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A retrospective analysis of outcome with triplet oral metronomic chemotherapy in head and neck cancers in a resource comprising setting during COVID 19 pandemic, a single institute experience

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Abstract
Introduction: The aim of this study was to assess the OS and toxicity of triplet oral triplet metronomic chemotherapy in patients with advanced / recurrent head and neck squamous cell carcinoma (HNSCC). Oral metronomic chemotherapy (OMCT) is regular administration of the chemotherapeutic drugs resulting in constant low blood level of the drug. It is economical and patient friendly especially in low resource setting.
Materials and Methods: This is a retrospective study Conducted over a period of 3 years during COVID 19 pandemic in a resource poor district in India with no Radiation facility. The study participants include histologically confirmed head and neck tumours who are either not willing for a radical approach or palliative iv chemotherapy due to logistic and poor social support or not fit for the same.
Patients received erlotinib 150 mg/100mg per oral once daily, capsule celecoxib 200 mg (Fixed dose) per oral twice daily and oral weekly methotrexate 9mg/m2. All the Statistical analysis were done using SPSS software version 16. Descriptive and Kaplan Meir Analysis were also performed.
Result: A total of 211 patients were recruited over a period of 3 years from 2021. The median age was 51 with major site being Buccal mucosa. 87 percent were having a stage IV disease. The majority had an ECOG PS status of 1-2 and 72% were having a primary disease.90% of them received a palliative RT from elsewhere. Only 10% developed TKI toxicity and less than 10% developed any other toxicities including hematological toxicities. Less than 20% needed any IP admissions. The major cause of death was due to Aspiration pneumonia. CR was achieved in 19% and Partial response was achieved in 39% of patients. The median follow up was 11 months (95% CI 9.65-12.35). The 2 year survival rate is 65%. Mean Survival time is 33.9 months (95% CI 30.44 - 37. 40). Univariate and multivariate analysis showed only CR/PR had a significant impact on OS with HR 0.08 (95% CI 0.04-0.17) and p value <0.001. PFS could not be calculated because many were lost to follow up. Median Survival time was also not achieved.
Conclusion: We conclude that there is a definite role of OMCT in terms of OS in treatment of head and neck SCC. OMCT can be even an alternative in patients who are not tolerable or affordable for standard palliative iv chemotherapy with or without palliative RT and also can be an option for patient who are not Willing for a curative treatment with either surgery or Radical RT especially in a resource poor setting which also warrants more prospective studies.

Keywords: Oral metronomic chemotherapy (OMCT), Head and neck squamous cell carcinoma (HNSCC)

Introduction
Despite significant advancements in cancer research, treatment options still face considerable hurdles. Chemotherapy, a principal treatment method, is often hampered by severe adverse drug reactions that diminish the overall effectiveness of anti-neoplastic agents and limit the safe dosage (Hanahan & Weinberg, 2011) [4]. This situation underscores the necessity of exploring alternative therapeutic strategies, particularly those targeting the tumor vasculature. Tumor endothelial cells have been recognized as a promising therapeutic target, a concept first introduced by Folkman in 1971 when he proposed anti-angiogenesis as a cancer treatment strategy (Folkman, 1971) [1].

Angiogenesis, defined as the development of new blood vessels, is crucial for tumor growth and metastasis (Carmeliet, 2005) [3]. As tumors grow, their demand for oxygen and nutrients escalates, which is fulfilled by the formation of new blood vessels. Inhibiting angiogenesis, particularly through the blockade of vascular endothelial growth factor (VEGF), has emerged as a critical focus in cancer therapy. Anti-VEGF antibodies and other specially designed molecular agents have shown efficacy in hindering tumor growth by disrupting their blood supply (Ferrara & Kerbel, 2005) [2]. When combined with traditional drugs that exhibit anti-angiogenic effects, these therapies provide innovative means to improve cancer treatment outcomes (Ferrara, 2004) [9].

Oral metronomic chemotherapy (OMCT) is gaining recognition as an alternative treatment, especially for head and neck squamous cell carcinoma (HNSCC). This type of cancer is notably prevalent in areas such as the Asian subcontinent, particularly India, where it ranks as the third most common cancer overall and second among males (Kalaichelvi *et al*., 2018) [6]. Regrettably, a significant proportion (60-80%) of HNSCC cases are diagnosed at advanced stages, complicating therapeutic interventions (Vermorken *et al*., 2008) [7]. The scarcity of accessible tertiary cancer facilities and financial constraints in these regions often lead to delays in patient treatment, resulting in poorer outcomes. Although surgery is the most effective option, waiting for surgical intervention allows the cancer to progress, highlighting the need for therapies that can preserve tumor operability during these delays (Patil *et al*., 2015) [5].

Conventional chemotherapy presents notable limitations, primarily due to its toxicity and the necessary rest periods between treatment cycles. These intervals enable tumor cells to repopulate, potentially undermining the treatment's overall efficacy. This has fueled interest in OMCT, which employs frequent, low-dose administration of chemotherapy drugs without the typical rest periods (Ferrara, 2004) [9]. This strategy aims to maintain stable drug levels in the bloodstream, providing a more consistent inhibition of tumor growth (Hanahan & Weinberg, 2011) [4].

OMCT functions through multiple mechanisms, primarily targeting angiogenesis by inhibiting the endothelial cells that contribute to blood vessel formation. It also has direct effects on tumor cells, making it a multi-targeted therapeutic approach (Patil *et al*., 2015) [5]. The low-dose regimen of OMCT minimizes toxicity while preserving efficacy, presenting a distinct advantage over traditional chemotherapy. The combination of drugs like celecoxib and methotrexate, extensively investigated in metronomic treatment protocols, enhances therapeutic effectiveness (Ghiringhelli *et al*., 2007) [8]. Celecoxib acts as a cyclooxygenase-2 (COX-2) inhibitor, which is frequently overexpressed in head and neck cancers [10], while methotrexate interferes with DNA synthesis (Kalaichelvi *et al*., 2018) [6].

OMCT offers a promising alternative for patients with HNSCC by providing continuous, low-dose chemotherapy that minimizes toxicity while delivering targeted anti-angiogenic effects. While further research is needed to solidify OMCT's status as a standard treatment option, preliminary findings indicate it is both effective and well-tolerated. This suggests potential for improved cancer outcomes, especially in resource-limited settings where access to advanced treatment options may be constrained.

Aims

To evaluate the overall survival (OS) and treatment tolerability of Triplet Oral Metronomic Chemotherapy (OMCT) in patients with advanced/recurrent head and neck squamous cell carcinoma (HNSCC) treated in a resource-constrained setting during the COVID-19 pandemic.

Objectives

1. To analyze the efficacy of OMCT in terms of complete response (CR) and partial response (PR).
2. To assess the incidence of treatment-related toxicities and their impact on patient compliance.
3. To identify prognostic factors influencing overall survival (OS) through univariate and multivariate analyses.
4. To examine the feasibility of OMCT as a viable alternative in resource-limited settings, especially for patients unable to access or tolerate standard intravenous therapies.
5. To evaluate the quality of life (QoL) outcomes associated with OMCT in advanced HNSCC patients.

Materials and Methods

This retrospective study was conducted over a four-year period, from January 2020 to February 2024, at the Department of Oncology, District Hospital Kanhangad, a resource-limited facility lacking access to radiation therapy.It is very important to note that the hospital covers a population of approximately 13 lakhs and does not have a radiation facility yet. The study adhered to Good Clinical Practice (GCP) guidelines and the principles outlined in the Declaration of Helsinki. Periodic monitoring and oversight of the study were provided by designated ethical and clinical committees.

Inclusion Criteria

Eligible participants were patients with histologically confirmed squamous cell carcinoma of the oral cavity. These included cases of de novo disease, or patients presenting with at least one measurable lesion that had progressed within six months of prior platinum-based chemotherapy or within one month following local treatments such as surgery or radiation therapy.

Additionally, patients met the inclusion criteria if they:

- Declined radical treatment approaches or intravenous palliative chemotherapy due to logistical challenges or inadequate social support,
- Or were deemed medically unfit for such interventions.

Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria:

- Primary malignancies of the salivary glands,
- Current participation in other investigational drug trials,
- Inability to swallow oral medications,
- Presence of uncontrolled comorbid conditions,
- Pregnancy or breastfeeding,
- Concurrent use of long-term COX-2 inhibitors or methotrexate for unrelated conditions,
- Age under 18 years,

- Eastern Cooperative Oncology Group (ECOG) performance status score greater than 2,
- Abnormalities in key organ functions.

Treatment Protocol

All patients received a metronomic chemotherapy regimen comprising the following:

- Erlotinib 150 mg (Fixed dose) administered orally once daily,
- Celecoxib 200 mg (Fixed dose) administered orally twice daily,
- Methotrexate (9 mg/m²) administered orally once weekly.

Patients undergoing this treatment regimen were regularly monitored for both therapeutic response and treatment-related toxicities. Initial assessments were conducted on Day 8 of Cycle 1 (C1D8), followed by evaluations on Day 30, and monthly thereafter until disease progression. Imaging scans were performed on 6 monthly or as needed.

Patients received Palliative Radiotherapy from neighbouring districts.

Results

Patient Demographics

- Total of 211 patients enrolled over four years (2020–2024).
- **Median age:** 51 years (Range 34–89); 54.5% male, 45.5% female.
- 30% had comorbidities, predominantly diabetes mellitus and hypertension.
- **ECOG performance status:** 72% scored 1, while 28% scored 2.

Disease Characteristics

- 87% of patients presented with stage IVA/IVB disease.
- **Primary cases:** 72.51%; recurrent cases: 27.48%.
- **Predominant sites:** Buccal mucosa (30%) and tongue (12%).

Treatment and Toxicity

1. OMCT regimen included erlotinib (150 mg daily), celecoxib (200 mg twice daily), and methotrexate (9 mg/m² weekly).
2. 90% did not experience tyrosine kinase inhibitor (TKI)-related toxicity.
3. Less than 20% required inpatient admissions.
4. Mucositis observed in 4.26%, anemia in 7.10%, and neutropenia in 3.31%.
5. Dose reductions required in 20.37% of patients.

Response Rates and Survival Outcomes

- **Complete response (CR):** 19%; Partial response (PR): 39%.
- **2-year survival rate:** 65%; mean survival time: 33.9 months (95% CI 30.44–37.40).
- Multivariate analysis revealed CR/PR as a significant predictor of OS (HR 0.08; $p < 0.001$).

Mortality and Follow-Up

- **Major causes of death:** Aspiration pneumonia (49%) and pancytopenia (18%).
- **Median follow-up:** 11 months (95% CI 9.65–12.35).
- Median survival time not reached due to ongoing responses.

Discussion

This section delineates the principal findings concerning the therapeutic efficacy of triplet oral metronomic chemotherapy in patients diagnosed with head and neck squamous cell carcinoma (HNSCC). The overall response rate, including complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD), was evaluated through imaging modalities and clinical assessments. The effectiveness of this chemotherapeutic regimen in mitigating tumor progression was substantiated by progression-free survival (PFS) and overall survival (OS) metrics.

We scrutinized the impact of triplet oral metronomic chemotherapy on overall survival in HNSCC cohorts, taking into account both short-term and long-term outcomes. Additionally, we assessed the influence of this treatment on patients' quality of life (QoL) and performance status, employing validated QoL assessment instruments and patient-reported outcome measures. Exploratory analyses were conducted to identify prognostic factors associated with treatment response and survival outcomes.

Statistical evaluations were executed using SPSS software version 16, incorporating descriptive statistics and Kaplan-Meier survival analysis.

A total of 211 patients were enrolled over four years, commencing in 2020. The majority of diagnoses occurred in 2020, with 54 cases (25.59%), followed closely by 2021 and 2023, each with 50 cases (23.69%). The predominant anatomical sites of malignancy included the buccal mucosa (30%) and the tongue (12%). The median age of participants was 51 years, with a range from 34 to 89 years. Of the total population, 115 were male (54.5%) and 101 were female (45.5%). Notably, 30% of patients presented with comorbidities, predominantly diabetes mellitus and hypertension, while the majority (72%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 1. Agarwala *et al*. [11] indicated that ECOG performance status (0-1 versus 2) and the type of therapeutic intervention (Cetuximab versus metronomic) significantly influenced OS.

A significant proportion (87%) of the patients exhibited stage IVA/IVB disease. Among the cohort, 153 (72.51%) had de novo disease, while 58 (27.48%) were recurrent cases. The higher incidence of recurrent cases may reflect challenges in the efficacy of initial therapeutic regimens including scarcity of a comprehensive cancer centre in the district or the aggressive biology of the cancer subtype. Conversely, the substantial number of primary cases could indicate successful preventive strategies, early detection initiatives especially prompt reference from primary and secondary health centres to the tertiary centre.

Ninety percent of patients underwent palliative/curative radiotherapy at external facilities outside the district. This intervention aims to alleviate symptom burden and enhance the quality of life for individuals with advanced or metastatic malignancies, addressing issues such as pain and obstruction. Understanding the proportion of patients receiving palliative radiotherapy provides insights into management strategies for advanced disease. Geetha M reported that prior to the initiation of metronomic chemotherapy, palliative radiation therapy was administered

to 11 patients, with curative intent in 2 patients [12]. Shobana Sekhar (13) noted that none of the patients received palliative chemotherapy, citing factors such as non-affordability, advanced age, and treatment reluctance as primary barriers.

A high incidence (90.99%) of patients did not experience any tyrosine kinase inhibitor (TKI) toxicity, indicating favorable tolerability to the treatment with minimal adverse effects. Of the 211 cases, 168 (79.62%) did not necessitate dose reduction, while 43 (20.37%) required modifications. However, the occurrence of TKI toxicity in 9.00% of cases underscores the importance of vigilant monitoring during treatment. Notable toxicities included gastrointestinal disturbances, dermatological reactions, fatigue, and hematological abnormalities.

The absence of neutropenia in 96.68% of cases suggests effective management strategies, including prophylactic antibiotics and timely hematopoietic growth factor support. Nevertheless, the presence of neutropenia in 3.31% of cases highlights the necessity for diligent monitoring of hematological toxicities and timely intervention. Khatwani [14] reported that grade 3/4 hematological toxicity was prevalent, with non-febrile neutropenia observed in 10% of cases, alongside anemia and thrombocytopenia in 3% of cases, all deemed manageable.

Anemia, a frequent complication in oncologic patients, was documented in 7.10% of cases, while 92.89% sustained adequate red blood cell levels. The effective management of anemia was done, utilizing blood transfusions and iron supplementation, which is imperative for ensuring treatment tolerance and enhancing quality of life. Gupta [15] identified prevalent grade 3 or 4 toxicities, including anemia, neutropenia, febrile neutropenia, nausea, and diarrhea, affecting 44%, 40%, 16%, 16%, and 12% of patients, respectively.

Out of the total cases, 205 (97.15%) did not experience thrombocytopenia, while 6 (2.84%) did. The management of thrombocytopenia is critical for preventing bleeding complications and ensuring safe administration of cancer therapies.2 patients received Inj romipolstim out of which one was benefitted.

In terms of weight dynamics, 151 patients (71.56%) did not experience a weight loss of 10% or more, indicating that most maintained stable body weights during treatment. However, the significant weight loss observed in 28.43% of patients underscores the impact of malignancy and its treatment on nutritional status. Proactive nutritional support and symptom management are essential for addressing the needs of patients at risk of weight loss.Many of our patients received Megesterol acetate and good nutritional support including protein supplementation with the help of a dietician.

Mucositis was not observed in 95.73% of cases, suggesting effective management strategies to maintain patients' quality of life. Majoriy of them received one form of prophylactic/therapeutic oral hygeine supplements like non-alcoholic antiseptic mouth wash, turmeric water or salt water mouth wash. However, the presence of mucositis in 4.26% of cases emphasizes the need for ongoing supportive care to ensure patient comfort and nutritional intake. Vamshi Krishna noted that dose reductions for erlotinib were necessitated in 7 patients due to dermatological toxicities, mucositis, or generalized weakness [16].

The majority of patients (79.62%) did not require a dose reduction, reflecting good tolerability of the treatment regimen. Nonetheless, a subset of 20.37% required dose adjustments, highlighting the challenges associated with treatment-related toxicities. Satheesan Balasubramanian reported grade 3–4 toxicity in 40% of patients, necessitating dose reductions in 26.7% of cases [17].

Reasons for inpatient admissions varied, with infectious complications such as Nodal/primary site abscesses (20%) and lower respiratory tract infections (40%) being notable contributors, alongside hematological issues and decreased oral intakeand related fatigue. The distribution highlights the variability in hospital admissions among patients, indicating the complexity of treatment courses and the necessity for intensive management.

The primary etiology of mortality was aspiration pneumonia (49%), followed by pancytopenia (18%). The increased mortality rate in 2021 (52%) necessitates further investigation into factors contributing to this trend, including disease severity and treatment resistance.The fact that this was the period of COVID 19 pandemic and people had a limited access to tertiary care centres is to be speciallly mentioned. Conversely, the lower mortality rate in 2024 may signify enhancements in patient care or the fact that COVID 19 pandemic had subsided by that time.

Among the total cases analyzed, only 10% of patients developed toxicity related to tyrosine kinase inhibitors (TKIs), highlighting the favorable safety profile of the triplet oral metronomic chemotherapy regimen employed in this cohort. This low incidence of TKI-related adverse events underscores the potential for chronic administration of this therapeutic approach, minimizing the risk of severe toxicities commonly associated with traditional chemotherapy protocols (Patil *et al*.; Rathi *et al*.) [18, 19]. Furthermore, less than 20% of the patient population required inpatient admissions during the treatment course, indicating effective outpatient management and suggesting that the regimen may be well-tolerated in a community-based oncology setting (Ghosh *et al*.) [20].

A notable clinical outcome was observed with a complete response (CR) achieved in 19% of patients, while partial response (PR) was noted in 39%. These response rates are significant, particularly in the context of advanced HNSCC, where traditional therapies often yield lower efficacy rates (Bourhis *et al*.) [21]. The achievement of CR and PR signifies not only tumor shrinkage but also potential improvements in symptomatology and quality of life for these patients.

The median follow-up duration for the entire cohort was 11 months (95% CI 9.65-12.35), which is critical for evaluating the sustainability of the treatment response and the longevity of survival benefits. During this follow-up period, a 2-year survival rate of 65% was documented, providing encouraging evidence for the long-term effectiveness of metronomic chemotherapy in this patient population (Sharma *et al*.) [22]. The mean survival time was calculated at 33.9 months (95% CI 30.44 - 37.40), indicating a relatively favorable prognosis when compared to historical controls in similar advanced disease states.

Statistical analyses were performed to discern the impact of clinical responses on overall survival (OS). Both univariate and multivariate analyses revealed that CR and PR were the only significant predictors influencing OS, with a hazard ratio of 0.08 (95% CI 0.04-0.17) and a p-value <0.001. This implies that patients achieving CR or PR had an 92%

reduction in the risk of mortality compared to those with stable disease or progressive disease, emphasizing the critical role of therapeutic response in determining patient outcomes (Agarwal *et al.*) [23].

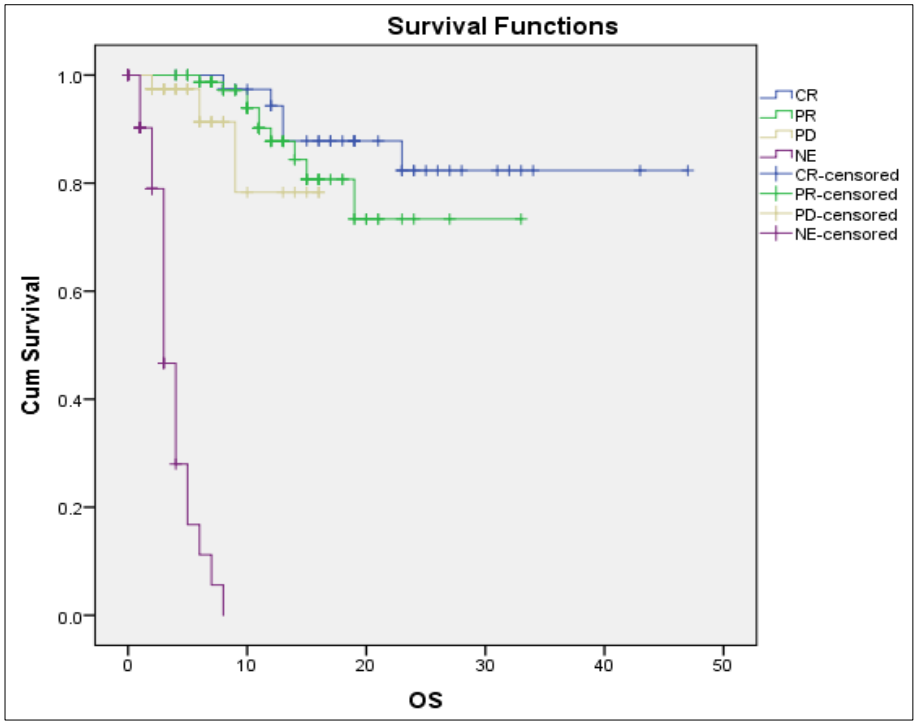

Fig 1: Survival based on complete response (CR), partial response (PR), progressive disease (PD), not evaluated (NE)

It is important to note that due to patient loss to follow-up, progression-free survival (PFS) could not be accurately calculated, which limits the comprehensiveness of survival analyses. Moreover, the median survival time was not reached, suggesting that a significant portion of patients would have continued to respond positively to treatment beyond the observed follow-up period, warranting further long-term studies to evaluate the full impact of metronomic therapy in this setting (Kumar *et al.*) [24].

Metronomic chemotherapy represents a promising therapeutic avenue for low- and middle-income countries, particularly in head and neck cancers. Following the pivotal phase III study by Patil *et al.* [27], various centers in India have embraced oral metronomic regimens. Experiences reported from different regions of India have highlighted lower adverse events and improved response rates associated with metronomic therapy, although most studies remain retrospective and lack comprehensive long-term outcome data.

The data suggest that oral metronomic regimens may be a viable treatment option for head and neck cancers, particularly for those who are metastatic or have undergone prior treatments. The low toxicity profile supports chronic administration, ensuring continuity of cancer care and potentially decreasing hospitalization rates. This is particularly advantageous for prioritizing hospital resources for more critically ill patients and offers a treatment alternative for frail elderly patients, who are frequently excluded from clinical trials.Moreover the iv chemotherapy may be reserved for a later progression.

Several studies indicate that metronomic therapy, utilizing various drugs and schedules, is safe, even for geriatric patients, making it a suitable option in palliative care scenarios. While robust evidence regarding the role of metronomic chemotherapy in various neoplasms is still nascent, preliminary results are promising. This approach may be especially beneficial for patients with adverse prognostic factors, including advanced age, comorbidities, and unfitness for conventional chemotherapy.

These findings support clinicians in making informed decisions regarding the implementation of lower drug doses in routine practice, particularly in resource-constrained settings. Additionally, this article may encourage regulatory authorities to develop drug-dosing policies that facilitate access to innovative therapies in India. Further prospective randomized studies are warranted to accurately evaluate the efficacy of specific metronomic regimens.

In this study, conducted in a district with a population of approximately 1.3 million and devoid of radiation facilities, the challenges faced by patients seeking cancer care were significantly exacerbated by the COVID-19 pandemic. The scarcity of resident oncologists and limited access to advanced treatment options severely constrained the therapeutic landscape for head and neck cancer patients. The pandemic imposed additional barriers to care, making travel difficult for patients and complicating follow-up appointments.

In this context, the introduction of oral metronomic chemotherapy (OMCT) offered a pragmatic and beneficial alternative. The ability to deliver treatment in an outpatient setting reduced the burden on patients, alleviating the need for frequent visits for intravenous chemotherapy, which typically demands more intensive monitoring and resource allocation. This approach is particularly advantageous in resource-limited settings, where healthcare infrastructure may struggle to support the demands of conventional treatment modalities.

The study demonstrated that patients receiving OMCT achieved a complete response (CR) in 19% of cases and a partial response (PR) in 39%. These response rates are

noteworthy, especially considering the backdrop of the COVID-19 pandemic, which limited access to more radical treatment approaches. It is important to acknowledge that the findings of this study may be confounded by the ongoing pandemic, as many patients faced delays in diagnosis and treatment due to restrictions and healthcare system overload during this period (Kumar *et al*.; Zhang *et al*.) [25, 26]. Nonetheless, OMCT not only facilitated disease control but also contributed positively to patients' quality of life, allowing them to manage their symptoms more effectively within the constraints of their local healthcare system.

Furthermore, the findings suggest that there remains a significant need for innovative treatment strategies in resource-constrained areas of India. In such settings, palliative radiotherapy from nearby facilities, combined with OMCT, could enhance patient outcomes. This dual approach would allow for initial symptom management through palliative radiation, followed by the sustained benefits of OMCT, which requires less frequent monitoring and minimizes patient burden.

The combination of palliative care strategies and OMCT could represent a model for managing cancer in similar resource-limited environments, ensuring that patients receive adequate care despite logistical challenges. However, the limitations of this study are primarily due to the COVID-19 pandemic, which may have influenced treatment adherence, patient follow-up, and overall outcomes. This underscores the necessity for further research to validate these findings in a post-pandemic context.

Currently, several prospective trials are underway to address long-standing questions related to this drug regimen. Notably, one key study is a comparative analysis of oral metronomic chemotherapy (OMCT) versus intravenous chemotherapy in patients with metastatic, recurrent, inoperable head and neck cancers, focusing on palliative intent treatment (CTRI/2015/11/006388) [28].

Forest plot

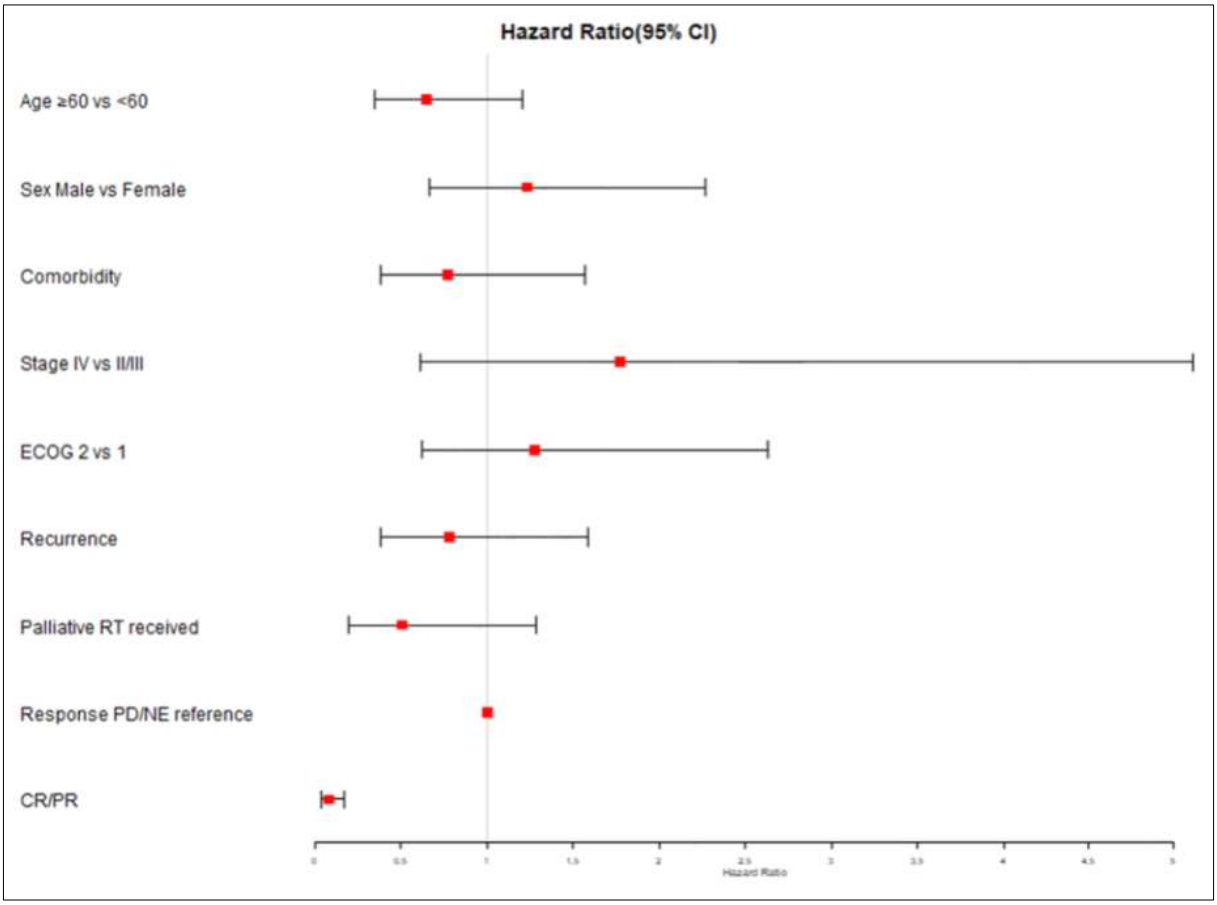

Fig 2: Response considered as total response (CR/PR) and non-response (PD /NE)

Conclusion

In conclusion, this study underscores the significant role of oral metronomic chemotherapy (OMCT) in enhancing overall survival (OS) for patients with head and neck squamous cell carcinoma (SCC). OMCT emerges as a viable alternative for patients who cannot tolerate or afford standard intravenous palliative chemotherapy, with or without palliative radiotherapy. It is also a suitable option for those unwilling to pursue curative treatments, such as surgery or radical radiotherapy, especially in resource-limited settings. The COVID-19 pandemic had compounded the challenges faced by patients, limiting access to conventional therapies and exacerbating existing disparities in cancer care. In this context, OMCT not only offers a practical treatment option but also improves the quality of life for patients who might otherwise experience delays or interruptions in their cancer management.

As we move forward, it is imperative to conduct more prospective studies to further validate the findings of this study and expand our understanding of OMCT's efficacy in diverse populations. Such research is essential to optimize treatment strategies and ensure that patients receive the most effective and accessible care possible.

Conflict of Interest
Not available

Financial Support
Not available

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