

Original Article

# Impact in Quality of Life with Gefitinib Plus Methotrexate Combination Metronomic Chemotherapy in Advanced and Metastatic Head and Neck Cancer - A Prospective Study from a Tertiary Cancer Centre, South India

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**Abstract** - Patients with advanced Squamous cell Carcinoma of the Head and Neck (SCCHN) have poor prognosis despite the available treatment options. QOL is an important end-point in evaluating treatment results in patients with advanced metastatic disease. This study looked into the impact of metronomic chemotherapy combining gefitinib and methotrexate on the quality of life in patients with advanced SCCHN. This was a single-center, prospective observational study conducted in our hospital over a period of 2 years (January 2021-December 2022). 131 patients with advanced or metastatic or recurrent head and neck squamous cell cancers who are not eligible for Platinum or 5 Fluorouracil-based IV chemotherapy due to poor performance status (or) already received palliative IV chemotherapy. It progressed in the same, and those who were unsuitable for loco-regional treatment were included in our study. They received Gefitinib 250mg daily plus methotrexate 15mg once a week orally on D1, D8, D15 and D22 of a 28-day cycle. Quality Of Life assessment before starting treatment and at 3 months and 6 months post-therapy was done with EORTC QLQC30 version 3.0 and EORTC QLQ-H&N35 questionnaires. Gefitinib, along with methotrexate, was well tolerated and was found to have a positive impact on the quality of life of patients with advanced SCCHN. The median improvement in quality of life was 42 points on a scale of 100. Head and neck cancer has severe effects on the quality of life. Assessing health-related quality of life should be an integral part of treatment planning and should be considered as important as treatment burden, toxicity, and survival benefit. Metronomic chemotherapy with gefitinib and methotrexate is associated with improvement in QOL and helps decrease the duration of time spent in the toxicity state.

**Keywords** - Advanced recurrent metastatic head and neck squamous cell cancer, Oral metronomic chemotherapy, Palliative chemotherapy in head and neck squamous cell cancers, Supportive care in head and neck cancers.

## 1. Introduction

Head and neck squamous cell carcinomas are the major contributors to India's health burden. According to GLOBOCAN 2020 data, cancers in the head and region are the leading cause of cancer incidence and cancer-related mortality in India.[1] There were 219722 new cases of Head and Neck cancers, and head and neck cancers lead to the death of 121096 patients annually. Most of the patients with head and neck cancers (60-70%) present in locally advanced stages requiring a combined modality of treatment involving surgery, radiation, and chemotherapy. Despite adequate treatment, the incidence of recurrence is high (nearly 50%).[2] Distant recurrences and loco-regional recurrences not amenable to further local treatment are a challenge as both radiation and surgery have been optimally utilized in most of these patients.

Patients are usually treated with palliative chemotherapy, with agents commonly used being platinum, taxanes and 5 FU.[3] Patients who receive palliative chemotherapy eventually progress, and there are not many options left for further treatment except targeted therapy with cetuximab or immunotherapy with Nivolumab or Pembrolizumab. Even patients who receive these agents do not have sustained responses, and they progress in a matter of months.[4] Furthermore, in developing nations like India, not all patients are eligible to receive immunotherapy due to socioeconomic conditions.[5] Hence, they are often referred for palliative and best supportive care. Metronomic chemotherapy is a palliative treatment option for advanced and metastatic Head and neck cancers. The concept of metronomic chemotherapy was introduced by Douglas Hanahan, in which low doses of chemotherapy



agents are delivered over an extended period without any gaps.[6] This is unlike the traditional method of chemotherapy administration, wherein rest periods are given for the recovery of normal tissues. This approach was based on the fact that the rest period given during the chemotherapy cycles would lead to the development of the re-growth of tumor cells and resistant clones. Metronomic chemotherapy is one of the proven treatment methods for patients with recurrent or metastatic head and neck cancers and has been widely studied by various researchers.[7-13] Metronomic chemotherapy exerts its anticancer activity by inhibiting tumor angiogenesis, stimulating an anticancer immune response and inducing tumor dormancy.[14] Many different combination metronomic chemotherapy regimens have been used in head and neck cancers. However, as found in various studies, none of them was clearly superior to each other. However, most studies analyzed responses based on clinical response rates like overall survival and progression-free survival rates. Although cure and response rates are of primary importance, the quality of survival is also a major consideration in patients with advanced head and neck cancers. [15-17]. Assessing health-related quality of life should be an integral part of treatment planning and should be considered as important as treatment burden, toxicity and survival benefit.[18]. In some circumstances, Quality of Life considerations could determine which treatment option is to be favored. This study looked at the effects of metronomic chemotherapy, which included the drugs gefitinib and methotrexate, on patients with advanced and metastatic head and neck malignancies. The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire, Version 3.0 (EORTC QLQC30), and EORTC Head and Neck Module (EORTC QLQ-HN35), which have been validated and used in many clinical trials to assess patients' quality of life across the globe, were used to conduct the quality-of-life assessment. [19]

## 2. Materials And Methods

### 2.1. Patient Selection

This prospective observational study was carried out at our facility between January 2021 and December 2022 on patients with metastatic and recurrent locally advanced head and neck squamous cell malignancies.

### 2.2. Criteria for Inclusion

- Must be at least 18 years old while presenting.
- Eastern Cooperative Oncology Group (ECOG) PS 0-3.
- Head and neck squamous cell carcinoma established histologically or cytologically to be progressed or metastatic (oral cavity oropharynx, hypopharynx, and larynx).
- Not eligible for IV treatment based on platinum or fluorouracil-5-phosphate due to poor performance status (or having received IV chemotherapy for palliative purposes).
- What are normal hematopoietic, hepatic, and renal functions?

- Absolute neutrophil counts  $>1.5 \times 10^9$  cell/ml, platelet counts  $>100,000$  cell/mm<sup>3</sup>, Hb levels  $>9.0$  g/dL, and total serum bilirubin concentrations within the upper range of normal are all positive indicators.
- Within 2.5xULN for alanine and aspartate aminotransferases (AST and ALT).
- No history of Interstitial Lung Disease (ILD).

### 2.3. Criteria for Exclusion

- Non-Squamous histology.
- People with known or suspected hypersensitivity to methotrexate/TKI.
- Severe cardiac, renal or hepatic illness.
- Breastfeeding or Pregnant women.
- Patients who do not give written informed consent.

## 3. Aims and Objectives

To investigate how oral metronomic chemotherapy in conjunction with gefitinib and methotrexate affects patients with recurrent, residual, and metastatic head and neck cancers quality of life.

After receiving informed consent, all patients with biopsied proven recurrent, residual, and metastatic head and neck malignancies were counselled with the possibility of metronomic chemotherapy and enrolled in the trial for treatment. The study involved 131 patients in total.

The given metronomic chemotherapy regimen is as follows:

- 15 mg of oral methotrexate once each week
- For oral administration, 250 mg of gefitinib once a day for at least six months or until progression or intolerable toxicity.

## 4. Assessment and Scoring of Quality of Life

The EORTC Head and Neck Module (EORTC QLQ-HN35) and the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire, version 3.0, assessed QOL. Prior to beginning metronomic therapy, or at month 0, as well as three and six months after therapy ended, were used for scoring. The patients' native tongue was used to administer the questionnaires. Patients took about 15 to 20 minutes to complete the questionnaire. The EORTC QLQC30 includes symptom scales, a global health status scale, and five functional scales (physical, role, emotional, cognitive, and social functioning). In this study, the functional scales and the global health scale were primarily examined.

Seven multiple-item measures are included in the EORTC QLQ HN-35 module to evaluate symptoms of discomfort, swallowing capacity, senses (taste/smell), speech, social eating, social contact, and sexuality. Eleven other single items are also included, and they pertain to teeth, mouth opening, dry mouth, sticky saliva, coughing, feeling sick, weight growth and loss, use of painkillers, nutritional supplements, and feeding tubes. In our study, the pain symptom scale received special attention. Other single item and symptom ratings were computed, but the

study's parameters did not cover them. The EORTC QLQ scoring manual's instructions were followed while calculating the scores. All scales have scores that range from 0 to 100. A high functional scale or global health status scale score indicates a high quality of life. A high score on a symptom scale, on the other hand, denotes poor quality of life.

## 5. Analysis of Statistics

Statistics Data was entered using a Microsoft Excel spreadsheet on a proforma that had already been created. The 23<sup>rd</sup> Version of the Statistical Package for Social Sciences (SPSS) software was used for the statistical analysis.

Categorical data was expressed in percentages. The QOL scores were calculated at baseline, at 3 months and 6 months from starting metronomic chemotherapy and compared to baseline values using the Friedman test. The P-value of < 0.05 is considered significant.

## 6. Results

One hundred and thirty-one patients with recurrent locally advanced or metastatic head and neck squamous cell carcinoma who satisfied the study eligibility criteria were enrolled in the study. All were started on metronomic chemotherapy with a Gefitinib methotrexate combination.

The baseline characteristics of the patients are shown in Table 1, and graphical data of the same are shown in Figure 1.

Of the 131 patients, 104 completed 6 months of treatment with metronomic chemotherapy and were included in the study.

5 patients defaulted during treatment, and 22 patients progressed before completing 6 months of metronomic chemotherapy and did not receive at least 6 months of treatment.

**Table 1. Baseline characteristics of the patients involved in this study**

S. No	Category	Subset	Number	%
1	Age	<31 years	7	5.3
		31-40 years	9	6.8
		41-50 years	34	25.9
		51-60 years	52	39.6
		>60 years	29	22.1
2	Sex	Male	95	72.5
		Female	36	27.5
3	ECOG PS at presentation	0	3	2.2
		1	33	25.2
		2	68	51.9
		3	27	20.6
4	Exposure to tobacco	Yes	112	85.4
		No	19	14.6
5	Primary site	Oral cavity	63	48
		Oropharynx	24	18.3
		Hypopharynx	32	24.4
		Larynx	12	9.1
6	Stage	III	1	0.7
		IVA	34	25.9
		IVB	78	59.5
		IVC	18	13.7
7	Prior treatment	Surgery & chemo& RT	57	43.5
		Surgery & RT alone	18	13.7
		Chemo & RT alone	45	34.3
		RT alone	11	8.3

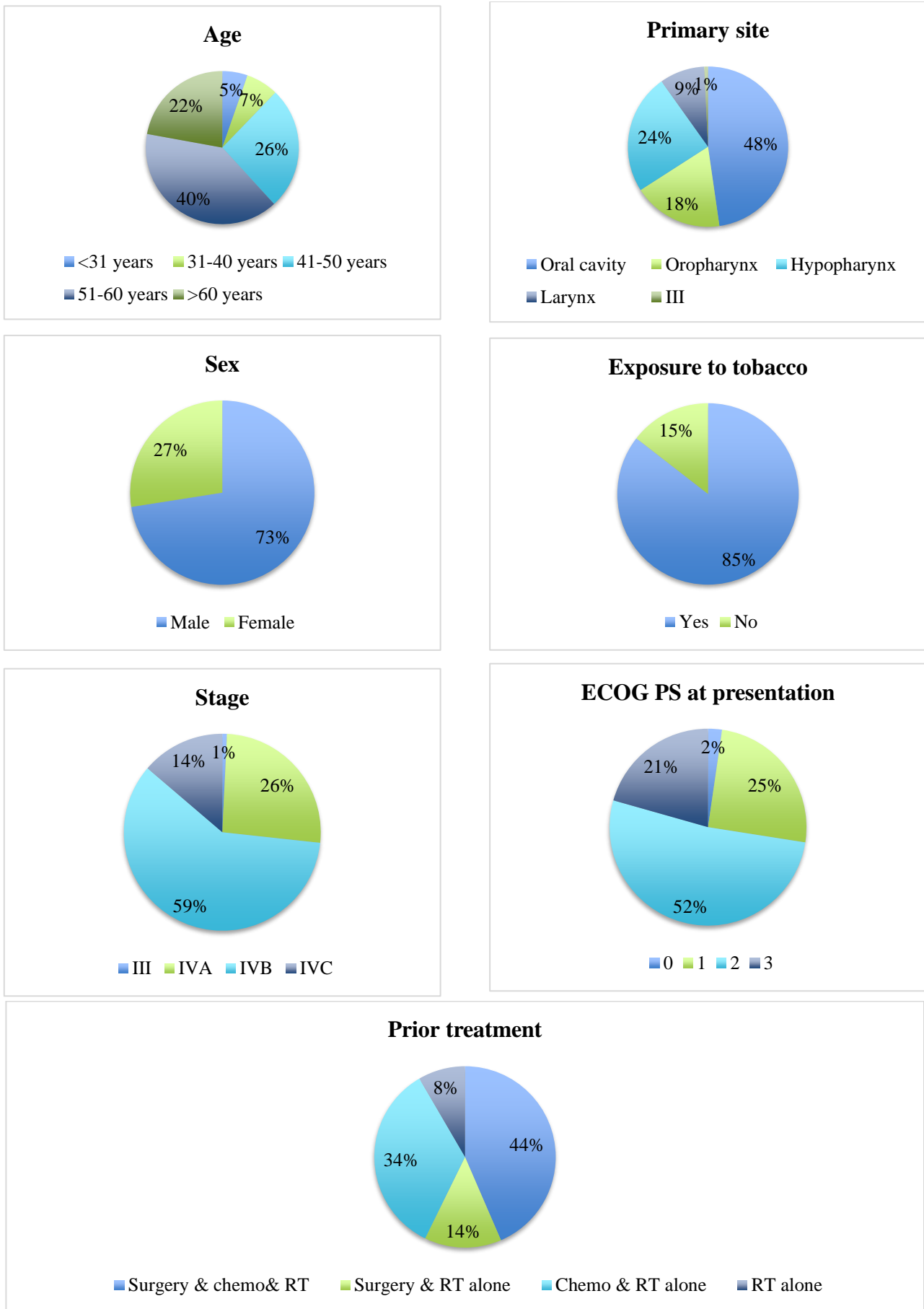
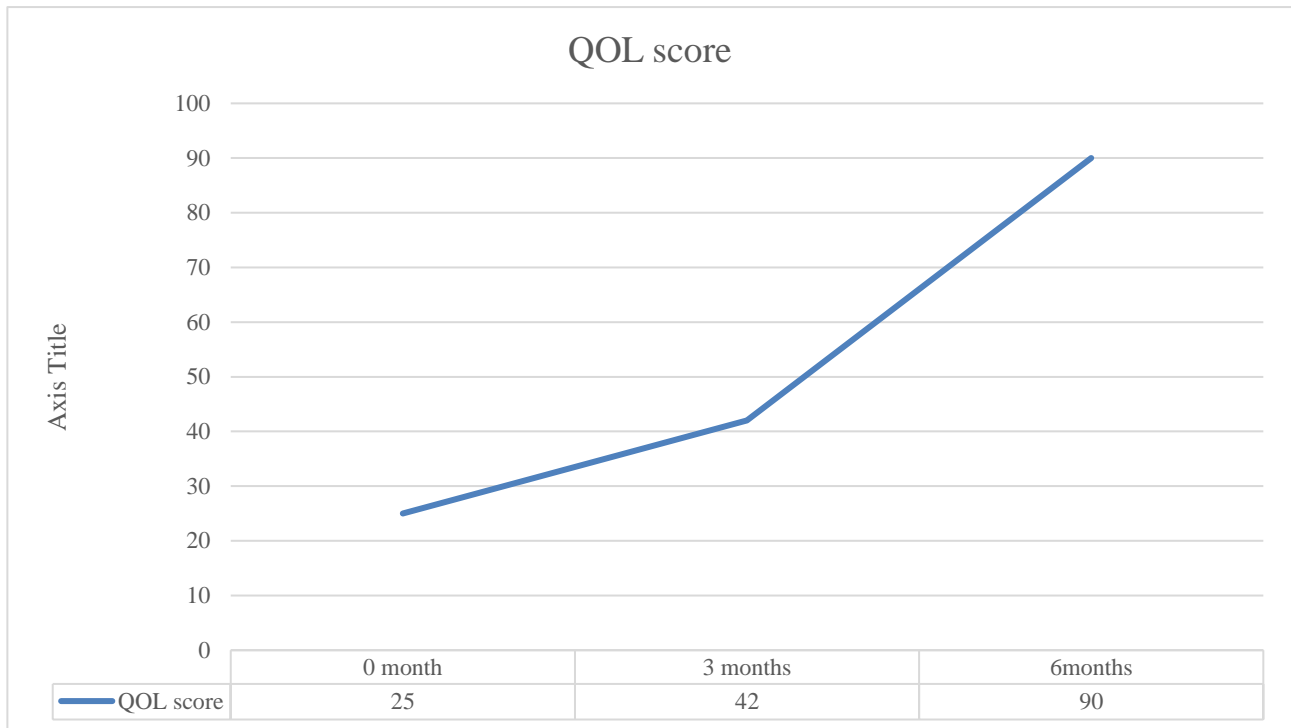


Fig. 1 Baseline characteristics of the patients involved in this study

**6.1. Global Health Status / Quality of Life**

The median Global Health Score (GS) at baseline was 25. This increased to 42 at 3 months (P=0.002) and 67 at 6 months(P=0.014).



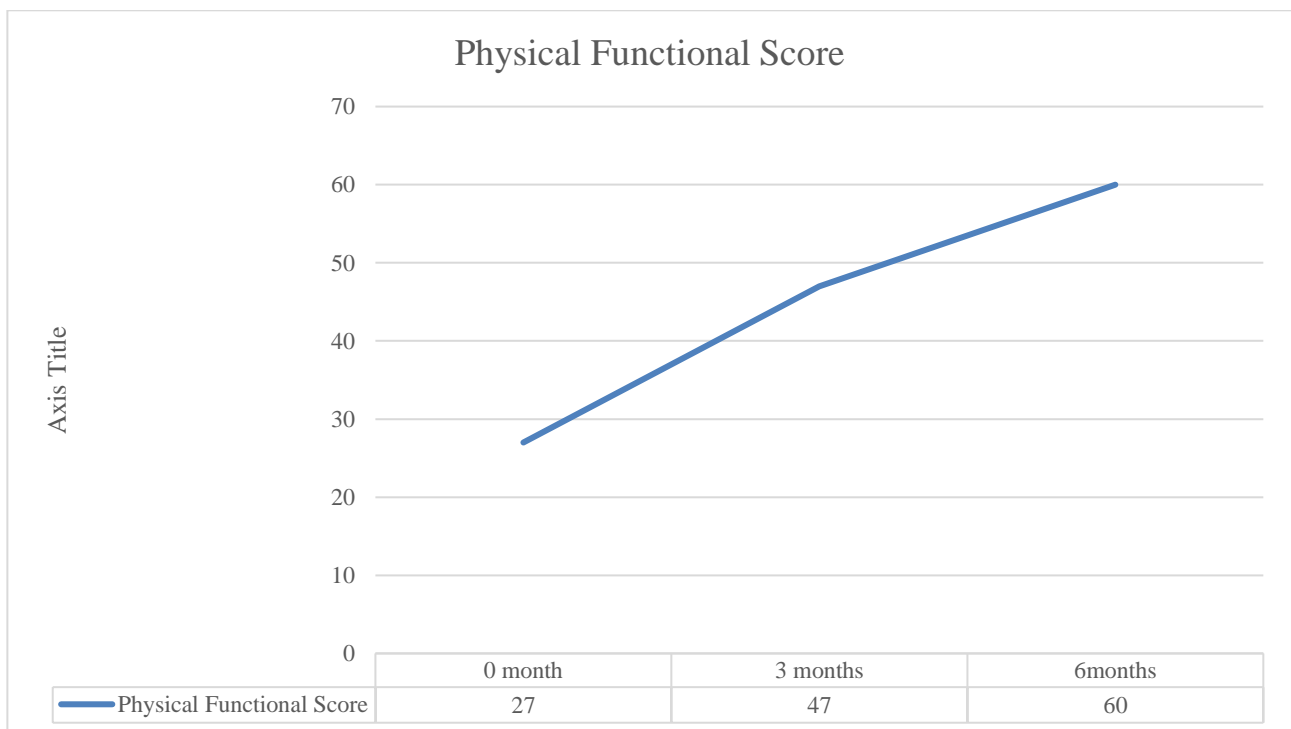
**Fig. 2 QOL score**

**6.2. Functional Scales**

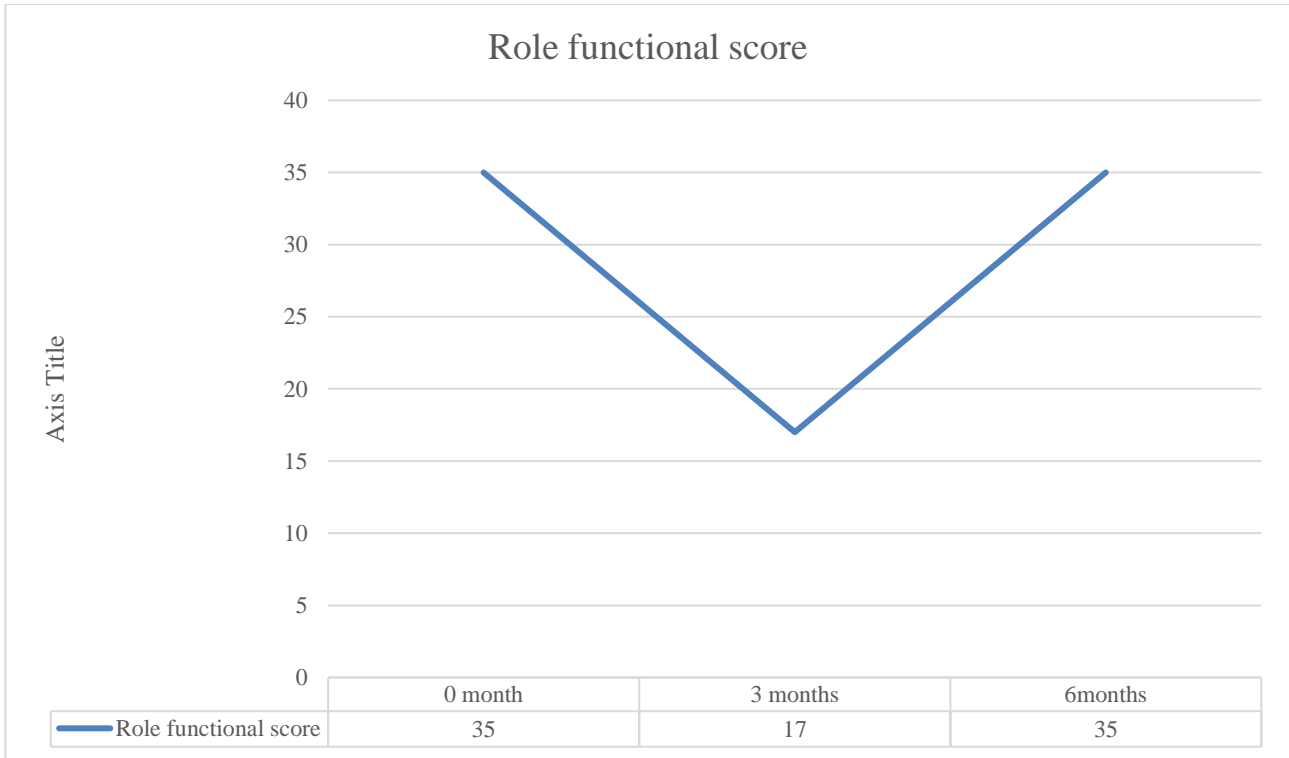
Five functional scales (physical, role, emotional, cognitive, and social functioning) are included in the EORTC QLQC30. The study examined each of them.

**6.3. Physical Functional Scale**

The median Physical Functional Score at baseline was 27. This increased to 47 at 3 months (p=0.717) and 60 at 6 months. (p=0.074)



**Fig. 3 Physical Functional Score**



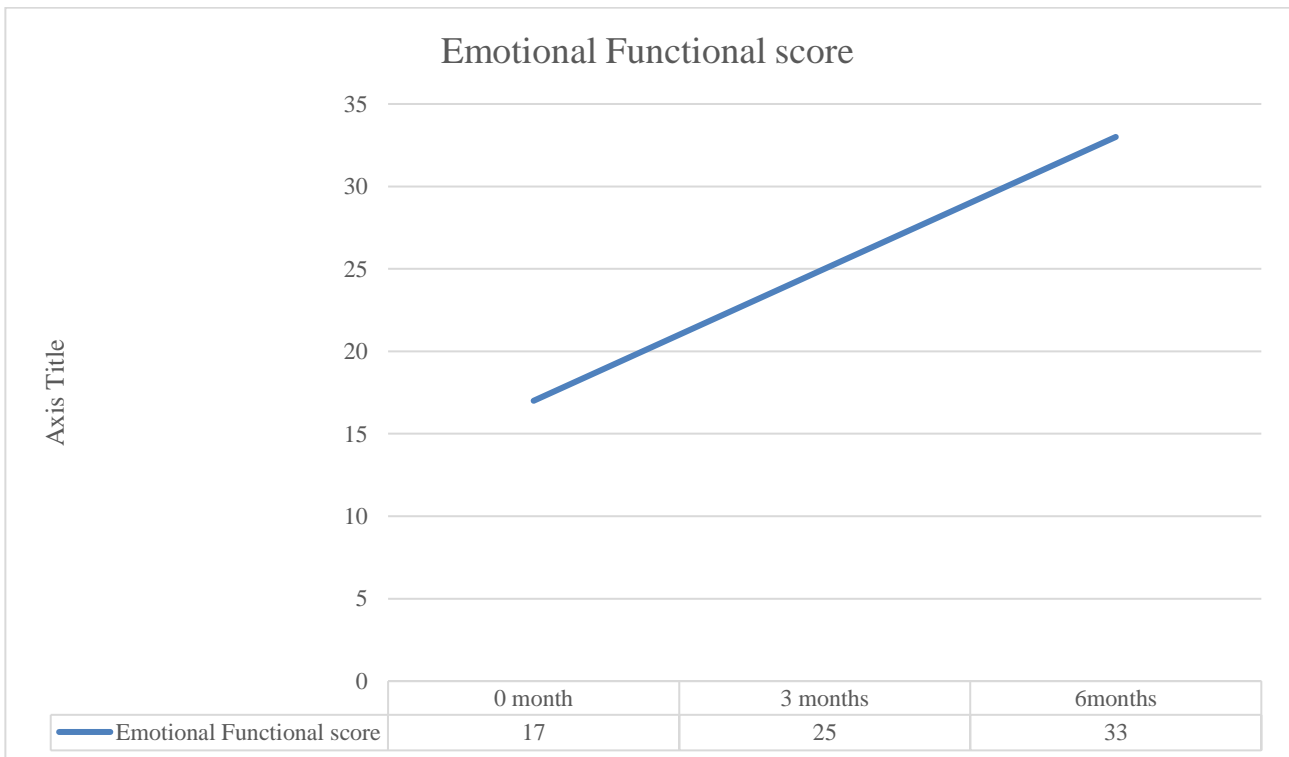
**Fig. 4 Role functional score**

**6.4. Role Functional Scale**

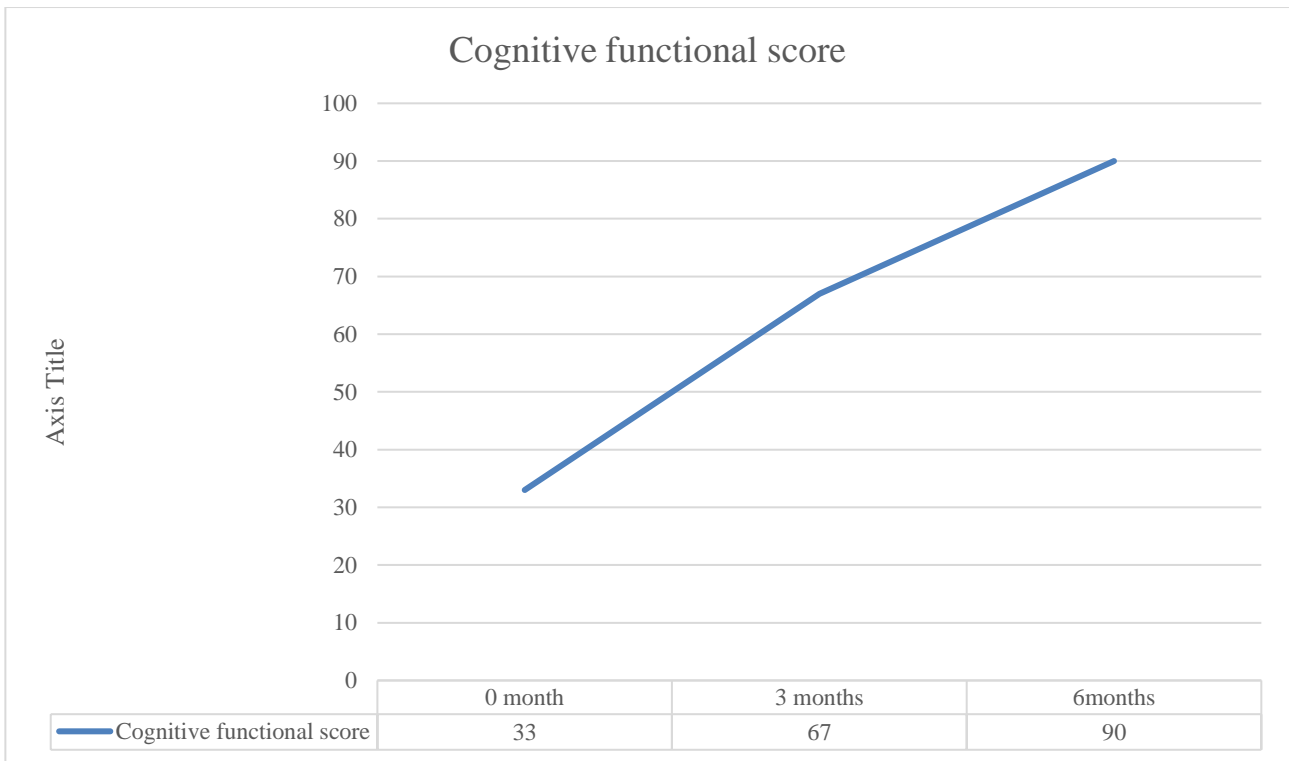
The median Role functional Score at baseline was 35. The median score at 3 months was 17 (p=0.040), and at 6 months was 35. (p=0.12).

**6.5. Emotional Functional Scale**

The median Emotional Functional Score at baseline was 17. (p=0.001) This increased to 25 at 3 months and to 33 at 6 months. (p=0.014).



**Fig. 5 Emotional functional score**



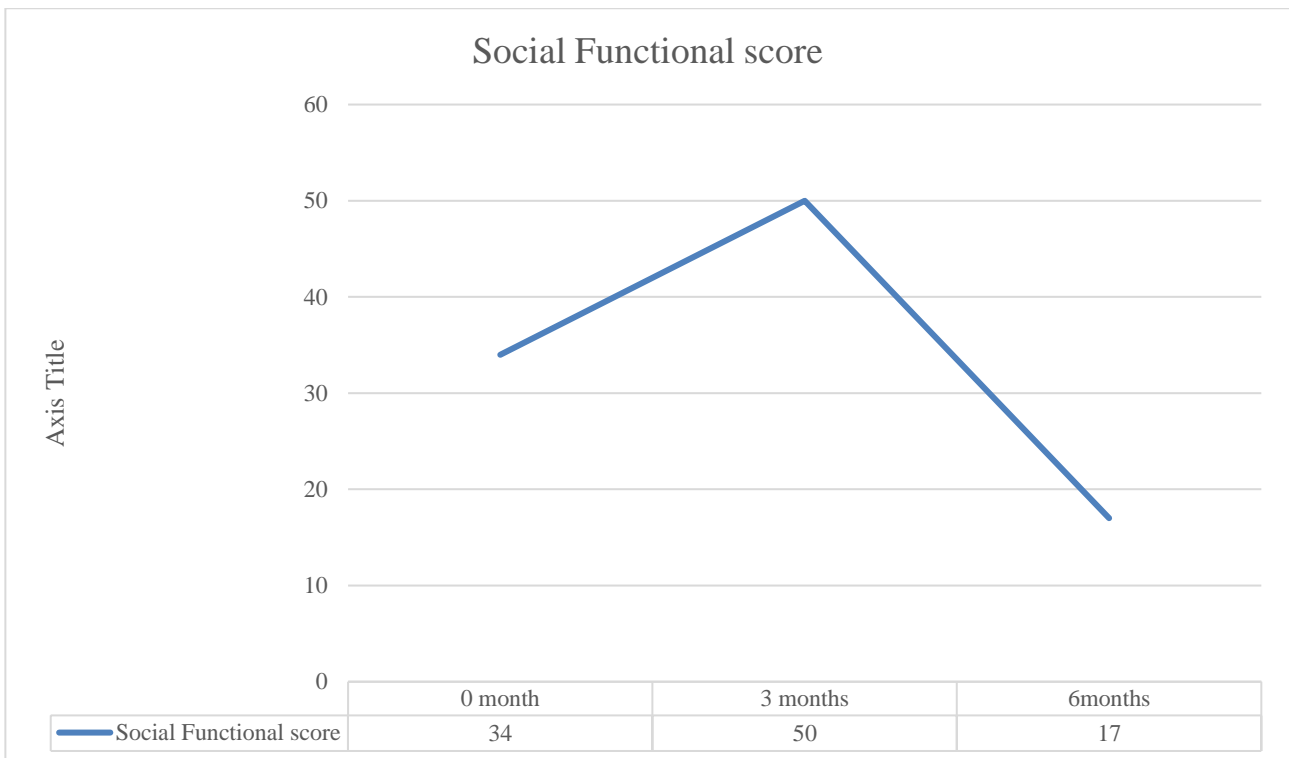
**Fig. 6 Cognitive functional score**

**6.6. Cognitive Functional Scale**

The mean Cognitive functional Score at baseline was 33. This increased to 67 at 3 months ( $p=0.564$ ) and 84 at 6 months. ( $p=0.106$ ).

**6.7. Social Functional Scale**

The mean Social Functional Score at baseline was 34. This increased to 50 at 3 months ( $p=0.006$ ) but decreased to 17 at 6 months. ( $p=0.415$ )



**Fig. 7 Social Functional score**

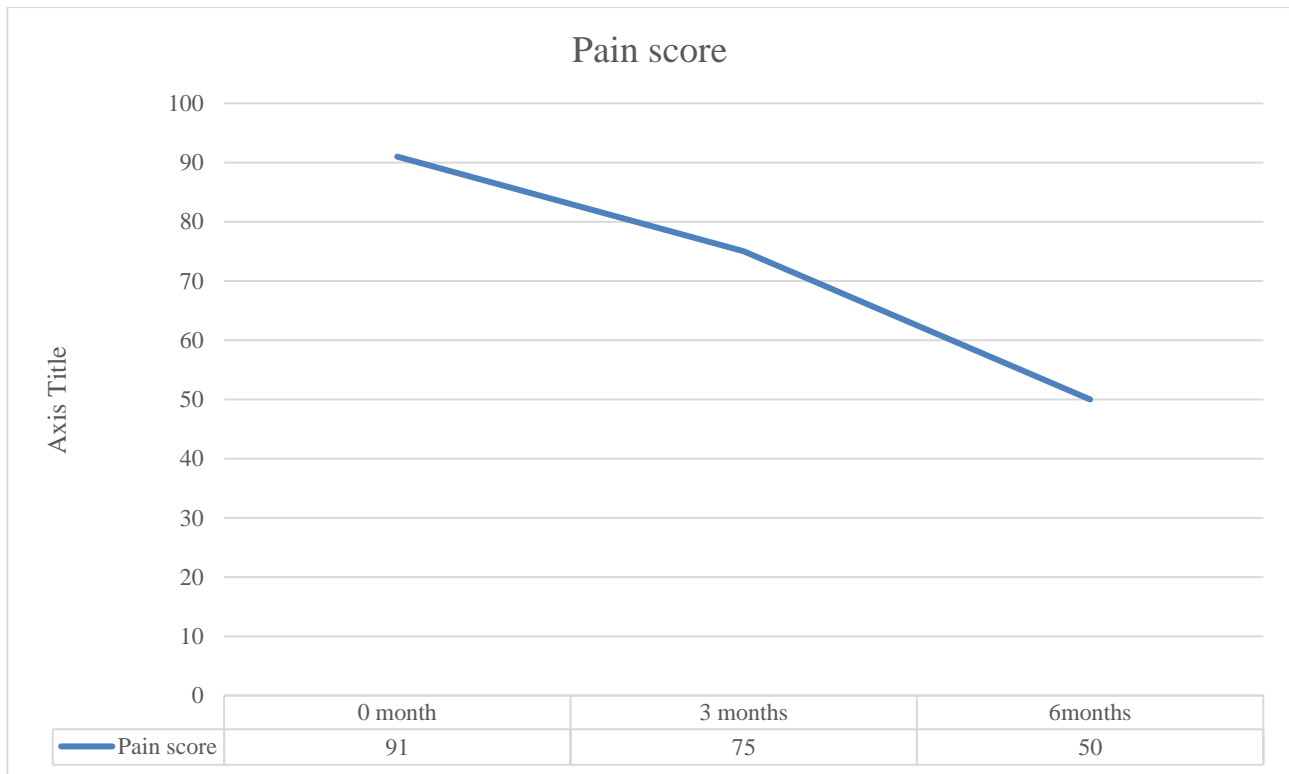


Fig. 8 Pain score

**6.8. Symptom Scale**

In symptom scales, the pain scale was analyzed in this study using the EORTC QLQ HN-35 module.

**6.9. Pain Scale**

The median Pain Score (PS) at baseline was 91. This decreased to 75 at 3 months and 50 (p=0.004) at the end of 6 months with statistical significance (p=0.0005).

**7. Discussion**

In our study, we found a statistically significant improvement in Quality-of-life score at 3 months (p=0.002) and 6 months (p=0.014) from the start of metronomic chemotherapy.

Physical functional score improvement was seen both at 3 months and 6 months. However, the improvement seen in 3<sup>rd</sup> month was not statistically significant (p=0.717), whereas the improvement seen in 6<sup>th</sup> month was statistically significant (p=0.074).

In role functional score, there was a decrease at 3 months with statistical significance (p=0.040) and at 6 months, there was no difference in score compared to baseline but with no statistical significance (p=0.12)

The emotional functional score showed a statistically significant improvement at 3 months (p=0.001) and 6 months (p=0.014).

In the cognitive functional score, there was an improvement at 3 months (p=0.564) and 6 months (p=0.106), but the results were not statistically significant.

In the social functional score, there was a statistically significant improvement seen at 3 months (p=0.006), but at 6 months, there was a decrease in the social functional score with no statistical significance (p=0.415)

In pain symptom score, there was a statistically significant improvement seen at 3 months (p=0.004) and 6 months (p=0.0005).

Patients treated in this study with oral metronomic chemotherapy combination of gefitinib and methotrexate tolerated the treatment well.

The main toxicity observed was grade 1/2 mucositis was observed in 31% of the patients. Grade 1/2 neutropenia was seen in 8% of the patients. However, none of the patients developed febrile neutropenia.

There were no treatment-related mortalities. Patients who completed at least 6 months of treatment with the Gefitinib Methotrexate combination showed an improved Quality of life, reflected in their functional, social and emotional behavior.

**8. Conclusion**

Oral metronomic therapy with methotrexate and gefitinib is a feasible option for patients who are unable to afford the immunotherapy drugs or targeted agents.

Gefitinib, along with methotrexate, was well tolerated and was found to have a positive impact on the quality of life of patients with advanced SCCHN.



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