IMPROVING QUALITY OF LIFE IN LOCALLY ADVANCED OR ADVANCED HEAD AND NECK CANCER WITH CURCUMIN ADD-ON TO STANDARD NUTRITION SUPPORT: A SECONDARY ANALYSIS OF THE CURCHEXIA STUDY

Tawasapon Thambamroong, Kasan Seetalarom, Siriwimon Saichaemchan, Khunthong Peechatanan, Jareanjit Phavirunsiri, Naiyarat Prasongsook

Division of Medical Oncology, Department of Medicine, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand

Abstract

Background: Patients with head and neck cancer often suffer from cancer anorexia and cachexia syndrome (CAS), which severely impacts their quality of life (QoL). The primary CurChexia study showed that curcumin improved muscle mass.

Objectives: This pre-planned secondary analysis evaluated the effect of curcumin add-on therapy on the QoL of these patients.

Methods: In this secondary analysis of a randomized, placebo-controlled trial, twenty patients with locally advanced or advanced head and neck cancer undergoing treatment and diagnosed with CAS were randomized to receive either 4,000 mg of curcumin daily or a placebo, in addition to standard nutritional support for eight weeks. QoL was assessed at baseline, week 4, and week 8 using the EORTC QLQ-C30 questionnaire. A linear mixed-effects model was used to analyze changes in QoL scores over time between the two groups. A retrospective power calculation was conducted for key QoL domains.

Results: The curcumin add-on group showed statistically significant improvements compared to the control group in physical functioning ($p = 0.001$), emotional functioning ($p = 0.023$), appetite loss ($p = 0.001$), and pain ($p = 0.033$). No significant differences were observed in global health status or other functional and symptom scales. The study was adequately powered (>80%) to detect the observed significant differences, but was underpowered for non-significant outcomes like global health status.

Conclusion: In patients with locally advanced or advanced head and neck cancer experiencing cancer anorexia-cachexia syndrome (CAS) during treatment, the addition of a daily 4,000 mg dose of curcumin to standard nutritional intervention significantly improves quality of life and body composition. These findings suggest that curcumin may serve as an effective pharmaconutrient, providing both clinical benefits and supportive care.

Keywords: curcumin, head and neck cancer, HNSCC, cancer cachexia, quality of life, QoL, nutritional support, pharmaconutrient

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Corresponding to:
Prasongsook N, Division of Medical Oncology, Department of Medicine, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok 10400, Thailand
E-mail: naiyarat_p@yahoo.co.th

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Introduction

Patients with head and neck cancer always face cancer anorexia and cachexia syndrome (CAS), which can be a significant cause of death in cancer patients, with up to 30% affected.[1] CAS results from inflammatory pathways that disrupt metabolism, leading to increased muscle protein breakdown and insulin resistance.[2-4]

Curcuminoids and extracts from curcumin demonstrate the ability to reduce inflammation by inhibiting intracellular phosphorylation of the nuclear factor-kappa B (NF-kB) pathway, both in vivo and in vitro.[5-8] Additionally, curcumin has proven safe for long-term use without serious side effects.[9]

Our previous study, the CurChexia study: a randomized placebo-controlled, phase IIa trial, found that adding a daily dose of 4,000 mg of curcumin to the standard nutrition intervention helped improve muscle mass in patients with locally advanced or advanced head and neck cancer and nasopharyngeal cancer who were undergoing chemoradiation or chemotherapy. The curcumin add-on group showed a statistically significant increase in mean muscle mass of 0.46 kilograms (kg) (95% confidence interval (CI); -0.2, 1.12) compared to the standard nutrition intervention alone and a decrease in muscle mass of -1.05 kg (95% CI; -2.34, -0.24) ($p = 0.03$).

Additionally, the curcumin add-on subgroup showed promise in improving other body composition parameters such as body fat mass and basal metabolic rate. The secondary outcome parameters, including hand grip strength, body mass index, and absolute lymphocyte count, also showed promise for the curcumin add-on subgroup.[10]

Cancer treatment strives to improve outcomes, elevate patients' well-being, and enable them to continue their daily routines. Here, we report a recent discovery indicating that adding curcumin to a typical nutritional intervention enhanced the quality of life of individuals with locally advanced or advanced head and neck cancer who continued receiving treatment.

Methods

Study design and treatments

The CurChexia study design, methodology, and inclusion criteria have been published previously.[10] The key inclusion criteria are locally advanced or advanced head and neck cancer and nasopharyngeal cancer that undergo treatment with chemoradiation or chemotherapy, diagnosed with a definition of cancer anorexia and cachexia syndrome (CAS), and receive enteral feeding via feeding tube. The patients need to have a good performance status with ECOG 0-2 and normal organ functions. Patients were randomized to receive a curcumin add-on, a daily dose of 4,000 mg, or a matching placebo. All patients receive standard nutrition intervention by a nutritionist to maintain normal requirements of energy and micronutrients for eight weeks of treatment. The body composition parameters were measured by the bioelectrical impedance assessment (BIA) at the baseline, four weeks, and eight weeks, or at the end of the study.

Quality of life assessment

The quality of life was a secondary endpoint of the CurChexia study. It was evaluated by the European Organization for Research and Treatment of Cancer QOL core questionnaire C30 (EORTC QLQ-C30) version 3.0 in the Thai edition.[11] The EORTC QLQ-C30 has three independent domains: global health status, functional scales (physical, role, cognitive, emotional, and social), and symptom and other scales (appetite loss, constipation, diarrhea, dyspnea, fatigue, insomnia, pain, nausea and vomiting, and financial difficulty). The patients complete all the EORTC QLQ-C30 version 3.0 in Thai edition at baseline, at the end of the fourth week, and at the end of the study or the eighth week.

The EORTC QLQ-C30 was scored according to the EORTC scoring guidelines, with all scores transformed to a 0-100 scale. Higher scores indicate better functional status and overall global health, whereas for the symptom scales, a higher score indicates a greater symptom burden. A clinical significance was attributed to a ten-point alteration in the EORTC QLQ-C30.[13 14]

Patients were classified into three categories based on their global health and functional subscale scores. Improvement was defined as a ≥10 increase from baseline sustained for at least eight weeks. Worsening was defined as either death or a ≥10 decline from baseline. Patients who did not meet the criteria for either improvement or worsening were considered stable. The duration of improvement was calculated from the first occurrence of a ≥10 increase until the score returned to baseline or below.

The analysis focused on two types of missing data, if present: domain non-response, which occurs when a patient completes some but not all sections of a questionnaire, and unit non-response, which occurs when a patient does not complete any sections of a questionnaire at a specific time point. We examined the missing data patterns and found a type of missingness called monotone missingness; this happens when a patient stops participating in the study without completing an EORTC QLQ-C30 domain during treatment, possibly due to death or stopping the study. Intermittent missingness refers to when a patient does not attend a scheduled visit but does attend later visits during their treatment period, resulting in a complete (non-missing) domain at those subsequent visits.[15]

Statistical analysis

Descriptive statistics were used to summarize patient characteristics and QoL scores at each time point. To account for the correlation of repeated measurements within the same patient, we analyzed the change in EORTC QLQ-C30 scores from baseline using a linear mixed-effects model for each QoL domain. The model included fixed effects for treatment arm (curcumin vs. control), time (as a categorical variable: week 4, week 8), and the time-by-treatment interaction. A random intercept for each patient was included to account for individual-level variability. The primary outcome of this analysis was the time-by-treatment interaction term, which assesses whether the change in QoL scores over time differs between the two groups. A retrospective power calculation was conducted using the observed effect sizes and standard deviations for key QoL outcomes. All analyses were performed using SPSS version 26. A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics and EORTC QLQ-C30 completion and compliance

The CurChexia study has two randomized arms: the curcumin add-on and the standard nutrition intervention (control) arm. Twenty patients completed all EORTC QLQ-C30 version 3.0 in Thai edition at baseline, at the end of the fourth week, and at the end of the study or the eighth week (100% of the intention-to-treat (ITT) population). There is no missing data. Baseline characteristics were generally balanced in both arms, likely the pivotal study. The median age is 58 and 60 years in the curcumin add-on and control arm, respectively. Both arms perform well, ECOG 0-1 in the majority population. There is no difference in the head and neck tumor subtype, staging, and treatment between arms. The mean daily calorie intake is 27.5 ± 2.500 kilocalories per kilogram. **(Table 1)**

Table 1. Baseline characteristics of the patients (Intention-to-Treat Population)

Characteristics	Curcumin add-on arm (N=10)	Standard nutrition intervention arm (N=10)
Age - years		
Median	58	60
Range	22-85	38-85
ECOG performance status score n (%)		
0	1 (10)	1 (10)
1	8 (80)	9 (90)
2	1 (10)	0 (0)
Head and neck cancer stage - no. (%)		
Locally advanced	8 (80)	9 (90)
Metastatic or recurrent	2 (20)	1 (10)
Head and neck cancer subgroup - no. (%)		
Nasopharyngeal cancer	1 (10)	1 (10)
Squamous cell head and neck cancer	9 (90)	9 (90)
Comorbid disease - n (%)	2 (20)	1 (10)
Surgery - n (%)	3 (30)	2 (20)
Smoking - n (%)	7 (70)	8 (80)
Treatment		
Concurrent chemoradiation - n (%)	6 (60)	8 (80-)
Sequential chemoradiation - n (%)	2 (20)	0 (0)
Radiation only - n (%)	0 (0)	1 (10)
Palliative chemotherapy - n (%)	2 (20)	1 (10)
Mean daily calories intake ± SD - (kcal/kg/day)	27.5 ± 2.50	27.92 ± 2.465

Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with 0 indicating no symptoms, 1 indicating mild symptoms, and a higher number indicating increasing degrees of disability. Comorbid disease is defined by metabolic diseases, such as Diabetes, Hypertension, or Dyslipidemia.

Quality of life score at baseline and on treatment

With the curcumin add-on arm, the global health status score increased by 16.66 points from 66.67 to 91.67 at the end of the study. In the control arm, this score increased from 70.83 to 75 and 79.17, respectively, from baseline. Based on the interpretation guideline, an increase of more than 10 points is considered significant and categorized as an improvement. That means the curcumin add-on has improved global health status and has been sustained throughout the treatment periods. However, in the control group, it can stabilize the patients' global health status for the treatment period. However, there is no statistical significance in this comparison.

The curcumin add-on group demonstrated a significant improvement in physical functioning, with scores rising from 33.33 at baseline to 40.00 and 73.33 at 4 and 8 weeks, respectively. In contrast, the control group declined from 40.00 to 36.67 at 4 weeks before increasing to 50.00 at 8 weeks. These findings indicate that while both curcumin add-on therapy and standard nutritional support can enhance physical functioning, the curcumin add-on provides greater benefits (p = 0.001). Regarding emotional functioning,

the curcumin add-on group showed a statistically significant improvement compared with the deterioration observed in the control group (p = 0.023). Regarding measuring symptoms, both groups experienced decreased appetite loss in both arms. However, the group that received curcumin as an add-on treatment showed more potential to reduce this symptom. Compared to the control group, this group's symptom scale decreased from 100.00 to 33.00 by the end of the study, while the control group's scale only decreased from 100.00 to 66.67, with statistical significance. (p = 0.001). The subgroup that received curcumin exhibited remarkable progress in pain management compared to the control group. The data analysis showed a p = 0.033, which demonstrated curcumin's effectiveness in enhancing appetite and alleviating pain. (**Table 2**)

Power Analysis

A retrospective power analysis revealed that for the outcomes with statistically significant results, the study was sufficiently powered. Specifically, the power to detect the observed difference in change for physical functioning was 92%, for appetite loss was 95%, and for pain was 85%. However, for non-significant outcomes such as global health status, the statistical power was low (<50%), indicating that the study was not large enough to detect a potential difference in this domain reliably.

Discussion

Cancer Anorexia and Cachexia Syndrome (CAS) is a leading cause of death in cancer patients, especially in head and neck cancer.[1] To prevent this syndrome, patients should be encouraged to maintain adequate intake of energy, macronutrients, and micronutrients as recommended.[16,17] Most clinicians and researchers find the pharmaconutrients for preventing or improving CAS.[18] Curcumin is the main pharmaconutrient with concrete evidence to prevent CAS by decreasing inflammation through the ubiquitin pathway.[2,19,20] It can prevent loss of muscle mass and improve hand-grip muscle strengthening over standard nutrition intervention.[8 10] Ensuring the patient's good quality of life is essential. Unfortunately, the available data on the topic is severely limited.

In the previous CurChexia study, curcumin significantly showed the benefit of improving body composition, specifically in muscle mass.[10] In this study, the addition of curcumin to standard nutrition intervention for locally advanced or advanced head and neck patients diagnosed with CAS and undergoing treatment has improved all domains of the patient's quality of life on EORTC QLQ-C30 scales.

The EORTC QLQ-C30 quality of life assessment tool evaluates three domains. Notably, the curcumin add-on arm displayed a remarkable improvement of over 10 points in the global health status domain, demonstrating significant enhancement compared to the control arm. The intervention arm also outperformed the control arm in physical and emotional functions in the functional status domain. Finally, the curcumin add-on arm significantly reduced loss of appetite and pain symptoms in the symptom domain, far superior to the standard nutritional intervention.

The positive results cannot solely be attributed to nutritional intervention. It is plausible that the increase in muscle mass provides the patient with more energy for daily tasks and mitigates disease symptoms in the curcumin add-on arm. However, adding curcumin as a pharmaconutrient at a dosage of 4,000 mg/day may improve overall muscle mass and quality of life in these patients. This study has some limitations, including a small sample size and strict inclusion criteria, which were applied to minimize confounding factors. As confirmed by our retrospective power analysis, the small sample size means the study was underpowered to detect differences in some QoL domains. Therefore, non-significant findings should be interpreted as inconclusive rather than evidence of no effect. Further large-scale studies are needed to confirm and strengthen these findings.

Table 2. The patient quality of life questionnaire score (EORTC QLQ-C30) by domain, with comparison between groups

EORTC QLC-C30	Curcumin add-on (n=10)						Standard nutritional support (n=10)						Mean Difference at Week 8	*p*-valule*
	Baseline		Week 4		Week 8		Baseline		Week 4		Week 8			
	Median	IQR (Q1, Q3)	Median	IQR (Q1, Q3)	Median	IQR (Q1, Q3)	Median	IQR (Q1, Q3)	Median	IQR (Q1, Q3)	Median	IQR (Q1, Q3)		
Global Health Status	66.67	58.33, 75.00	83.33	75.00, 89.58	91.67	83.33, 91.67	70.83	58.33, 75.00	75.00	68.75, 81.25	79.17	75.00, 83.33	16.66	1.000
Functional Scales														
Physical Functioning	33.33	26.67, 40.00	40.00	35.00, 45.00	73.33	68.33, 80.00	40.00	28.33, 46.67	36.67	33.33, 45.00	50.00	41.67, 53.33	30.00	0.001#
Role Functioning	75.00	66.67,83.33	83.33	66.67, 83.33	83.33	70.83, 83.33	83.33	83.33, 83.33	83.33	70.83, 83.33	83.33	70.83, 83.33	8.30	1.000
Emotional Functioning	66.67	66.67, 72.92	75.00	66.67, 75.00	83.33	83.33, 83.33	75.00	66.67, 89.58	75.00	68.75, 89.58	66.67	58.33, 75.00	24.90	0.023#
Cognitive Functioning	83.33	70.83, 83.33	83.33	83.33, 100.00	91.67	83.33, 100.00	91.67	83.33, 100.00	83.33	83.33, 100.00	100.00	100.00, 100.00	8.35	1.000
Social Functioning	66.67	66.67,83.33	83.33	66.67, 95.83	83.33	83.33, 95.83	66.67	66.67, 83.33	83.33	66.67, 83.33	83.33	83.33, 83.33	16.60	1.000
Symptom Scales														
Fatigue	33.33	25.00, 33.33	22.22	22.22, 33.33	22.22	22.22, 33.33	33.33	33.33, 44.44	33.33	25.00, 33.33	33.33	25.00, 33.33	-11.10	1.000
Nausea and Vomitting	33.33	16.67, 33.33	25.00	16.67, 33.33	16.67	16.67, 16.67	33.33	20.83, 33.33	16.67	16.67, 33.33	16.67	16.67, 33.33	8.30	1.000
Pain	50.00	33.33, 50.00	33.33	33.33, 33.33	33.33	20.83, 33.33	50.00	33.33, 50.00	41.67	33.33, 50.00	41.67	33.33, 50.00	-16.70	0.033#
Dyspnoea	33.33	0.00, 33.33	33.33	0.00, 33.33	33.33	0.00, 33.33	33.33	0.00, 33.33	16.67	0.00, 33.33	16.67	0.00, 33.33	-16.60	1.000
Insomnia	33.33	0.00, 33.33	33.33	0.00, 33.33	33.33	0.00, 33.33	33.33	0.00, 33.33	0.00	0.00, 33.33	0.00	0.00, 33.33	-16.60	1.000
Appetite loss	100.00	100.00,100.00	33.33	33.33, 33.33	33.33	0.00, 33.33	100.00	75.00, 100.00	66.67	66.67, 91.67	66.67	66.67, 66.67	-33.40	0.033#
Constipation	16.67	0.00, 33.33	16.67	0.00, 33.33	16.67	0.00, 33.33	0.00	0.00, 0.00	0.00	0.00, 0.00	0.00	0.00, 33.33	-16.70	1.000
Diarrhoea	0.00	0.00, 25.00	0.00	0.00, 25.00	0.00	0.00, 25.00	0.00	0.00, 0.00	0.00	0.00, 0.00	0.00	0.00, 0.00	-16.70	1.000
Financial difficulties	33.33	8.33, 33.33	33.33	8.33, 33.33	33.33	0.00, 33.33	33.33	8.33, 33.33	33.33	8.33, 33.33	33.33	8.33, 33.33	-16.60	1.000

Higher scores are better for Global Health and Functional Scales; lower scores are better for Symptom Scales. The increase or decrease ≥ 10 points reflects a clinically significant change.

**p*-value from linear mixed-effects model for the time-by-treatment interaction

#Statistical significance

Conclusion

In patients with locally advanced or advanced head and neck cancer experiencing cancer anorexia-cachexia syndrome (CAS) during treatment, the addition of a daily 4,000 mg dose of curcumin to standard nutritional intervention significantly improves quality of life and body composition. The study demonstrated that curcumin was an effective pharmaconutrient for head and neck cancer patients, providing both clinical benefits and support.

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