	6 WEEKS	10 WEEKS

Name	Ms M
Diagnosis	Ca Buccal Mucosa
Stage at Accrual of Treatment	cT4bN2cM0
Number of Cycles of Metronomic Chemotherapy Given	1
Partial Response	No PR. Progressed
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	5 Months

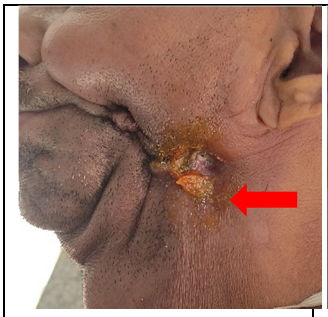
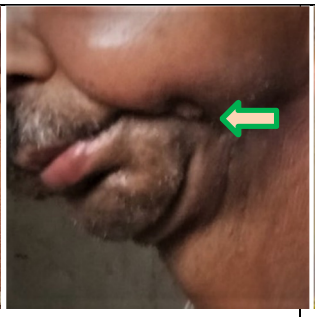
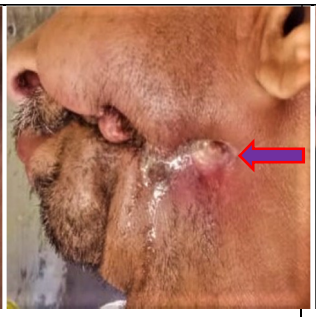
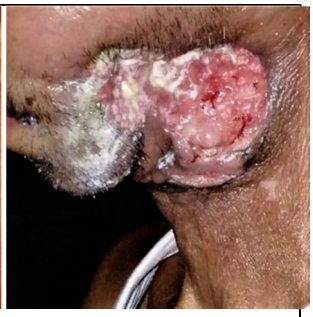
			
BEFORE MTX	2 WEEKS	4 WEEKS	6 WEEKS

Name	Ms NB
Diagnosis	Ca Buccal Mucosa
Stage at Accrual of Treatment	cT4bN2aM0
Number of Cycles of Metronomic Chemotherapy Given	1
Partial Response	No PR. Progressed
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	3 Months

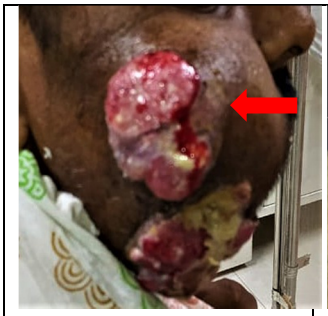
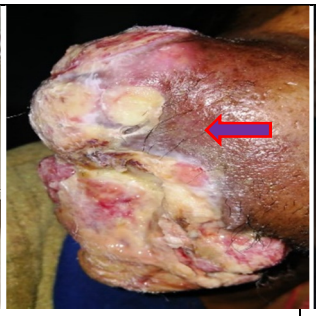
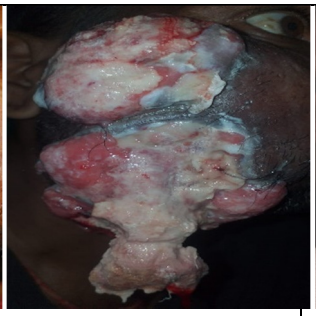
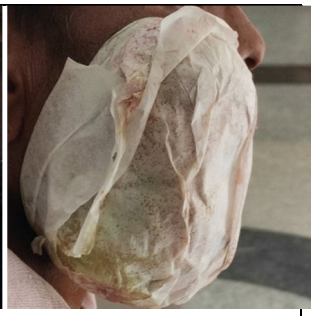


BEFORE MTX	1 WEEK	4 WEEKS	6 WEEKS

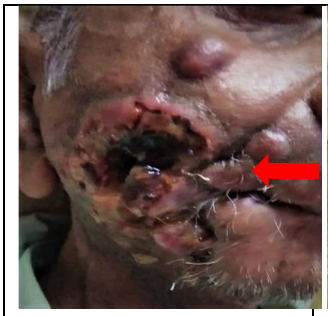
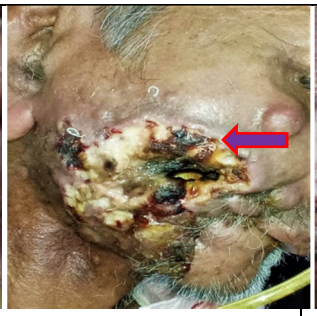
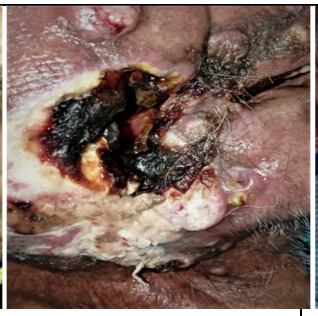
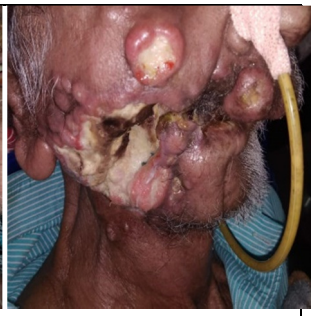
Name	Mr PK
Diagnosis	Recurrent Ca Buccal Mucosa (Post CTRT recurrence)
Stage at Accrual of Treatment	rcT4bN1M0
Number of Cycles of Metronomic Chemotherapy Given	3
Partial Response	PR at 4 weeks. Progressed at 8 Weeks
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	8 Months

			
BEFORE MTX	4 WEEKS	8 WEEKS	24 WEEKS

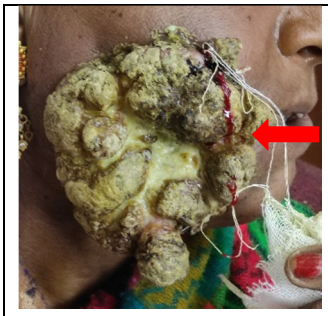
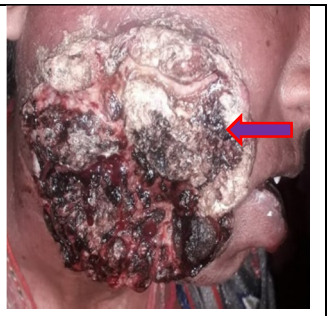
Name	Mr RC
Diagnosis	Ca right Buccal Mucosa
Stage at Accrual of Treatment	cT4bN3bM1 (Lung Metastasis)
Number of Cycles of Metronomic Chemotherapy Given	1
Partial Response	No PR. Progressive local disease
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	2

			
BEFORE MTX	2 WEEKS	4 WEEKS	6 WEEKS

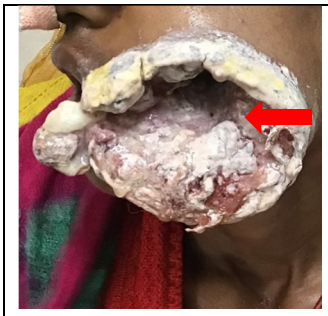
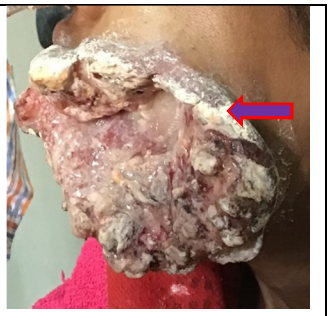
Name	Mr RCH
Diagnosis	Recurrent Ca Rt Lower Alveolus & BM
Stage at Accrual of Treatment	rcT4bN3bM0
Number of Cycles of Metronomic Chemotherapy Given	1
Partial Response	No PR. Only Progressive Disease
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	2

			
BEFORE MTX	2 WEEKS	4 WEEKS	6 WEEKS

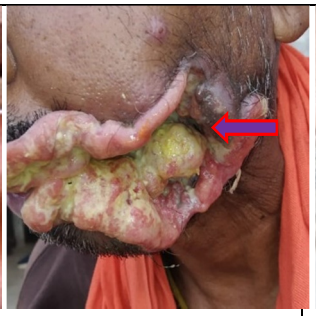
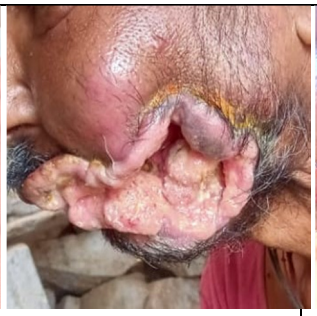
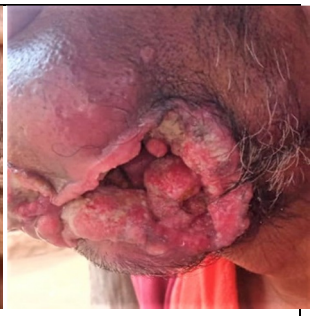
Name	Ms SKA
Diagnosis	Ca right Buccal Mucosa
Stage at Accrual of Treatment	cT4bN1M0
Number of Cycles of Metronomic Chemotherapy Given	1
Partial Response	No PR. Progressed
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	3

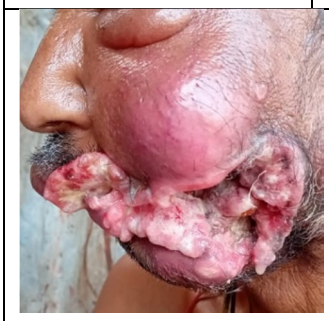
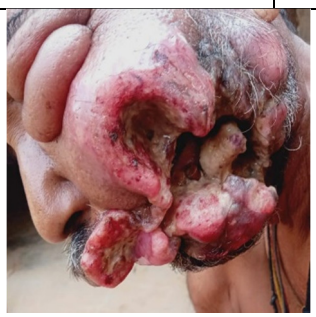
	
BEFORE MTX	4 WEEKS

Name	Ms PRK
Diagnosis	Ca Left Buccal Mucosa
Stage at Accrual of Treatment	cT4bN3bM0
Number of Cycles of Metronomic Chemotherapy Given	2
Partial Response	No PR. Progressed
Treatment after PD on Metronomic Chemotherapy	Palliative Radiation Therapy
Survival in months	2

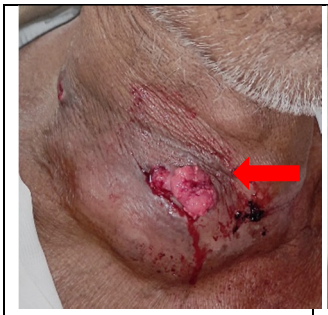
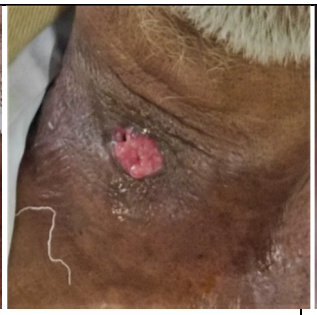
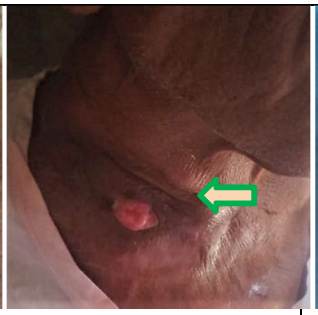
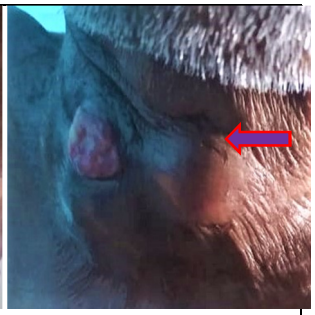
	
BEFORE MTX	4 WEEKS

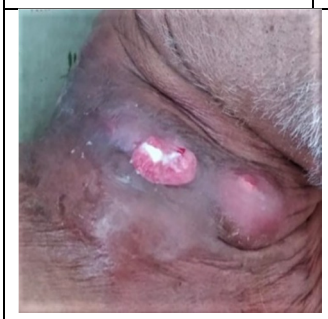
Name	Mr TJR
Diagnosis	Ca Left Buccal Mucosa
Stage at Accrual of Treatment	cT4bN2bM0
Number of Cycles of Metronomic Chemotherapy Given	2
Partial Response	No PR. Progressed
Treatment after PD on Metronomic Chemotherapy	Palliative Radiation Therapy
Survival in months	5 Months

			
BEFORE MTX	1 WEEK	2 WEEKS	4 WEEKS

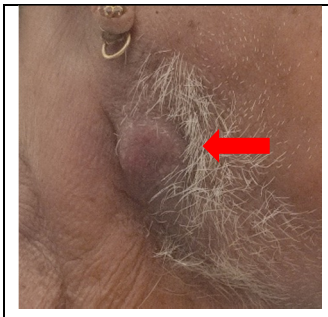
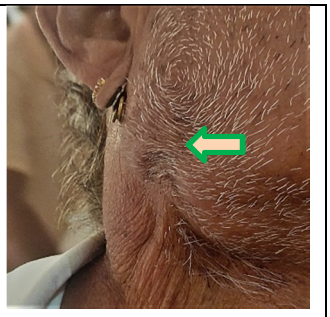
	
6 WEEKS	8 WEEKS

Name	Mr TAR
Diagnosis	Sec Neck with Primary Unknown
Stage at Accrual of Treatment	cTxN3bM0
Number of Cycles of Metronomic Chemotherapy Given	1
Partial Response	At 1 week. Then Progressed at 2 weeks
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	1

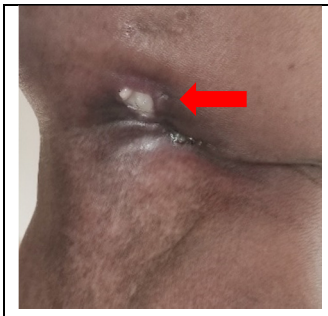
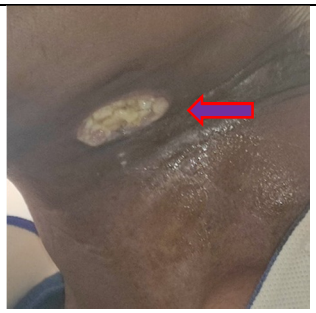
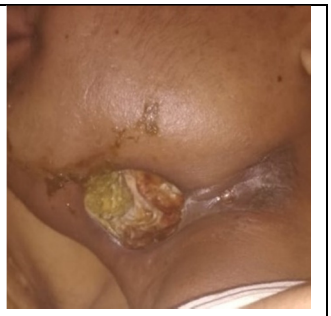
			
BEFORE HEMOSTATIC RT	7 DAYS AFTER HEMOSTATIC RT	1 WEEK ON MTX	2 WEEKS ON MTX


4 WEEKS ON MTX

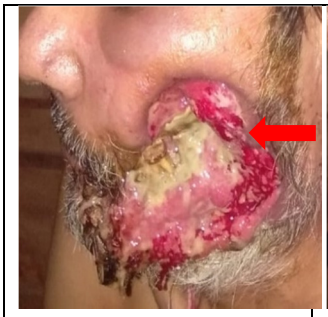
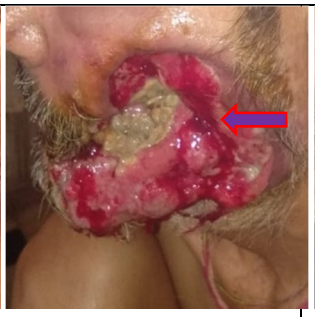
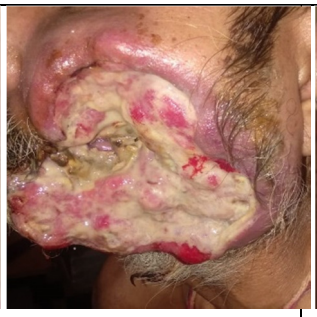
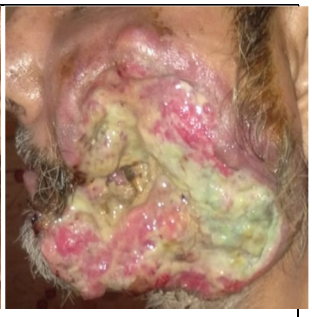
Name	Mr BOR
Diagnosis	Ca Base of Tongue with Lung Mets
Stage at Accrual of Treatment	cT3N2bM1 (Lung Mets)
Number of Cycles of Metronomic Chemotherapy Given	2
Partial Response	At 6 weeks neck node regressed
Treatment after PD on Metronomic Chemotherapy	Continued on Metronomic Chemotherapy till the time of analysis
Survival in months	3+ Alive at the time of analysis

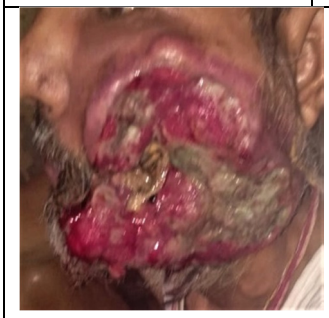
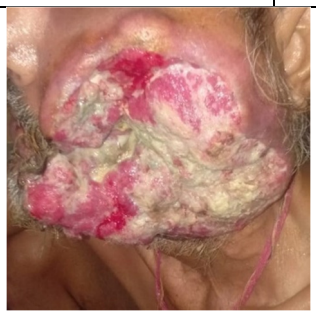
	
BEFORE MTX	6 WEEKS

Name	Mr NIA
Diagnosis	Ca Left Buccal Mucosa
Stage at Accrual of Treatment	cT4aN3bM0
Number of Cycles of Metronomic Chemotherapy Given	2
Partial Response	No PR. Progressed
Treatment after PD on Metronomic Chemotherapy	Best Supportive Care
Survival in months	2

		
2 WEEKS ON MTX	4 WEEKS ON MTX	6 WEEKS ON MTX

Name	Mr BAS
Diagnosis	Ca Left Buccal Mucosa
Stage at Accrual of Treatment	cT4bN0M0
Number of Cycles of Metronomic Chemotherapy Given	1
Partial Response	No PR. Progressed
Treatment after PD on Metronomic Chemotherapy	Palliative Radiation Therapy followed by Palliative Platinum Based Chemotherapy
Survival in months	3+ Months. Patient alive at the time of analysis

			
BEFORE MTX	1 WEEK	2 WEEKS	3 WEEKS

	
4 WEEKS (On Pall RT also PD)	6 WEEKS

DISCUSSION

DISCUSSION

Treatment options for the locally advanced, recurrent and metastatic head and neck cancers are limited and challenging (60). Palliative care is the main treatment for such a patient population. Hypofractionated palliative radiation therapy courses, platinum based chemotherapy and best supportive care are the standard palliative oncology treatments which are often used along with care for pain, nutrition and counselling (8,12). The sequence and objective advantages of such treatments is often not studied. Recently immunotherapy for affordable patients and metronomic chemotherapy for most of the patients, have been shown to produce palliation(5–7,13). The present prospective study objectively studied the metronomic combination of Methotrexate with Celecoxib, its sequencing with other treatment methods and effects on quality of life of such patients besides survival. The study thus added more objective evidence of the use of this combination, similar to the real life scenarios.

Patient Characteristics

After the approval from the Institute Ethics Committee, the study started accrual from January, 2020 and accrued a total of 43 patients till October 2021. Thus a median follow-up of 9 months was achieved. These 43 patients were started on metronomic chemotherapy protocol, however gradually, the number of patients available for QOL measurements and analysis fell down to 35 after 1st cycle of chemotherapy. 2 patients (5%) died after the 1st cycle due to bleeding from the large ulcerative tumours while 6 (15%) patients could continue only best supportive care alone due to deteriorating performance status and lockdowns during COVID19. Only 13 patients were available after 2nd cycle and 8 after 3rd cycle of chemotherapy. Most of the 22 patients after 2 cycles and 8 patients after the 3rd cycle had progressive disease and thereafter received either best supportive care or palliative radiation therapy or platinum based chemotherapy. Only one patient of Ca Larynx with local recurrence and lung metastasis continued to receive 16 cycles of metronomic chemotherapy showing excellent palliative response, after which he started progressing symptomatically.

Similar to other studies, in our present study, the most of the cases were male (77%) while the rest were female (23% of the cases). 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 and most patients are in advanced stages. Patients in India present in locally advanced disease, due to poverty and lack of awareness(3,61,62).

Tobacco is already a proven preventable causative factor for head and neck cancer. The Global Tobacco Survey Data summarized by Singh et al, showed that the cause of high incidence of cancers among males is the high prevalence of tobacco consumers among males as compared to females. A 2005-2006 nationwide survey estimated that the prevalence of tobacco consumption among males was 57.6% and that among females was 10.8% (63). In our study, 87% of patients were tobacco users, most of them being chewers of tobacco (smokeless use of tobacco), rather than smokers.

Most of the patients in our study are in the age group of 30-70 years of age (86%). Cancer of the oral cavity is the most common site (60%). Dikshit et al in their landmark publication in The Lancet had also found that most of the mortality in cancer patients in India happens at the age of 30-69 years with oral cancers leading the cause(2).

Almost all the patients at the time of their initial diagnosis were in stage III and IV (95%). Majority of the patients (66%) had progressed or recurred after their primary treatment. Initially advanced stage patients were unlikely to respond to their primary treatment and therefore were most likely candidates for recruitment in the study with palliative intent.

Locally advanced disease which was either progressive or recurrent (81%) was the most common type of problem in the study population, rather than the metastatic disease (19%). The problems related to local proliferation and recurrent disease are known to be more common in oral cancers than distant metastasis. Similar to the literature the most common site of distant metastasis (86 %), in our study population was lung(64).

Radiation therapy was the most common form of treatment (19%) received prior to accrual in the study. It was followed by palliative cisplatin based chemotherapy (16%). Overall only 7 patients (16%) were operable and underwent surgery earlier and had local or distant failures, while the majority 36 (84%) were inoperable. One patient was operable but had refused either radiation therapy or surgery. She had cT4acN0cM0 squamous cell cancer of the oral cavity and had chosen to be treated by this protocol.

Quality of Life Measurements

Locally advanced, recurrent and metastatic head and neck cancers are the leading cause of cancer mortality in India(2). In a cancer which currently has high mortality rates despite multimodal oncological interventions such as surgery, radiation therapy and systemic anticancer agents, the goal of the treatment is essentially palliative. The multimodal treatment strategies which may result in complete response in early disease are often futile and at the most may produce slight delay in progression or some benefit in the quality of life if used judiciously. Established QOL tool of EORTC H&N 35 was used to measure the effects of treatment. The H&N 35 QOL questionnaire measures 18 QOL domains relevant for head and neck cancers, using scales obtained by linear transformation of 35 validated and standardized questions.

At the baseline, the worst mean scores of the 43 patients were in the domain of pain (painkillers usage) (90.70%), weight loss (88.37%), mouth opening (55.04%), sticky saliva (48.84%), speech (46.51%) and social eating (46.32%). The questions related to sexual domain, were not answered by almost 1/4th of the patients. The problems of cough, feeding tube and weight gain were least. The results emphasize that local growth of head and neck cancers caused intense problems of pain, weight loss and mouth opening problems etc. in patients(65).

CHANGES IN QOL WITH METRONOMIC CHEMOTHERAPY

Changes in QOL were analysed between baseline and at the end of 1 cycle (1 month) and thereafter after the 3rd cycle (3 months) of metronomic chemotherapy.

Changes in QOL after 1 cycle of Metronomic Chemotherapy

After a month of metronomic chemotherapy, as shown in plot 16 the top QOL H&N 35 symptom scales with highest number of patients reporting a change indicating an improvement in the QOL were in Social Eating (45.7%), Speech (42.8%), Teeth (40%), Dry Mouth (40%), Swallowing (34.2%), Sticky Saliva (34.2 %), Senses (34.2%), Pain (31.4%) while least improvement was seen in feeding tube use (11.4%), painkiller usage (11.4%) and

wait gain (14.3%). Thus QOL indicators pointed towards improvement in a large number of patients, although many others reported the same choices indicating stable QOL.

From the subgroup analysis of patients after 1st cycle, stage IV had statistically significant worsening in swallowing, stickiness of saliva, and dryness of mouth, mouth opening and cough with p values < 0.05. Patients aged >/= 40 had worsening of stickiness of saliva (p=0.03). Patients with metastatic disease had statistically significant improvement in senses scores (p=0.01) as well as felt ill scores (p=0.006).Statistically significant weight loss was observed in patients with ca larynx (p=0.02) at the end of first cycle. There was significant worsening in cough scores with a p value of 0.03.

The difference in mean of linear transformed scores of these domains was also analysed statistically. The QOL of cough had a median difference of + 33.3 (p = 0.03) which indicated that patients reported more cough at the end of 1st cycle of treatment. There were no statistically significant changes in the remaining any of the 17 domain scales of H&N 35. The painkiller requirement became 100% with most patients pain assessment of 'A little pain' which is an expected outcome as all palliative patients with pain were on counselling and pain medications, with none having severe pain. Celecoxib, a NSAID is a part of metronomic chemotherapy protocol and added to pain relief of patients.

Absence of statistically significant changes in 17 out of 18 QOL symptom scales of H&N35 implies that there was neither major improvement nor deterioration reported in QOL by the patients. They mostly had maintained mean QOL parameters.

Changes in QOL after 3 cycles of Metronomic Chemotherapy

After 3 cycles (3 months) of metronomic chemotherapy, as shown in plot 17 the top QOL H&N 35 symptom scales with highest number of patients reporting a change indicating an improvement in the QOL were in Pain (62.5%), Dry Mouth (50%), Senses (50%), Social Eating (50%), Social Contact (50%), Mouth Opening (37.5%), Sticky Saliva (37.5%), Swallowing (25%) while least improvement was seen in Feeding Tube use (0%), Painkiller Usage (0%) and Wait Gain (0%). Thus QOL indicators pointed towards improvement in a large number of patients, although many others reported the same choices indicating stable QOL.

The difference in mean of linear transformed scores of these domains was also analysed statistically. There were no statistically significant changes in any of the 18 domain scales of H&N 35. Again, absence of statistically significant changes in 18 QOL symptom scales of H&N35 implies that there was neither major improvement nor deterioration reported in QOL by the patients. They mostly had maintained mean QOL parameters.

Treatment Related Toxicity

The most common toxicities encountered by the patients while on metronomic chemotherapy were mucositis, nausea, constipation, anaemia, dysphagia, neutropenia, and thrombocytopenia. None of the patients had deranged liver or kidney functions. Most of the toxicities appeared within a month of starting metronomic chemotherapy. However, the most toxicities were low grade CTCAE adverse effects. At the end of 1 month, 75% patients had grade 1 or grade 2 mucositis and none had grade 3 or more mucositis. Similarly, none of the patients had grade 3 or more mucositis in further cycles. Nausea grade 1 or 2 was reported by only 28.6% patients. Constipation was seen in 31.4 % of patients. Both nausea and constipation can be caused by pain medications as well. Only one patient (AR) had dramatic grade 4 neutropenia and thrombocytopenia within a week of starting metronomic chemotherapy. He had no fever or complications of the same and was promptly managed with prophylactic antibiotics and injections of G-CSF as per the institute protocol. Interestingly the patient had also had dramatic response in the form of 70% regression in his ulcerated neck node within a week of 1st dose of treatment. He might be having mutations in methotrexate transport or metabolism (reduced folate carrier or P-glycoprotein or MTHFR). However, in view of costs involved, genetic studies were not pursued further for the patient and he was continued on treatment with reduced doses and close observations on the blood counts.

In the phase 3 randomized clinical trial conducted by Patil et. al. and published in Lancet Global Health, grade 3 toxicities were seen in 19% patients on metronomic chemotherapy while 30% patients in cisplatin based chemotherapy arm. The majority of grade 3-5 toxicity was contributed by fatigue, mucositis and diarrhoea(13). In our study life threatening grade 3-5 neutropenia or thrombocytopenia was seen in only 1/ 35 patients (2%) at the end of 1st cycle which is similar to 2% of Neutropenia or thrombocytopenia grade 3-5 in the study by Patil et. al. In our study, the low incidence of grade 3 toxicities may reflect less side effect

profile of the regimen and additionally, many patients switched to best supportive care gradually and only few continued long enough on metronomic regimen to manifest more toxicity.

Thus similar to the literature, metronomic treatment with methotrexate and celecoxib is well tolerated. The treatment has least toxicities as compared to cisplatin and 5FU, Cetuximab or Pembrolizumab and Nivolumab based treatments without adding financial burden on the patients(5–7). In Keynote 048, a phase 3 randomized clinical trial, there were grade 3 or more toxicity in 55% patients treated with Pembrolizumab alone and 85% in Pembrolizumab and chemotherapy arms. The death due to adverse effects of treatment was as high as 8% in Pembrolizumab alone and 12% in the combination arm(6).

Survival Analysis

Patients on metronomic chemotherapy with methotrexate and celecoxib were mostly monitored clinically and clinical photographs also taken. Radiological investigations were only done if indicated. Based on clinical and/or radiological information, any increase in the size of primary lesions or appearance of new lesions was defined as progression. On progression, patients were switched to either other modalities of treatment as radiation therapy if feasible or platinum based chemotherapy if not given already and tolerable. Those patients who had received multiple lines of treatment already or were in poor performance status were given only best supportive care. Kaplan Meier Analysis was performed for the survival analysis. The progression-free survival (PFS) was 1 month, while the overall survival (OS) was 5 months. The survival outcomes are as dismal as reported in most other studies using a variety of interventions(6,7,13,17,66).

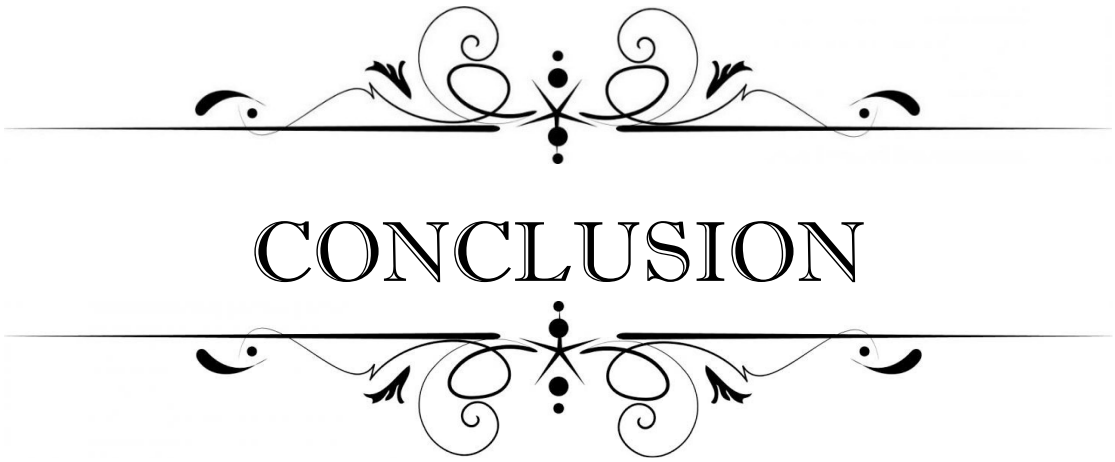
Treatment after progression on metronomic chemotherapy

Patients who had progressed on metronomic chemotherapy were continued on either best supportive care or other feasible oncology modality as palliative radiation therapy (if not received earlier) or platinum based chemotherapy. Out of 43 patients accrued in the study, 24 patients (55.8%) received only best supportive care. 11 patients (25.6%) received palliative radiation therapy. Out of these 11 radiated patients, 6 patients (54.5%) were fit enough to be continued on further platinum based palliative chemotherapy. Only 4 patients out of 43

(9.3%) were given platinum based chemotherapy alone. Interestingly, in patients who were continued on either radiation therapy or platinum based chemotherapy after progression on the metronomic chemotherapy, the median PFS for both the groups was 3 months and they had received a median 3 cycles of metronomic chemotherapy. Patients who were fit enough to continue in either of these arms also had good overall survival of 9 months.

On comparison of Kaplan Meier plots for patients who could receive only best supportive care after metronomic chemotherapy versus further feasible therapy in form of palliative radiation therapy or palliative platinum based therapy, there was significant difference in survival supporting the decision of continued treatment with other rationale and tolerable modalities available. Patients with poor performance status at the time of progression and were not fit for any further oncological intervention were justified to only receive best supportive care before they ultimately succumbed due to their disease. The median OS for the patients on best supportive care was only 3 months as compared to 9 months for those who could continue on further oncological interventions. This difference of 6 months in the median OS is significant (p=0.02). While improvement or stabilisation of QOL and PFS are reasonable objectives for any palliative treatment, any significant advantage in the overall survival (OS) is always a welcome result.

The median overall survival in oral cavity subgroup of patients in KEYNOTE-048 trial with Pembrolizumab (presently a very costly drug in India) was 4 months(6). In our study 60% of patients are oral cavity cancers with PFS of 1 month and OS of 5 months for the complete study population. The outcomes of our study also speak as strong in the favour of oral methotrexate based metronomic treatment as Patil et.al. randomized clinical trial outcomes and discussion(13).



CONCLUSION

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 a meagre amount of survival of a few months. While palliative radiation therapy is an important pillar for radiation naive patients, those who recur or progress despite radical doses of radiation need systemic agents as platinum based chemotherapy, methotrexate, anti-EGFR cetuximab or recently immunotherapy. Clinical studies have neither established clear superiority of any of these agents over each other, nor defined the best sequence of their use. Modalities such as cetuximab and immunotherapy carry great financial toxicity for the mostly poor population of patients from India and Asia, where the cost of their treatment is borne by the state or from out of pocket expenses by patients' families.

Metronomic chemotherapy strategies such as combination of oral methotrexate tablets are very inexpensive as compared to all other agents and are mostly ignored by the pharma industry sponsored large trials. Their use has been exemplified by mostly investigator initiated studies from various academic institutes.

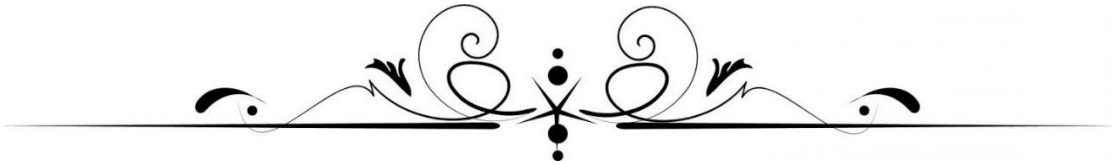
The current study explored the usage of methotrexate and celecoxib based metronomic chemotherapy in real life situations where it was offered in locally advanced, recurrent or metastatic head and neck cancers. Many patients had a history of prior radical treatments with surgery or radiation therapy. Quality of life was measured objectively. As expected, a large number of patients progressed within a few months despite methotrexate. A few showed good partial response and later on progression, continued on the next available modality as palliative radiation, if not received earlier and /or palliative platinum based chemotherapy. Those patients who progressed rapidly despite metronomic methotrexate had significantly lower survival than those who had good partial response and were fit for further oncological

interventions. In neither of these groups patients had any significant grade 3 or more toxicity. All patients could tolerate the regimen comfortably without any financial concerns. The quality of life indicators neither dramatically improved nor deteriorated, hence were essentially stabilized by contributions from metronomic therapy as well as pain and palliative care.

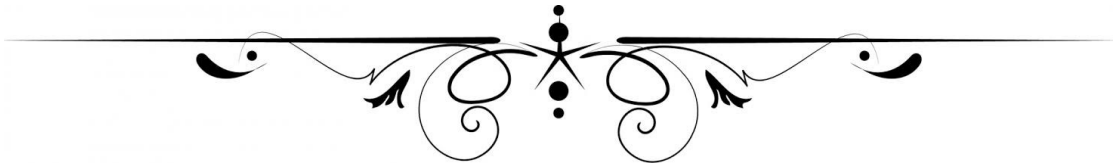
In the present world where the terms ‘new’, ‘more’ and ‘costlier’ are often equated to better, the study reassured that, in absence of any proven superiority of any modality of treatment in locally advanced or recurrent head and neck patients, metronomic methotrexate based combination chemotherapy maintains an established and safe role. Such metronomic regimens can be positioned at any possible place in the sequence of feasible treatment options for such patients and more so for those with financial constraints.

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 (NCDC) programs by the Government of India.

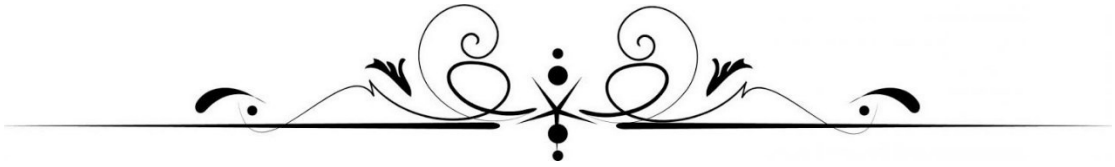


LIMITATIONS OF THE STUDY

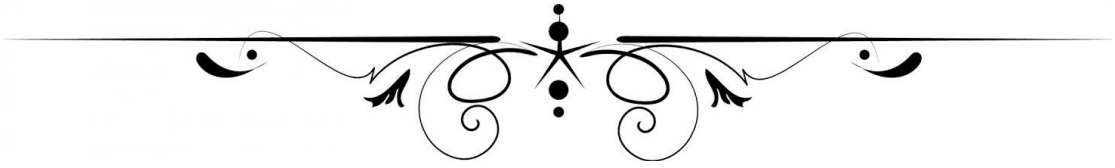


LIMITATIONS OF THE STUDY

The present study only recruited 43 patients in a single arm prospective design. There was no control arm. The QOL of patients do not necessarily depends on oncological treatment as radiation, surgery or chemotherapy but are also affected by factors as pain medications, nutritional support, socioeconomic support and alternative treatments. Similarly, the response to treatment as well as toxicities may depend on host factors such as drug transport and metabolism and tumour heterogeneity. A large sample size which is easily available in our country and a randomised study design with other arms as platinum based chemotherapy, EGFR inhibitors or immunotherapeutic agents as Pembrolizumab and Nivolumab may be able to take care of confounding factors and clarify effectiveness of the different modalities of treatment in this large population of locally advanced and recurrent cancers.



REFERENCES



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ANNEXURES

ANNEXURE I

ETHICS CLEARANCE

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

No. AIIMS/IEC/2020/2029 Date: 01/01/2020

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: AIIMS/IEC/2019-20/991

Project title: "Quality of life in patients receiving palliative sequential metronomic chemotherapy and radiotherapy in advanced and recurrent head and neck cancers"

Nature of Project:	Research Project
Submitted as:	M.D. Dissertation
Student Name:	Dr.Sanjay Santhyavu
Guide:	Dr.Puneet Pareek
Co-Guide:	Dr.Amit Goyal, Dr.Jeewan Ram & Dr. Darwin

This is to inform that members of Institutional Ethics Committee (Annexure attached) met on **23-12-2019** and after through consideration accorded its approval on above project. Further, should any other methodology be used, would require separate authorization.

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.

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

Dr. Praveen Sharma
Member Secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Enclose:
1. Annexure 1

Page 1 of 2

Basni Phase-2, Jodhpur, Rajasthan-342005, Website: www.aiimsjodhpur.edu.in, Phone: 0291-2740741 Extn. 3109
Email: ethicscommittee@aiimsjodhpur.edu.in

ANNEXURE II

PYTHON CODE

```
import pandas as pd
from scipy import stats
from scipy.stats import shapiro
import matplotlib.pyplot as plt
from scipy.stats import mannwhitneyu

import pandas as pd

df1 = pd.read_excel ('/home/sujoy/Downloads/CORELATION DATA1.xlsx')

df1_male=df1[df1['SEX'] != 'F']

print(df1_male)

df1_female=df1[df1['SEX'] != 'M']

print(df1_female)


# normality test
stat, p = shapiro(df1_male['WG LT B1'].dropna())
print('Statistics=%.3f, p=%.3f' % (stat, p))
# interpret
alpha = 0.05
if p > alpha:
   print('Sample looks Gaussian (fail to reject H0)')
else:
   print('Sample does not look Gaussian (reject H0)')



my_dict = {'Before': list(df1_male['WG LT B1'].dropna()), 'After': list(df1_male['WG LT A1'].dropna())}

fig, ax = plt.subplots()
ax.boxplot(my_dict.values())
ax.set_xticklabels(my_dict.keys())
plt.savefig("WG_LT B1_male.png")



print(stats.ttest_ind(df1_male['WG LT B1'].dropna(), df1_male['WG LT A1'].dropna()))



# Take batch 1 and batch 2 data as per above example

# perform mann whitney test
print(stats.mannwhitneyu(df1_male['WG LT B1'].dropna(), df1_male['WG LT A1'].dropna()))
```

ANNEXURE III

All India Institute of Medical Sciences

Jodhpur, Rajasthan

Informed Consent Form

Title of Thesis/Dissertation : "**Quality of life in patients receiving palliative sequential metronomic chemotherapy and radiotherapy in advanced and recurrent head and neck cancers**"

Name of PG Student : Dr. Sanjay Santhyavu Tel. No.8848057610

Patient/Volunteer Identification No. : _____

I, _____ S/o or D/o _____

R/o_____

___

give my full, free, voluntary consent to be a part of the study titled "**Quality of life in patients receiving palliative sequential metronomic chemotherapy and radiotherapy in advanced and recurrent head and neck cancers**" the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.

I understand that my participation is voluntary and am aware of my right to opt out of the study at any time without giving any reason.

I understand that the information collected about me and any of my medical records may be looked at by responsible individual from **AIIMS Jodhpur** or from regulatory authorities. I give permission for these individuals to have access to my records.

Date: _____ _____

Place: _____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date: _____ _____

Place: _____ Signature of PG Student

1. Witness 1

_____

Signature

Name: _____

Address: _____

_____

2.Witness

_____

Signature

Name: _____

Address: _____

_____

ANNEXURE IV

अखिल भारतीय आयुर्विज्ञान संस्थान

जोधपुर, राजस्थान

सूचित सहमति प्रपत्र

थीसिस / शोध प्रबंध का शीर्षक: उन्नत और आवर्तक सिर और गर्दन के कैंसर में अनुक्रमिक मेट्रोनोमिक कीमोथेरेपी और रेडियोथेरेपी प्राप्त करने वाले रोगियों में जीवन की गुणवत्ता का मूल्यांकन करने के लिए अध्ययन पीजी छात्र का नाम: डॉ। संजय संथावु Tel No.8848057610

रोगी / स्वयंसेवक पहचान संख्या: _____मैं,

_____ S/o **या** D / o

_____आर/ओ_____

_____ अध्ययन का एक हिस्सा बनने के लिए मेरी पूर्ण, स्वतंत्र, स्वैच्छिक सहमति दें। उन्नत और आवर्तक सिर और गर्दन के कैंसर में अनुक्रमिक मेट्रोनोमिक कीमोथेरेपी और रेडियोथेरेपी प्राप्त करने वाले रोगियों में जीवन की गुणवत्ता का मूल्यांकन करने के लिए एक एकल हाथ संभावित अध्ययन, जिसकी प्रक्रिया और प्रकृति रही है अपनी पूरी संतुष्टि के लिए मुझे अपनी भाषा में समझाया। मैं पुष्टि करता हूं कि मुझे सवाल पूछने का अवसर मिला है।मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और बिना किसी कारण के किसी भी समय अध्ययन से बाहर निकलने के मेरे अधिकार से अवगत हूं।

मैं समझता हूं कि मेरे और मेरे किसी भी मेडिकल रिकॉर्ड के बारे में एकत्रित जानकारी को एम्स जोधपुर के जिम्मेदार व्यक्ति या नियामक अधिकारियों से देखा जा सकता है। मैं इन व्यक्तियों को अपने रिकॉर्ड तक पहुंचने की अनुमति देता हूं।

दिनांक: _____

जगह: _____ हस्ताक्षर / बाएं अंगूठे का निशान

यह प्रमाणित करने के लिए कि मेरी उपस्थिति में उपरोक्त सहमति प्राप्त हुई है।

दिनांक: _____

जगह: _____ **पीजी छात्र के**

हस्ताक्षर

1. **गवाह** 1 2. **गवाह** 2

हस्ताक्षर **हस्ताक्षर**

नाम: **नाम**:

पता: **पता**:

ANNEXURE V

Patient Information Sheet

Part-1

You are invited to take part in this study entitled "**Quality of life in patients receiving palliative sequential metronomic chemotherapy and radiotherapy in advanced and recurrent head and neck cancers".** It is informed that it is entirely voluntary and you may refuse to take part or discontinue at any time without losing your right to adequate clinical care.

This research is aimed at studying the quality of life and disease status with metronomic chemotherapy in advanced and recurrent advanced head and neck cancers. If the outcome with Metronomic chemotherapy is better than conventional modalities of treatment, a protocol for treatment of advanced head and neck malignancy may be set keeping in mind the financial burden and systemic toxicities with conventional chemotherapy and the advantage metronomic chemotherapy offers..

Extra test or Investigations may be needed as a part of the study. Follow up is needed every month. You might need to fill up questionnaires looking into personal life.

The expected duration of your participation in this study is till disease progression or death whichever may occur early.

All the records will be kept confidential.

You have the right to ask for any further information that you require.

In case of any doubt regarding the study you are welcome to contact the undersigned personally or telephonically.

Part-2

Investigator's statement

I have explained the purpose, procedures, benefits and harms of the study in detail to the patient/ patient's relative.

All information regarding the study has been disclosed.

Enough Time and Opportunity for asking questions regarding the study was given to the patient/ patient's relative.

Investigator signature: -

Witness signature: -

Phone no.

ANNEXURE VI

रोगी सूचना पत्र

भाग ---- पहला

आपको इस अध्ययन में भाग लेने के लिए आमंत्रित किया गया है, "उन्नत और आवर्ती सिर और गर्दन के कैंसर में अनुक्रमिक मेट्रोनोमिक कीमोथेरेपी और रेडियोथेरेपी प्राप्त करने वाले रोगियों में जीवन की गुणवत्ता का मूल्यांकन करने के लिए अध्ययन"।

यह सूचित किया जाता है कि यह पूरी तरह से स्वैच्छिक है और आप पर्याप्त नैदानिक देखभाल के अपने अधिकार को खोए बिना किसी भी समय हिस्सा लेने या बंद करने से इनकार कर सकते हैं।

इस शोध का उद्देश्य उन्नत और आवर्तक उन्नत सिर और गर्दन के कैंसर में मेट्रोनोमिक कीमोथेरेपी के साथ जीवन की गुणवत्ता और रोग की स्थिति का अध्ययन करना है। यदि उपचार के पारंपरिक तौर-तरीकों से मेट्रोनोमिक कीमोथेरेपी का परिणाम बेहतर है, तो पारंपरिक कीमोथेरेपी के साथ वित्तीय बोझ और प्रणालीगत विषाक्तता को ध्यान में रखते हुए उन्नत सिर और गर्दन की दुर्बलता के उपचार के लिए एक प्रोटोकॉल निर्धारित किया जा सकता है।

अध्ययन के एक हिस्से के रूप में अतिरिक्त परीक्षण या जांच की आवश्यकता हो सकती है। 3 महीने के लिए हर महीने फॉलोअप की जरूरत होती है। आपको निजी जीवन की तलाश में प्रश्नावली भरने की आवश्यकता हो सकती है।

इस अध्ययन में आपकी भागीदारी की अपेक्षित अवधि 9 महीने है।

सभी रिकॉर्ड गोपनीय रखे जाएंगे।

आपके पास कोई और जानकारी मांगने का अधिकार है, जिसकी आपको आवश्यकता है।

अध्ययन के संबंध में किसी भी संदेह के मामले में आप व्यक्तिगत या टेलीफोन पर अधोहस्ताक्षरी से संपर्क करने का स्वागत करते हैं।

भाग 2

जांचकर्ता का बयान

मैंने रोगी/रोगी के रिश्तेदार को अध्ययन के उद्देश्य, प्रक्रियाओं, लाभों और हानियों के बारे में विस्तार से बताया है।

अध्ययन से संबंधित सभी जानकारी का खुलासा कर दिया गया है।

रोगी/रोगी के रिश्तेदार को अध्ययन के संबंध में प्रश्न पूछने के लिए पर्याप्त समय और अवसर दिया गया था।

अन्वेषक के हस्ताक्षर:-

फोन नंबर।

गवाह के हस्ताक्षर: -

ANNEXURE VII

EORTC H&N 35 ENGLISH VERSION

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

ANNEXURE VIII

EORTC H&N 35 HINDI VERSION

HINDI

EORTC QLQ - H&N35

मरीज कभी कभी निम्न रोग लक्षणों या परेशानियों की शिकायत करते हैं | कृपया इंकित करे कि पिछले एक सप्ताह के दौरान आपने किस हद तक इन रोग लक्षणों या परेशानियों का अनुभव किया है | आपको जो उत्तर सबसे अधिक सही लगे, उसके अंक पर कृपया अंकित करे ||

पिछले एक सप्ताह के दौरान	बिलकुल नही	थोडासा	थोडा अधिक	बहुत अधिक
३१.क्या आपके मुँह में दर्द उठा था?	१	२	३	४
३२.क्या आपके जवडों में दर्द उठा था?	१	२	३	४
३३.क्या आपके मुँह में कसौलापन हुआ था?	१	२	३	४
३४.क्या आपके गले में दर्द हुआ था?	१	२	३	४
३५.क्या आपको तरल पदार्थ निगलने में तकलीफ हुई थी?	१	२	३	४
३६.क्या आपको पिसा हुआ पदार्थ निगलने में तकलीफ हुई थी?	१	२	३	४
३७.ठोस खाना निगलने में क्या आपको तकलीफ हुई थी?	१	२	३	४
३८.निगलने के दौरान क्या आपका दम घुटता है?	१	२	३	४
३९.क्या आपके दॉतो को लेकर आपको कोई परेशानी हुई थी?	१	२	३	४
४0.कया आपका मुँह ज्यादा खोलने में तकलीफ हुई थी?	१	२	३	४
४१.क्या आपके मुँह में कभी सूखापन महसूस हुआ था?	१	२	३	४
४२.क्या आपका थूक चिपचिपा हुआ था?	१	२	३	४
४३.क्या आपकी सूंघने की क्षमता के बारे में आपको कोई समस्या हुई थी?	१	२	३	४
४४.क्या आपके स्वाद की क्षमता के बारे में आपको कोई समस्या हुई थी?	१	२	३	४
४५.क्या आपको खॉसी हुई थी?	१	२	३	४
४६.क्या आपको गले में खराश थी?	१	२	३	४
४७.क्या आपको लगताा था कि आप बीमार हैं?	१	२	३	४
४८.क्या आपका स्वरूप आपको परेशान करता था?	१	२	३	४

अगले पन्ने पर

पिछले एक सप्ताह के दौरान	बिलकुल नही	थोडासा	थोडा अधिक	बहुत अधिक
४९. क्या आप खाने में कठिनाई महसूस करते थे?	१	२	३	४
५0. क्या आपको अपने परिवार के सामने खाना-खाने में कठिनाई हुई थी?	१	२	३	४
५१. क्या आपको दूसरे लोगों के सामने खाना खाने में कठिनाई हुई थी?	१	२	३	४
५२. अपने भोजन का आनंद उठाने में क्या आपको तकलीफ हुई थी?	१	२	३	४
५३. क्या आपको दूसरे लोगों के साथ वात करने में तकलीफ हुई थी?	१	२	३	४
५४. क्या आपको टेलीफोन पर वात करने में तकलीफ हुई थी?	१	२	३	४
५५. क्या आपको अपने परिवार के साथ सामाजिक संपर्क रखने में तकलीफ हुई थी?	१	२	३	४
५६. क्या आपको अपने दोस्तों के साथ सामाजिक संपर्क करने में तकलीफ हुई थी?	१	२	३	४
५७. क्या आपको आम जनता के सामने जाने में तकलीफ हुई थी ?	१	२	३	४
५८. क्या आपको परिवार या दोस्तों के साथ शरीरिक संपर्क करनें में तकलीफ हुई थी?	१	२	३	४
५९. क्या आपको यौन संवंध में रूचि कम लगती थी?	१	२	३	४
६0. क्या आपको यौन संवंधी आनंद में कमी लगती थी?	१	२	३	४

पिछले एक सप्ताह के दौरान	नही	हॉ
६१. क्या आपने दर्द निवारक दवाई ली थी?	१	२
६२. क्या आपने (जीवनसत्व छोडकर)कोई पूरक पोषण पदार्थ का सेवन किया था?	१	२
६३. क्या आपने खाने के लिए नली का प्रयोग किया था?	१	२
६४. क्या आपका वजन कम हुआ था?	१	२
६५. क्या आपका वजन वढ गया था?	१	२

ANNEXURE IX

AJCC 8TH EDITION TNM CLASSIFICATION OF HEAD AND NECK CANCERS (EXCEPT CARCINOMA NASOPHARYNX)

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(+).

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

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.

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(+).

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

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

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

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(+).

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

American Joint Committee on Cancer (AJCC)
TNM Staging System for Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck (8th ed., 2017)
(Squamous cell carcinoma and salivary gland carcinoma of all head and neck sites *except* HPV-related oropharynx cancer, nasopharynx cancer, melanoma, thyroid carcinoma, and sarcoma. Staging of the patient who presents with an occult primary tumor and EBV-unrelated and HPV-unrelated metastatic cervical lymphadenopathy is also included.)

Regional Lymph Nodes (N)

Clinical N (cN): For patients who are treated with primary nonsurgical treatment without a cervical lymph node dissection.

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 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, 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) with clinically overt ENE(+) (ENE_c)[2]
- N3a Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
- N3b Metastasis in any node(s) with clinically overt ENE(+) (ENE_c)[2]

[1]Midline nodes are considered ipsilateral nodes.
[2]ENE_c is defined as invasion of skin, infiltration of musculature, dense tethering or fixation to adjacent structures, or cranial nerve, brachial plexus, sympathetic trunk, or phrenic nerve invasion with dysfunction.

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(+).

American Joint Committee on Cancer (AJCC)
TNM Staging System for Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck (8th ed., 2017)
(Squamous cell carcinoma and salivary gland carcinoma of all head and neck sites *except* HPV-related oropharynx cancer, nasopharynx cancer, melanoma, thyroid carcinoma, and sarcoma. Staging of the patient who presents with an occult primary tumor and EBV-unrelated and HPV-unrelated metastatic cervical lymphadenopathy is also included.)

Regional Lymph Nodes (N)

Pathological N (pN): For patients who are treated surgically with a cervical lymph node dissection.

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 node(s), 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 3 cm or less 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 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 a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral nodes any size and ENE(+) in any node; *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 size and ENE(+) in any node; *or* a single contralateral node of any size and ENE(+)

[1]Midline nodes are considered ipsilateral nodes.
[2]ENE detected on histopathologic examination is designated as ENE_{mi} (microscopic ENE ≤ 2 mm) or ENE_{ma} (major ENE > 2 mm). Both ENE_{mi} and ENE_{ma} qualify as ENE(+) for definition of pN.
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(+).

Anatomic Stage/Prognostic Groups

Stage III	T0	N1	M0
Stage IVA	T0	N2	M0
Stage IVB	T0	N3	M0
Stage IVC	T0	Any N	M1

Continued

ANNEXURE X

CTCAE 5.0 COMMON TOXICITIES AND GRADING

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability. **Navigational Note:** -					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements. **Navigational Note:** -					
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; operative intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting. **Navigational Note:** -					
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by difficulty in swallowing. **Navigational Note:** -					
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the oral mucosal. **Navigational Note:** -					
Generalized muscle weakness	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites. **Navigational Note:** -					
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels. **Navigational Note:** -					

ANNEXURE XI

MASTER DATA