CHAPTER-8

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APPENDICES

APPENDICES

Annexure-1 Written Informed Consent

INFORMED CONSENT DOCUMENT सूचित सहमति प्रपत्र

Part I: Subject/Patient Information document Dated-

भाग 1 : विषयक / रोगी का जानकारी प्रपत्र

Title of the study/protocol: "PROGNOSTIC SIGNIFICANCE OF NUTRITION AND IMMUNITY IN HEAD AND NECK CANCER- A PROSPECTIVE OBSERVATIONAL STUDY."

अध्ययन / प्रोटोकॉल का शीर्षक: "सिर और एनईकेके कैंसर में पोषण और आबादी का प्रामाणिक हस्ताक्षर - एक व्यावहारिक निरीक्षण अध्ययन।"

Ethics committee approval letter no.....dated.....आचार सहिंता समिति अनुमोदन पत्रांक संख्या दिनांक

CTRIRegistration no, (if applicable).....CTRI पंजीकरण संख्या (यदि लागू हो तो)

Principal Investigator with qualifications: Dr. Anshika Arora(M.B.B.S) (M.S. Surgery) मुख्य अन्वेशक योग्यता सहित डा० अंशिका अरोड़ा (एम०बी०बी०एस०), (एम० एस० सर्जरी)

Name & address of institution: CRI, SRHU, Jolly Grant Dehradun संस्था का नाम व पता:– सी०आर०आई० एस०आर०एच०यू०. जौलीग्रान्ट. देहरादून।

Contact No: 8126923475दूरभाष 8126923475

Subject's /Patient's Name.....विषयक / रोगी का नाम.

Introduction: This is an observational study for patients undergoing treatment for head and neck cancer at this institute.

परिचय अध्ययन की प्रकृति व प्रकार. यह इस संस्थान में सिर और गर्दन के कैंसर के इलाज से ग्रस्त मरीजों के लिए एक अवलोकन अध्ययन है।

Purpose: To have a better understanding of nutritional status during treatment and its effect on immunity. Also to develop a low cost prognostic tool for these patients

उददेशय उपचार के दौरान पोषण की स्थिति और प्रतिरक्षा पर इसके प्रभाव की बेहतर समझ रखने के लिए। इन मरीजों के लिए कम लागत वाले प्रोनोस्टिक टूल भी विकसित करना

Methods: Patients being treated for head and neck cancer at CRI, SRHU, Dehradun will be screened for inclusion in the study. An informed consent will be taken and thereafter they will be enrolled in the study. They will be observed for nutritional status and nutritional status at various times before and after completion of treatment. The total period of observation will be upto 6 months after completion of treatment.

विधियाँ : सीआरआई, एसआरएचयू, देहरादून में सिर और गर्दन के कैंसर के लिए मरीजों का इलाज किया जाएगा अध्ययन में शामिल करने के लिए जांच की जाएगी। एक सूचित सहमति ली जाएगी और इसके बाद वे अध्ययन में नामांकित होंगे। इलाज के पूरा होने से पहले और बाद

में उन्हें पोषण की स्थिति और पोषण की स्थिति के लिए कई बार देखा जाएगा। उपचार पूरा होने के 6 महीने तक अवलोकन की कुल अवधि होगी।

Risk involved: nil जोखिम : कुछ नहीं।

Potential benefits: nil संभावित लाभः कुछ नहीं।

Reasonable alternatives/ possible variant treatment available: nil उचित विकल्प/उपलब्ध संभव उपचार के प्रकारः कुछ नहीं।

Subject's responsibility: nil विषयक के दायित्व– कुछ नहीं।

Compensation: No मुआवजा – कुछ नहीं।

Confidentiality: Yes गोपनियता – हाँ।

Voluntary participation: Yes स्वैच्छिक भागीदारी– हाँ।

Financial cost of participation involved: nil वित्तीय लागत में शामिल भागीदारी : कुछ नहीं।

Contact person: Dr. Sunil Saini (Professor, Dept of Surgical Oncology) & Ethics Committee (Member secretary),Dr. D.C. Dhasmana for further information on any query at any time in an event of a problem.संपर्क व्यक्ति (गाइड) ऐथिक्स कमिटी (सदस्य सचिव), किसी भी समस्या या अधिक जानकारी के लिए किसी भी समय।

Patient /legal representative initials .....Date.....रोगी /कानुनी प्रतिनिधि दिनांक

(Thank you for taking time to read this document .If you decide to take part in this study, you will be given a copy of this information document and signed consent form to keep with you)(इस दस्तावेज को समय निकालकर पढने के लिए धन्यवाद । आप इस अध्ययन में भाग लेने का फैसला करते हैं तो जानकारी प्रपत्र की प्रतिलिपि एवं हस्ताक्षरित सहमति प्रपत्र का एक प्रति दी जाएगी ।

Principal Investigator' Name: Dr. Anshika Arora प्रधान अन्वेशक का नाम. डा0 अंशिका अरोड़ा (एम0बी0बी0एस0), (एम0 एस0 सर्जरी)

Name of the Institute: CRI, SRHU, Jolly Grant, Dehradun संस्थान का नाम– सी0आर0आई0 एस0आर0एच0यू0, जौलीग्रान्ट, देहरादून।

Part II: Informed consent form सूचित सहमति प्रपत्र

Name of the study/trial: "PROGNOSTIC SIGNIFICANCE OF NUTRITION AND IMMUNITY IN HEAD AND NECK CANCER- A PROSPECTIVE OBSERVATIONAL STUDY."

अध्ययन का नाम परीक्षण– अध्ययन / प्रोटोकॉल का शीर्षक: "सिर और एनईकेके कैंसर में पोषण और आबादी का प्रामाणिक हस्ताक्षर - एक व्यावहारिक निरीक्षण अध्ययन।"

Name of the Investigator: *(Guide)* Dr. Sunil Saini, Professor Department of General Surgery

प्रधान अन्वेशक का नाम– डा0 सुनील सैनी, प्रोफेसर सर्जरी विभाग।

Study code: ..... अध्ययन सहिंता
Patient Name ..... रोगी का नाम
Date of birth..... जन्म तिथि age..... .आयु

1. I confirm that I have read and understood the patient information sheet dated..... for the above study on .....(drugs /procedures etc).... and had the opportunity to ask questions which were answered to my satisfaction

1. *मैं पुष्टि करता/करती हूँ कि मैंने उपरोक्त ..... अध्ययन के लिए रोगी सूचना प्रपत्र दिनांक..... ..... को भली–भांति पढ़ व समझ लिया है और इस के बारे में मुझे प्रश्न पूछने के पूर्ण अवसर मिले जिनके सन्तोशजनक उत्तर प्राप्त हुए।*
2. I have been well informed about the potential anticipated risks, discomfort and side effects associated with ....(the trial drugs/procedures etc).... and what I will be expected to do?
2. *मुझे ..... अध्ययन से जुड़े संभावित प्रत्याशित `जोखिम, परेशानी व दुशप्रभाव और इसके लिये मुझे क्या करना है के बारे में भली–भांति सूचित किया जा चुका है।*
3. I understand that my participation is voluntary and I am free to withdraw from the study at any time without giving any reason, without affecting my future medical care or legal rights. I shall inform the principal investigator in this regard for any precaution/ medical care required to follow.
3. *मुझे ज्ञात है कि मेरी सहभागिता स्वैच्छिक है और मैं कभी भी बिना कारण बताये इस अध्ययन से भविष्य में अपने/अपनी चिकित्सा व्यवस्था या कानूनी अधिकार को किसी भी प्रकार से प्रभावित करे बिना हटा सकता/सकती हूँ । इस संबंध में मैं किसी भी सावधानी /चिकित्सा सुविधा की जरूरत पडने पर प्रधान अन्वेशक को सूचित करूंगा/करूंगी ।*
4. I understand that the principal investigator, others workers on the principal investigator's behalf and the ethics committee HIHT University will not need my permission to look at my health record both in the respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study/ trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.
4. *मुझे ज्ञात है कि प्रधान अन्वेशक, प्रधान अन्वेशक की ओर से अन्य कार्यकर्ताओं और स्वामी राम हिमालयन विश्वविधालय की नैतिकता समिति को वर्तमान अध्ययन और इससे सम्बन्धित आगे किसी भी अन्वेशण के संबंध मेंमेरे स्वास्थ्य संबधी अभिलेखों को देखने के लिए मेरी सहमति की आवश्यकता नहीं होगी, चाहे मैं इस अध्ययन/परीक्षण से अलग भी क्यों न हो जाऊं । इसके लिये मै अपनी सहमती प्रदान करता/करती हूँ। मैं समझता हूँ कि किसी अन्य व्यक्ति/संस्था या किसी भी प्रकाशित समाग्री मे मेरी पहचान का खुलासा नहीं किया जायेगा ।*
5. I agree not restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose.
5. *मै इस अध्ययन से उपजित के किसी भी डेटा या परिणामों के इस्तेमाल को प्रतिबन्धित ना करने को अपनी सहमति प्रदान करता हूँ बशर्ते इनका प्रयोग केवल वैज्ञानिक उद्देश्यों के लिए किया जा रहा हो।*
6. I am aware that investigator will inform, whenever the situation arises, about any new finding that develop anywhere in the world, related to my treatment which may affect any decision to continue participation in the study.
6. *मुझे ज्ञात है की विश्व में कहीं भी मेरे उपचार से सम्बन्धित किसी भी नई खोज विकसित होने की स्थिति में, जो मेरे इस अध्ययन में भागीदारी जारी रखने के किसी भी निर्णय को प्रभावित कर सकता है, मुझे अन्वेशक के द्वारा सूचित किया जाएगा।*
7. I had have time to make my decision whether or not to take part in this study/trial. I agree to take part in the above study; I have received a signed and dated copy of this consent form for my records.
7. *मुझे इस अध्ययन/परीक्षण में भाग लेने या न लेने के लिये पर्याप्त समय प्रदान किया गया। मै उपरोक्त अध्ययन में भाग लेने के लिये अपनी सहमति प्रदान करता/करती हूँ। मुझे इस सहमति प्रपत्र की एक हस्ताक्षरित व दिनांकित प्रतिलिपि अपने अभिलेखों के लिये प्राप्त हो चुकी है।*

Patient/ Legally Acceptable Representative (LAR) Name

Patient's LAR's Signature Date and Time

Investigator/ Designee Name

Investigator/ Designee's Name Date and Time

Witness Name

Witness's Signature Date and Time

Annexure-2 Case recording form

Prognostic significance of Nutrition and Immunity in Head and Neck Cancer- a prospective observational study.

NAME: **AGE:** yrs **GENDER: F / M**
UHID: **PHONE NO.:**
ADDRESS: **DATE:** **SERIAL NO.:**

Base Line Data

	Primary site	Regional metastasis	Distant metastasis	TNM stage	Biopsy	FNAC	Co-morbidities	-
Diagnosis				c T N M				-
Plan of treatment	---------	Description	Date of starting	Planned dose	Planned cycles/regimen	-	Date of completion	-
Surgery	Y /N			---------	----------	-	----------	-
RT	Y /N	EBRT IMRT CTRT Pall RT		GY/#		-		-
CT	Y /N	NACT CTRT Pall CT				-		-
Final biopsy report	Size (mm)	Grade/ type	Invasion of adjacent structures	Nearest Margin (mm)	Tumor necrosis	PNI	Vascular invasion	LN/ ENE
p T N M			Y / N		Y / N	Y/N	Y / N	
TIL	Y / N	Mild /mod/ severe						

Nutritional Assessment

	Before treatment	End of treatment 1	End of treatment 2
Date			
ECOG PS			
Weight(kg)			
Height (cm)			
MUAC (cm)			
Pallor			
Bitot spots			
SGA score			

Systemic Immunity

	Before treatment		End of treatment 1		End of treatment 2	
Date						
Hb	gm/dl		gm/dl		Gm/dl	
PCV						
TLC						
	%	Absolute	%	Absolute	%	Absolute
N						
L						
E						
Mono						
Baso						
N/L ratio						

Treatment Received

	Date	Description	Dose(Gy)/ fraction	Regimen/ cycles	Complications	Delay (weeks)	Interruption (days)	Additional treatment
Surgery			----------	--------				
RT		EBRT IMRT CTRT Pall RT						
CT		NACT CTRT Pall CT	----------					

Disease outcome on follow up after completion of treatment

	At treatment completion	6 wks	3 months	6 months
Date				
Primary site	Stable Progression Clear	Stable Progression Clear	Stable Progression Clear	Stable Progression Clear
Regional site	Stable Progression Clear	Stable Progression Clear	Stable Progression Clear	Stable Progression Clear
Metastatic site	Stable Progression Clear	Stable Progression Clear	Stable Progression Clear	Stable Progression Clear
		Date	Cause	
Completed treatment	Y / N			
Delay intreament	Y / N			
Interruption in treatment	Y / N			
DefaultedTreatment	Y / N			
Loss to follow up	Y / N			
Death	Y / N		Cancer Unrelated	

Annexure-3 AJCC 8 schema for TNM STAGING

"Staging for Nasopharynx Cancer

T0 No primary tumor but EBV + neck nodes

T1 Tumor confined to Nasopharynx or extends to oropharynx, nasal cavity without parapharyngeal space invasion

T2 Tumor with extension to parapharyngeal space and / or adjacent soft tissue involvement (Pterygoids, prevertebral musc)

T3 Tumor with infiltration of bony skull base, cervical vertebrae, pterygoid plates, or paranasal sinuses

T4 Tumor with intracranial extension, invasion of cranial nerves, hypophaynx, orbit, parotid, or extensive soft tissue disease lateral to lateral pterygoid muscle

N0 No metastases

N1 Unilateral nodes < 6 cms above the lower border of cricoid or uni or bilateral retropharyngeal nodes

N2 Bilateral neck nodes , < 6 cms above lower border of cricoid

N3 Unilateral or bilateral nodes > 6 cms or extension of nodes caudal to lower border of cricoids"

"Staging for Oropharynx Cancer (p16 -)

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 largest dimension

T3 Tumor larger than 4 cm in dimension or extension to lingual surface of the epiglottis

T4 Moderately advanced or very advanced disease

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral node < 3 cm and Extra nodal extension (ENE) –

N2 Metastasis in a single ipsilateral node 3-6 cm and ENE – or multiple ipsilateral nodes < 6 cm and ENE

N2a Metastasis in a single ipsilateral or contralateral node 3-6 cm and ENE –

N2b Metastasis in multiple ipsilateral nodes <6cm and ENE –

N2c Metastasis in cotralateral or bilateral nodes <6 cm and ENE –

N3a Metastasis in a single node >6cm and ENE –

N3b Metastasis in a single ipsilateral, multiple ipsilateral, contraletral or bilateral nodes of any size and ENE"

"Staging for oropharynx (p16+)

T categories remain the same as p16–ve tumors, except there is no Tis and T4b

N0 No regional lymph node metastasis

N1 One or more ipsilateral lymph node < 6 cms

N2 Contralateral or bilateral nodes, all < 6 cms

N3 Any lymph node /s > 6 cms.

Staging for Oral cavity cancer

T1 - Tumor ≤ 2 cms , Depth of invasion (DOI) ≤ 5 mm

T2 - Tumor > 2 cm but ≤ 4 cm, and DOI ≤ 10 mm or Tumor ≤ 2 cm, DOI > 5 mm ≤ 10 mm

T3 - Tumor > 4 cm or tumor of any size and DOI > 10 mm

T4 - T4a : Locally advanced tumor T4b : Very advanced tumor

N- same as orophaynx (p16-)"

"Staging of Hypopharyngeal cancer

Tis Carcinoma in situ

T1 Tumor limited to one subsite of hypopharynx and/or ≤ 2 cms in greatest dimension

T2 Tumor invades more than one subsite of hypopharynx, or an adjacent site, or measures more than 2 cm and not larger than 4 cm without fixation of hemilarynx

T3 Tumor larger than 4 cm in largest dimension or with fixation of hemilarynx or extension to oesophagus

T4 Moderately advanced or very advanced disease

N- same as orophaynx (p16-)

"Staging for laryngeal cancer

Tis Carcinoma in situ

T1 Tumor limited to one subsite with normal cord mobility

T2 Tumor invades adjacent subsite

T3 Tumor limited to larynx with cord fixation

T4 Moderately advanced or very advanced disease

N- same as orophaynx (p16-)"

Annexure-4 Subjective Global Assessment Sheet

"Assign SGA SCORE to each criteria (where A is well nourished and C is severely malnourished)

A. Weight Change in last 6 months usual weight…….kg current weight……kg amount wt lost……..kg %wt loss…….
   1. A: <5%
   2. B: 5-10%
   3. C: >10%

B. Weight change in last 2 weeks
   1. A: Increased
   2. B: Unchanged
   3. C: Decreased

C. Dietary intake overall change
   1. A: Increased
   2. B: Unchanged
   3. C: Decreased

D. Dietary Change Duration …… weeks
   1. A: no change; adequate
   2. B: no change; inadequate
   3. C : change; decreasing

Type of dietary change
   4. A:intake borderline; increasing
   5. B: intake suboptimal or decreasing or full liquid diet
   6. C: intake poor and decreasing or hypocaloric liquid diet or starvation

E. Gastrointestinal symptoms persisting >2 weeks

Nausea, Vomiting, Diarrhea, Anorexia
   1. A: none; intermittent
   2. B: some daily > 2 weeks
   3. C: all daily > 2 weeks

F. Functional capacity overall Impairment Change Duration …… weeks
   1. A: no dysfunction
   2. B: difficulty with ambulation/ normal activities
   3. C: bed ridden

G. Functional Capacity Progression
   1. A: Getting better
   2. B: Unchanged
   3. C: Getting Worse

H. Physical findings (rated as A = normal and C=Severe)

Physical examination	A(1)	B(2)	C(3)
SUBCUTANEOUS FAT			
Under the eyes	Slightly bulging are		Hollowed look, depression, dark circles
Triceps	Large space between fingers		Very little space between fingers, or fingers touch
Biceps	Large space between fingers		Very little space between fingers, or fingers touch
MUSCLE WASTING			
Temple	Well-defined muscle/flat	Slight depression	Hollowing, depression
Clavicle	Not visible in Males; may be visible but not prominent in females	Some protrusion; may not be all the way along	Protruding/prominent bone
Shoulder	Rounded	No square look; acromion process may protrude slightly	Square look; bones prominent
Scapula/ ribs	Bones not prominent; no significant depressions	Mild depressions or bone may show slightly; not all areas	Bones prominent; significant depressions
Quadriceps	Well rounded; no depressions	Mild depression	Depression; thin
Calf	Well developed		Thin; no muscle definition
Knee	Bones not prominent		Bones prominent
Interosseous muscle between thumb and forefinger	Muscle protrudes; could be flat in females		Muscle depression
Oedema(related to malnutrition)	No sign	Mild to moderate	Severe
Ascitis (related to malnutrition)	No sign	Mild to moderate	Severe

I. Primary underlying condition affecting nutrition
    1. A: Mild
    2. B: Moderate
    3. C: Severe

J. Primary underlying conditions affect on metabolic demand
    1. A: None
    2. B: Low to Moderate
    3. C; High

L. Using the above ratings estimate an overall SGA Score:
    1. A: Well Nourished
    2. B: Moderately malnourished
    3. C: Severely malnourished

Interpretation"

TOTAL SCORE:

Annexure- 5

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Ethics Committee

SRHU/HIMS/ETHICS/2018/115 Dated: 2.8.2018

The Ethics committee in its meeting held on 1.08.2018 approved the Ph.D Synopsis entitled:

"Prognostic significance of nutrition and immunity in head and neck cancer- A prospective observational study."

Submitted by Principal investigator, Dr. Anshika Arora, Asstt. Professor, Deptt. of Surgery, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University.

Dt: -2.08.2018

Dr. D.C. Dhasmana
Member Secretary,
Ethics Committee

Annexure-6

Supportive Care in Cancer
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ORIGINAL ARTICLE

Pattern of nutritional status in node-negative versus node-positive head and neck cancer patients undergoing treatment: a prospective cohort study

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Abstract

Purpose The aim of this study was to study the nutritional profile of node-negative and node-positive patients undergoing treatment for head and neck squamous cell cancer (HNSCC).

Methods This prospective cohort study was conducted between 2018 and 2020. Patients diagnosed with HNSCC, planned for treatment, were enrolled after written informed consent. In node-negative (N0) and node-positive (N+) cohorts of patients, nutritional status was determined using anthropometric measures and Subjective Global Assessment (SGA) scale pre-treatment, and during and after treatment. Statistical analysis was performed using SPSS version 22. Data was analyzed using parametric and non-parametric tests, and p value of 0.05 was considered significant.

Results In total, 161 patients were analyzed. 73 N0 and 88 N+ cohorts. Pre-treatment, 9.6 to 20.4% patients in N0 and 23.9 to 32.8% patients in N+ cohorts were malnourished. Incidence of malnutrition at completion of treatment was 40.8 to 52.5% overall, 20.5 to 41.1% N0, and 39.5 to 62.8% N+. Mean reduction in weight (11.1% ± 7.82 vs 6.26% ± 8.3, $p = 0.000$), mean reduction in BMI (2.57 ± 1.87 vs 1.29 ± 1.62, $p = 0.000$), median reduction in MUAC (2 cm vs 1 cm, $p = 0.000$), and median increase in SGA score (13 vs 6, $p = 0.000$) were higher in multi-modality as compared to those in a single-modality treatment. Similar findings were noted in N0 and N+ cohorts.

Conclusion As compared to N0, N+ patients had higher burden of malnutrition at diagnosis, and more worsening of nutritional parameters during treatment. More decline in nutritional status was seen in patients receiving multi-modality as compared to single-modality treatment.

Keywords Malnutrition in cancer · Node-positive head and neck cancer · Subjective Global Assessment scale · Nutrition support in cancer

Background

Head and neck squamous cell cancer (HNSCC) is the 6th most common cancer in the world; in 2018, there were 890,000 new cases and 450,000 deaths. The incidence is anticipated to increase by 30% by 2030 (Global Cancer Observatory (GLOBOCAN)) [1–3]. In India, the estimated age-standardized rate for incidence of HNSCC was > 10.7 per 100,000 (GLOBOCAN 2018); in the USA, this is 7.5–10.7 per 100,000. The high incidence in the South Asian region is associated with consumption of carcinogenic-containing products like oral tobacco and areca nut, and alcohol abuse, whereas oropharyngeal infection with HPV contributes to the high incidence in the West [4–6]. HNSCC is treated with a single-modality or multi-modality

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approach—surgical resection, radiation, or chemotherapy plus radiation depending on the disease stage.

Malnutrition is seen in 30–50% of HNSCC patients; around 30% patients have severe malnutrition and weight loss since 6 months prior to diagnosis. Chemotherapy worsens the nutritional intake due to digestive tract–related symptoms like loss of taste, mucositis, nausea, and vomiting [7]. Impairment related to swallowing and speech and xerostomia occur in ~ 50% of HNSCC patients following radiotherapy and these are often persistent long term [8]. The 2-year prevalence of dysphagia in HNSCC survivors is 45%; this is 4–8 times more than those who never had cancer [9]. Several studies have shown higher rates of treatment interruptions and less treatment effectiveness with high-grade mucositis [10]. Increased mortality and worse prognosis have been proposed to be associated with fat-free body mass loss related to malnutrition in cancer patients [11]. Indian data on nutritional profile of patients undergoing treatment for HNSCC with regard to node-negative and node-positive cohorts is lacking.

The aim of this study was to study the nutritional profile of node-negative and node-positive patients undergoing treatment for HNSCC.

Methods

This prospective cohort study was carried out at Cancer Research Institute, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, India, between 2018 and 2020, under Institutional Ethics Committee clearance number SRHU/HIMS/ETHICS/2018/115. The study population were patients starting treatment for HNSCC.

Inclusion criteria

Patients with diagnosed and previously untreated HNSCC planned for treatment.

Exclusion criteria

1. Previously treated for HNSCC with surgery, radiotherapy, or chemotherapy.
2. Metastatic disease at presentation.
3. Patient with skin, nasopharynx, or esophagus cancer or with metastasis from primary sites other than the head and neck.
4. Age less than 18 years.

Patients once diagnosed with HNSCC and planned for curative or palliative oncological treatment with single or multi-modality were approached for enrollment in the study and an informed written consent was obtained. They were assessed for nutritional status before starting treatment, at the end of each treatment modality, and at completion of planned treatment. The following data were recorded:

(a) Baseline data regarding patient demographics, disease, and treatment plan.
(b) ECOG performance status (PS).
(c) Nutritional status: weight, Subjective Global Assessment (SGA) score, mid-upper arm circumference (MUAC), body mass index (BMI), and hemoglobin

Based on the assumption that nutritional status may be different in patients with or without neck nodal metastasis, two cohorts were made based on the neck node status of the patient:

(a) N0 cohort: patients with no node metastasis at presentation
(b) N + cohort: patients with node metastasis at presentation

The data were recorded, anonymized, and analyzed using the following statistical methods.

Statistical analysis

The data were entered in MS Excel 2010. Statistical analysis was performed using SPSS software version 22. The one-sample Kolmogorov–Smirnov test was used to determine whether datasets were different from normal distribution. Normally distributed data was analyzed using a parametric test: unpaired Student T test, paired-sample T test; non-normally distributed data using non-parametric tests: Mann–Whitney U test, Wilcoxon-signed rank test, marginal homogeneity test; and categorical data using Pearson Chi-square test. The level of significance was taken as $p < 0.05$.

Results

A total of 161 patients were enrolled in the study: 73 in N0 and 88 in N + cohorts, 88.2% were male, mean age 56.32 (± 13.27 SD) years, 60.8% in T3/4 stage, 40.4% patients received single-modality and 59.6% multi-modality treatment. The pre-treatment mean weight was 57.75 (± 11.77 SD) kg; BMI 21.58 (± 4.2 SD); hemoglobin 13.42 (± 1.77 SD) g/dl; MUAC 24.71 (± 3.78 SD) cm. The distribution of central tendencies of these parameters was similar in N0 and N + cohorts. Pre-treatment mean weight loss in N0 and N + cohorts was 4.25% and 7.93% ($p = 0.004$), mean SGA score 36.95 and 42.74 ($p = 0.000$) respectively (Table 1). In N0 and N + cohorts,

Table 1 Pre-treatment nutritional parameters (central tendencies) compared in node-negative and node-positive cohorts

Variable		Overall ($N=161$)	Node negative ($N=73$)	Node positive ($N=88$)	p value*
Weight (kg)	Mean	57.750	59.121	56.614	0.179
	Median	56	57	55	
	Range	30–97	38–97	30–85	
	SD	11.7713	12.0118	11.5125	
BMI	Mean	21.5822	22.2396	21.0368	0.070
	Median	21	22	21.0368	
	Range	12.84–37.02	14.86–34.0	12.84–37.02	
	SD	4.19650	4.36728	3.99239	
Percentage pre-treatment weight loss	Mean	6.26	4.25	7.93	0.004
	Median	4.00	0	6	
	Range	0–36	0–32	0–36	
	SD	8.081	6.658	8.786	
Hemoglobin (g/dl)	Mean	13.4213	13.3928	13.4445	0.854
	Median	13.4100	13.4250	13.3400	
	Range	7.0–18.0	7.0–18.0	9.0–17.50	
	SD	1.76753	1.87076	1.68890	
MUAC (cm)	Mean	24.711	25.219	24.290	0.121
	Median	25	25	24	
	Range	16–49	20–34	16–49	
	SD	3.7793	2.9368	4.3283	
SGA score	Mean	40.11	36.95	42.74	0.000
	Median	39	34	42	
	Range	26–65	26–59	27–65	
	SD	10.304	8.839	10.732	

*Unpaired Student T test for mean

BMI body mass index, *SGA* Subjective Global Assessment, *SD* standard deviation

13.7% and 28.4% ($p=0.034$) patients had lost more than 10% weight pre-treatment, 9.6% and 22.8% ($p=0.036$) patients had low MUAC, 10.9% and 27.2% ($p=0.015$) had SGA score of ≥ 50, and 4.1% and 18.2% ($p=0.006$) patients had Bitot spots respectively (Table 2).

Nutritional parameters in node-negative and node-positive cohorts

gMean weight in kilograms (± SD) reduced from 57.83 (11.79) to 52.22 (10.51) ($p=0.000$), 58.94 [12] to 53.66 (11.24) ($p=0.000$), and 56.74 (11.56) to 51 (9.75) ($p=0.000$) in overall, N0, and N + cohorts (Tables 3, 4, 5). Mean % reduction in weight in kilograms (SD) at the end of the first treatment modality was 4.69 (6.46) overall, 6.21 (5.84) N0, and 3.59 (6.73) N + ; at the end of the second treatment modality was 7.49 (6.99) overall, 6.71 (8.19) N0, and 8.04 (6.03) N + ; at completion of all treatment 9.17 (8.33) overall, 8.93 (7.97) N0, and 9.37 (8.66) N + . Weight loss ≥ 10% was seen at the end of the first treatment modality in 27.2% patients overall, 26.4% N0, and 27.9% N + ; at the end of the second modality treatment in 38.1% overall, 37% N0, and 38.9% N + ; at completion of all treatment 45.3% overall, 41.1% N0, and 48.8% N + . Mean reduction in BMI (95% confidence interval) at the end of the first treatment modality was 1.45 (1.2–1.7) overall, 1.52 (1.2–1.9) N0, and 1.39 (1.0–1.7) N + ; at the end of the second treatment modality was 2.71 (2.2–3.2) overall, 2.83 (2.0–3.7) N0, and 2.62 (1.9–3.3) N + . Low BMI was present at baseline in 22.8% patients overall, 20.9% N0, and 24.4% N + ; at the end of the first treatment modality 38% overall, 33.3% N0, and 41.9% N + ; at the completion of all treatment 43.4% overall, 35.5% N0, and 50% N + . Low MUAC was found at baseline in 17.2% patients overall, 9.6% N0, and 22.7% N + ; at the end of the first treatment 27.2% overall, 18.1% N0, and 34.9% N + ; at the completion of all treatment 30.8% overall, 20.5% N0, and 39.5% N + . The median SGA score at baseline was 39 overall, 34 N0, and 42 N + ; at the end of the first treatment 47 overall, 46.5 N0, and 48 N + ; at completion of all treatment 50 overall, 48 N0, and 53 N + . SGA score of > 40 was found in 47.2% patients overall, 34.2% N0, and 58% N + at baseline; 69.6% overall, 63.9% N0, and 74.4% N + at the end of the first treatment; 87.4% overall, 79.5% N0, and 94.2%

Table 2 Pre-treatment nutritional parameters compared in node-negative and node-positive cohorts

Variable		Number of patients			*p* value*
		Overall *n*/*N*(%)	Node negative (*N* = 73) *n*/*N*(%)	Node positive (*N* = 88) *n*/*N*(%)	
Weight (kg)	< 50	37/161(23)	13/73(17.8)	24/88(27.3)	0.612
	≥ 50	124/161(77)	60/73(82.2)	64/88(72.2)	
Pre-treatment weight loss ≥ 10%		35/161(21.7)	10/73(13.7)	25/88(28.4)	0.034
BMI	≥ 18.5	122/161(75.8)	57/73(78.1)	65/88(73.9)	0.602
	< 18.5	36/161(22.4)	15/73(20.5)	21/88(23.9)	
	Missing value	3/161(1.9)	1/73(1.3)	2/88(2.3)	
MUAC (cm)	> 21	134/161(83.2)	66/73(90.4)	68/88(77.2)	0.036
	≤ 21	27/161(16.8)	7/73(9.6)	20/88(22.7)	
SGA score	24–29	33/161(20.5)	18/73(24.6)	15/88(17)	0.015
	30–39	52/161(32.3)	30/73(41.1)	22/88(25)	
	40–49	44/161(27.3)	17/73(23.3)	27/88(30.7)	
	50–59	26/161(16.1)	8/73(10.9)	18/88(20.4)	
	60–71	6/161(3.7)	0	6/88(6.8)	
Pallor	Present	10/161(6.2)	4/73(5.5)	6/88(6.8)	0.757
Bitot spots	Present	19/161(11.8)	3/73(4.1)	16/88(18.2)	0.006
Hemoglobin	Normal	110/161(68.3)	52/73(71.2)	58/88(65.9)	0.236
	Mild anemia	39/161(24.2)	14/73(19.2)	25/88(28.4)	
	Moderate/severe anemia	10/161(6.2)	5/73(6.8)	5/88(5.7)	
	Missing value	2/161(1.2)	2/73(2.7)	0	

*Pearson chi-square test

BMI body mass index, *MUAC* mid-upper arm circumference, *SGA* Subjective Global Assessment

N + at completion of all treatment. Moderate to severe anemia was found at baseline in 6.3% patients overall, 7.1% N0, and 5.7% N + ; at the end of the first treatment 16.3% overall, 12.5% N0, and 18.6% N + ; at completion of treatment 16.9% overall, 14.1% N0, and 19% N + .

Pattern of change in nutritional parameters in patients having received single-modality versus multi-modality treatment

Overall, there was no significant difference in PS, mean weight, mean BMI, median MUAC, mean hemoglobin, or median SGA score at completion of treatment between single- and multi-modality groups. Mean reduction of weight was higher (11.1% ± 7.82 vs 6.26% ± 8.3, $p = 0.000$), mean reduction in BMI was higher (2.57 ± 1.87 vs 1.29 ± 1.62, $p = 0.000$), median reduction in MUAC was higher (2 cm vs 1 cm, $p = 0.000$), and median increase in SGA score was higher (13 points vs 6 points, $p = 0.000$) in the multi-modality group (Table 6). In the node-negative cohort, mean reduction of weight was higher (10.85% ± 8.13 vs 6.79% ± 7.31, $p = 0.028$), mean reduction in BMI was higher (2.66 ± 1.98 vs 1.44 ± 1.64, $p = 0.006$), median reduction in MUAC was higher (2 cm vs 1 cm, $p = 0.009$), and median increase in SGA score was higher (15 points vs 8 points, $p = 0.009$) in the multi-modality group. In the node-positive cohort, mean reduction of weight was higher (11.12% ± 87.69 vs 6.95% ± 5.12, $p = 0.005$), mean reduction in BMI was higher (2.52 ± 1.81 vs 1.1 ± 1.61, $p = 0.001$), median reduction in MUAC was higher (3 cm vs 2 cm, $p = 0.001$), and median increase in SGA score was higher (12 points vs 4 points, $p = 0.009$) in the multi-modality group.

Discussion

The center where this study was conducted is a tertiary care cancer center, located at the foot of Himalayas in India. Approximately 1200 new cancer patients are treated at this center every year, 300 diagnosed with head and neck cancer. The patients are usually from low to middle socioeconomic strata. The median age at diagnosis for non-HPV-associated HNSCC is 66 years and that of HPV-associated oropharyngeal cancer is ~ 53 years in literature [12]. In the present study, the mean age was 56.3 years, as in India HNSCC is usually more non-HPV related, patients in this study were a decade younger. A majority of patients in this study were T3/4 stage, which is in keeping with other reports [13], and required multi-modality treatment in ~ 60% patients. Malnutrition in head and neck cancer affects 30–50% of patients

Table 3 Pattern of change in nutritional parameters before, during, and after completion overall ($N = 161$)

Variable		Baseline	End of first treatment modality	*p* value	End of second treatment modality	*p* value	At completion of treatment modality	*p* value
PS	Median	0	2		2		2	
Weight (kg)	Mean	57.83	53.88	0.000*	53.07	0.000*	52.22	0.000*
	(SD)	(11.79)	(11.3)		(8.72)		(10.51)	
< 50	n/N(%)	37/161 (23)	59/158 (37.3)	0.000***	22/64 (34.4)		67/159 (42.1)	0.000***
≥ 50		124/161 (77)	99/158 (62.7)		42/64 (65.6)		92/159 (57.9)	
Mean reduction in weight in kg from baseline (95%CI)			3.863 (3.19–4.53)	0.000*	7.428 (6.04–8.82)	0.000*	5.615 (4.82–6.41)	0.000*
Mean reduction in % weight from baseline (SD)			4.69 (6.46)	0.000*	7.48 (6.99)	0.032*	9.17 (8.33)	0.000*
Change in weight from baseline n/N(%)	≥ 10% loss of weight		43/158 (27.2)	0.000*	24/63 (38.1)	0.016***	72/159 (45.3)	0.000***
	< 10% loss of weight		85/158 (53.8)		31/63 (49.2)		68/159 (42.8)	
	No change/increase in weight		30/158 (19)		7/63 (11.1)		19/159 (11.9)	
BMI n/N(%)	Mean (SD)	21.59 (4.19)	20.14 (4.03)	0.000*	19.91 (3.13)	0.000*	19.54 (3.79)	0.000*
	Mean reduction from baseline (95%CI)		1.45 (1.2–1.7)	0.000*	2.71 (2.2–3.2)	0.000*	2.09 (1.79–2.4)	0.000*
	≥ 18.5	122/158 (77.2)	98/158 (62)	0.000***	44/64 (68.8)	0.000*	90/159 (56.6)	0.000***
	< 18.5	36/158 (22.8)	60/158 (38)		20/64 (31.2)		69/159 (43.4)	
MUAC (cm)	Median (IQR)	25 (22.5–26)	23 (21–25)	0.000**	23 (22–24)	0.000**	23 (21–24)	0.000**
n/N(%)	Normal	134/161 (83.2)	115/158 (72.8)	0.000***	52/64 (81.3)	0.003***	110/159 (69.2)	0.000***
	Malnutrition	27/161 (16.8)	43/158 (27.2)		12/64 (18.7)		49/159 (30.8)	
SGA score	Mean (SD)	40.11 (10.3)	46.18 (10.4)		49.63 (8.6)		49.88 (8.8)	
	Median (IQR)	39 (31–48.5)	47 (37–54)	0.000**	49.5 (43–56.75)	0.000**	50 (44–58)	0.000**
24–29	n/N(%)	33/161 (20.5)	9/158 (5.7)	0.000***	1/64 (1.6)	0.000***	2/159 (1.3)	0.000***
30–39		52/161 (32.3)	39/158 (24.7)		5/64 (7.8)		18/159(11.3)	
40–49		44/161 (27.3)	49/158 (31)		26/64 (40.6)		56/159 (35.2)	
50–59		26/161 (16.1)	41/158 (25.5)		21/64 (32.8)		55/159 (34.6)	
60–71		6/161 (3.7)	20/158 (12.7)		11/64 (17.2)		28/159 (17.6)	
Hemoglobin (g/dl)	Mean (SD)	13.5 (1.8)	12.5 (1.8)	0.000*	12.6 (1.4)	0.000*	12.5 (1.8)	0.000*
	Normal	110/159 (69.2)	62/147 (42.2)	0.000***	24/59 (40.7)	0.000***	59/148 (39.9)	0.000***
n/N(%)	Mild anemia	39/159 (24.5)	61/147 (41.5)		28/59 (47.5)		64/148 (43.2)	
	Moderate/severe anemia	10/159 (6.3)	24/147 (16.3)		7/59 (11.9)		25/148 (16.9)	
Bitot spots present		19/161 (11.8)	17/158 (10.8)		3/64 (4.7)		19/161 (11.8)	

*Paired-sample *T* test, **related-samples Wilcoxon signed rank test, ***related-samples marginal homogeneity test

SD standard deviation, *CI* confidence interval, *IQR* inter-quartile range, *PS* performance status, *BMI* body mass index, *MUAC* mid-upper arm circumference, *SGA* Subjective Global Assessment

Table 4 Pattern of change in nutritional parameters before, during, and after completion of treatment in the node-negative cohort

Node-negative group (N = 73 patients)								
Variable		Baseline	End of first treatment modality	*p* value	End of second treatment modality	*p* value	At completion of treatment modality	*p* value
PS	Median	0	2		2		2	
Weight (kg)	Mean (SD)	58·94 (12·0)	54·91 (11·6)	0.000[a]	53·67 (9·5)	0.000[a]	53·66 (11·24)	0.000[a]
< 50	n/N	13/73 (17·8)	23/72 (31·9)	0.000***	9/27 (33·3)		28/73 (38·4)	0.000***
≥ 50	n/N (%)	60/73 (82·2)	49/72 (68·1)		18/27 (66·7)		45/73 (61·6)	*
Mean reduction in weight from baseline (kg) (95%CI)			4·03 (3·35–5·81)	0.000[a]	7·81 (5·71–9·92)	0.000[a]	5·46 (4·27–6·65)	0.000[a]
Mean % reduction in weight from baseline (SD)			6·21 (5·84)	0.000[a]	6·71 (6·19)	0.821[a]	8·03 (7·97)	0.000[a]
Change in weight from baseline n/N(%)	≥ 10% loss of weight		19/72 (26·4)		10/27 (37)		30/73 (41·1)	0.069***
	< 10% loss of weight		40/72 (55·6)		13/27 (48·1)		34/73 (46·6)	
	No change/increase in weight		13/72 (18)		4/27 (14·8)		9/73 (12·3)	
BMI n/N(%)	Mean(SD)	22·17 (4·35)	20·65 (4·36)	0.000[a]	20·33 (2·92)	0.000[a]	20·23 (4·38)	0.000[a]
	Mean reduction from baseline (95%CI)		1·52 (1·15–1·88)	0.000[a]	2·83 (2·01–3·65)	0.005[a]	2·01 (1·55–2·46)	0.000[a]
	≥ 18·5	57/72 (79·2)	48/72 (66·7)	0.000***	21/27 (77·8)		47/73 (64·4)	0.000***
	< 18·5	15/72 (20·8)	24/72 (33·3)		6/27 (22·2)		26/73 (35·6)	
MUAC (cm) n/N(%)	Median (IQR)	25 (23·75–26·75)	24 (22–25·75)	0.000**	23 (22–24)	0.000**	23 (22–24)	0.000**
	Normal	66/73	59/72	0.034***	23/27	0.157***	58/73	0.011***
	Malnutrition	7/73 (9·6)	13/72 (18·1)		4/27 (14·5)		15/73 (20·5)	
SGA n/N(%)	Mean (SD)	36·95 (8·81)	44·83 (10·07)		48·81 (8·64)		47·42 (8·76)	
	Median (IQR)	34 (29·5–43·5)	46·5 (36–52·75)	0.000**	48 (42–54)	0.000**	48 (40·5–53·5)	0.000**
	24–29	18/73 (24·7)	5/72(6·9)		0		0	
	30–39	30/73 (41·1)	21/72 (29·2)		3/27 (11·1)		15/73 (20·5)	
	40–49	17/73 (23·3)	23/72 (31·6)		12/27 (44·4)		29/73 (39·7)	
	50–59	8/73 (11)	17/72 (23·6)		8/27 (29·6)		21/73 (28·8)	
	60–71	0	7/72 (9·7)		4/27 (5·5)		8/73 (11)	
Hemoglobin (g/dl) n/N(%)	Mean(SD)	13·5 (1·9)	12·86 (1·81)	0.001*	12·77 (1·58)	0.117*	12·86 (1·8)	0.001*
	Normal	52/71 (73·2)	32/64 (50)		13/25 (52)		33/64 (51·6)	
	Mild anemia	14/71 (19·7)	24/64 (37·5)		8/25 (32)		23/64 (34·4)	
	Moderate/severe anemia	5/71 (6)	8/64 (12·5)		4/25 (16)		9/64 (14·1)	
Bone spots	Present	3/73 (4·1)	3/72 (4·2)		1/27 (3·7)		4/73 (5·5)	

[a]Paired-sample *T* test, *Related-samples Wilcoxon signed rank test, ***related-samples marginal homogeneity test

SD standard deviation, *CI* confidence interval, *IQR* inter-quartile range, *PS* performance status, *BMI* body mass index, *MUAC* mid-upper arm circumference, *SGA* Subjective Global Assessment

Table 5 Pattern of change in nutritional parameters before, during, and after completion of treatment in the node-positive cohort

Node-positive group ($N=88$ patients)								
Variable		Baseline	End of first treatment modality	*p* value	End of second treatment modality	*p* value	At completion of treatment modality	*p* value
PS	Median	0	2		3		3	
Weight (kg) n/N(%)	Mean(SD)	56.74 (11.56)	53.02 (11.04)	0.000*	53.1 (8.58)	0.000*	51 (9.75)	0.000*
	< 50	24/88 (27.3)	36/86 (41.9)	0.000***	13/37 (35.1)		39/86 (45.3)	0.000***
	≥ 50	64/88 (72.7)	50/86 (58.1)		24/37 (64.9)		47/86 (54.7)	
Mean reduction in weight from baseline (kg) (95%CI)			3.72 (2.79–4.65)	0.000*	7.15 (5.22–9.07)	0.000*	5.74 (4.65–6.84)	0.000*
Mean % reduction in weight from baseline (SD)			3.59 (6.73)	0.000*	8.04 (6.03)	0.005*	9.37 (8.66)	0.000*
Change in weight from baseline	≥ 10% loss of weight		24/86 (27.9)		14/36 (38.9)		42/86 (48.8)	0.000***
	< 10% loss of weight		45/86 (52.3)		18/36 (50)		34/86 (39.5)	
	No change/ increase in weight		17/86 (19.8)		4/36 (11.1)		6/86 (7)	
BMI n/N(%)	Mean(SD)	21.11 (4.01)	19.72 (3.98)	0.000*	19.59 (3.28)	0.000*	18.95 (3.51)	0.000*
	Mean reduction from baseline (95%CI)		1.39 (1.04–1.74)	0.000*	2.62 (1.9–3.33)	0.000*	2.16 (1.74–2.57)	0.000*
	≥ 18.5	65/86 (75.6)	50/86 (58.1)	0.000***	23/37 (62.1)		43/86 (50)	0.000***
	< 18.5	21/86 (24.4)	36/86 (41.9)		14/37 (37.8)		43/86 (50)	
MUAC (cm) n/N(%)	Median (IQR)	24 (22–26)	23 (20–25)	0.000**	23 (22–24.25)	0.000**	22 (20–24)	0.000**
	Normal	68/88 (77.3)	56/86 (65.1)	0.001***	29/37 (78.4)	0.008***	52/86 (60.5)	0.000***
	Malnutrition	20/88 (22.7)	30/86 (34.9)		8/37 (21.6)		34/86 (39.5)	
SGA n/N(%)	Mean(SD)	42.74 (10.73)	47.3 (10.58)		50.22 (8.57)		51.97 (8.42)	
	Median (IQR)	42 (32.25–50.75)	48 (38–57)	0.000**	50 (44.5–58)	0.000**	53 (47–59)	0.000**
	24–29	15/88 (17)	4/86 (4.7)	0.000***	1/37 (2.7)	0.000***	2/86 (2.3)	0.000***
	30–39	22/88 (25)	18/86 (20.9)		2/37 (5.4)		3/86 (3.5)	
	40–49	27/88 (30.7)	27/86 (31.4)		14/37 (37.8)		27/86 (31.4)	
	50–59	18/88 (20.5)	24/86 (27.9)		13/37 (35.1)		34/86 (39.5)	
	60–71	6/88 (6.8)	13/86 (15.1)		7/37 (18.9)		20/86 (23.3)	
Hemoglobin (g/dl) n/N(%)	Mean(SD)	13.43 (1.73)	12.17 (1.81)	0.000*	12.41 (1.16)	0.000*	12.13 (1.67)	0.000*
	Normal	58/88 (65.9)	30/83 (36.1)		11/34 (32.4)		26/84 (31)	
	Mild anemia	25/88 (28.4)	37/86 (44.6)		20/34 (58.8)		42/84 (50)	
	Moderate/severe anemia	5/88 (5.7)	16/86 (18.6)		3/34 (8.8)		16/84 (19)	
Bitot spots present		16/88 (18.2)	14/86 (16.3)		2/37 (5.4)		15/88 (17)	

*Paired-sample *T* test, **related-samples Wilcoxon signed rank test, ***related-samples marginal homogeneity test

SD standard deviation, *CI* confidence interval, *IQR* inter-quartile range, *PS* performance status, *BMI* body mass index, *MUAC* mid-upper arm circumference, *SGA* Subjective Global Assessment

Table 6 Nutritional parameters at completion of treatment compared in patients that received single- versus multi-modality treatment

Variable			Overall			Node-negative group			Node-positive group		
At completion of treatment			Single modality	Multi-modality	*p* value	Single modality	Multi-modality	*p* value	Single modality	Multi-modality	*p* value
PS n/N(%)		0–1	18/63 (28.57)	17/96 (17.71)	0.075*	13/36 (36.11)	13/36 (36.11)	0.075*	5/27 (18.52)	7/59 (11.86)	0.459*
		2–4	45/63 (71.43)	79/96 (82.29)		23/36 (63.89)	23/36 (63.89)		22/27 (81.48)	52/59 (88.14)	
Mean weight kg (SD)			51.25 (11.95)	52.85 (9.46)	0.349**	53.81 (13.21)	53.51 (9.1)	0.913**	47.85 (9.21)	52.44 (9.73)	0.042**
Change in weight	Mean reduction kg (SD)		3.64 (4.25)	6.89 (5.15)	0.000**	4.07 (4.45)	6.78 (5.18)	0.019**	3.07 (3.99)	5.56 (9.57)	0.000**
	Mean reduction % (SD)		6.26 (8.3)	11.01 (7.82)	0.000**	6.79 (7.31)	10.86 (8.13)	0.028**	6.95 (5.12)	11.12 (7.69)	0.005**
BMI	Mean (SD)		19.19 (4.33)	19.77 (3.39)	0.347**	20 (4.72)	20.46 (3.22)	0.628**	18.11 (3.56)	19.34 (3.46)	0.133**
	Mean reduction (SD)		1.29 (1.62)	2.57 (1.87)	0.000**	1.44 (1.64)	2.66 (1.98)	0.006**	1.1 (1.61)	2.52 (1.81)	0.001**
MUAC (cm)	Median (IQR)		23 (20–24)	23 (21–24)	0.466***	23.5 (22–24.75)	23 (22–24.25)	0.832***	21 (18–23)	23 (20.5–24)	0.067***
	Median reduction (IQR)		1 (0–2)	2 (1–4)	0.000***	1 (0–2)	2 (0.88–4)	0.009***	2 (0–2)	3 (1–4)	0.001***
Hemoglobin (g/dl)	Mean (SD)		12.35 (2.04)	12.51 (1.58)	0.579**	12.82 (1.98)	12.89 (1.66)	0.879**	11.79 (2)	12.27 (1.5)	0.228**
	Mean reduction (SD)		0.84 (1.27)	1.17 (1.43)	0.161**	0.49 (1.25)	0.86 (1.62)	0.320**	1.25 (1.19)	1.37 (1.27)	0.688**
SGA score	Mean (SD)		48.9 (10.16)	50.52 (7.85)	0.261**	45.53 (9.48)	49.27 (7.68)	0.068**	53.41 (9.42)	51.31 (7.92)	0.285**
	Mean increase (SD)		4.4 (12.86)	12.36 (8)	0.000**	8.03 (6.19)	12.86 (7.69)	0.004**	–0.1 (17.1)	12.05 (8.25)	0.000**
	Median (IQR)		49 (40–58)	50.5 (46–57)	0.380***	47 (37.25–50)	49 (44.5–54)	0.082***	55 (47–62)	51 (47–58)	0.168***
	Median increase (IQR)		6 (2–10)	13 (7–18)	0.000***	8 (3.25–11.75)	15 (6.5–19)	0.009***	4 (0–9)	12 (8–17)	0.000***
Bitot spots present			12/65 (18.46)	7/96 (7.29)	0.045*	3/36 (8.33)	1/37 (2.7)	0.358*	9/29 (31.03)	6/59 (10.17)	0.019*

*Pearson chi-square test, **unpaired Student *T* test, ***independent-samples Mann–Whitney *U* test

PS performance status, *SD* standard deviation, *IQR* inter-quartile range, *BMI* body mass index, *MUAC* mid-upper arm circumference, *SGA* Subjective Global Assessment

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[10, 13]. In a review article published in 2017 [14], it was noted that up to 80% of HNSCC patients are malnourished because of one their lifestyle and second the risk factors associated with HNSCC. In the present study among node-negative patients, only 13.7% had lost the critical ≥ 10% weight within 6 months prior to starting treatment, only 10.9% had SGA score ≥ 50, only 9.6% had low MUAC, and 20.4% patients had low BMI. Thus, 9.6 to 20.4% patients were observed to suffer from malnutrition at diagnosis in the node-negative cohort. This is lower than the international literature. In the node-positive cohort, 28.4% patients had lost ≥ 10% weight within 6 months prior to starting treatment, 27.2% had SGA score ≥ 50, 32.8% had low MUAC, and 23.9% low BMI. Thus, 23.9 to 32.8% patients were malnourished in the node-positive cohort at diagnosis. The burden of malnutrition was found to be higher in node-positive patients; this could be due to multiple factors like a more advanced disease causing symptoms like swallowing or chewing difficulty, longer duration of disease with longer nutritional challenges, pain, and other symptoms associated with advanced disease which reduce oral intake. In HNSCC patients, cancer is close to structures vital for eating, leading to numerous nutritional challenges before, during, and after treatment. They experience treatment side effects, like odynophagia, dysphagia, xerostomia, dysgeusia, mucositis, sticky saliva, fatigue, nausea, and vomiting [15]. These further impair patient's ability to sustain adequate intake orally. A systematic review found "dysphagia" to be the most commonly studied symptom during treatment for HNSCC [16]. During or after treatment, malnutrition and unintentional weight loss in HNSCC patients are associated with increased morbidity and mortality, poor treatment outcome, and poor quality of life [17]. The nutritional journey, as experienced by HNSCC patients undergoing treatment, may be different from the measured nutritional parameters. A qualitative study on 10 HNSCC patients undergoing treatment aimed to study the experience of patients regarding their nutritional situation and perception of nutritional support during treatment. Patients experienced surgery as a poor starting point for radiotherapy from the nutritional aspect. Patients customized their diet as radiotherapy started; they experienced virtually no oral food intake about halfway into radiotherapy. This leads to tube-feeding and hospital admissions. All patients were recommended ONS, but supplements became unbearable eventually. After completion of radiotherapy, patients experienced discouragement from persistent side effects; this prevented patients from eating [18].

The response to treatment, in HNSCC patients, is affected by their unique nutritional problems. To adequately manage these patients, the treating team must accurately and systematically assess nutritional status and execute timely metabolic treatment [19]. In the present study, all nutritional parameters declined significantly from baseline during the treatment. At the end of treatment, the mean reduction in weight was 9.17% (±8.33 SD) from baseline weight; ≥ 10% weight loss was present in 45.3% patients, low BMI 43.4% patients, low MUAC 40.8% patients, ≥ 50 SGA score 52.5% patients, and moderate to severe anemia 16.9% patients. The incidence of malnutrition at completion of treatment in this study was 40.8 to 52.5% overall, in the node-negative cohort 20.5 to 41.1%, and in the node-positive cohort 39.5 to 62.8%. In the node-positive cohort, 15% more patients had low BMI, 19% more patients low MUAC, and 23% more patients ≥ 50 SGA score at completion of treatment as compared to the node-negative cohort. The nutritional challenges for patients undergoing treatment for node-positive HNSCC are far greater than those for node-negative patients. A retrospective study published in 2019 aimed to assess the impact of prophylactic feeding gastrostomy (FG) and predictors of malnutrition in patients undergoing treatment for HNSCC [20]. They studied 111 patients and found that patients without prophylactic FG had more hospital readmissions ($p = 0.042$), greater relative weight loss at 6 weeks ($p < 0.0001$), symptoms like dysphagia, and higher rate of severe malnutrition. They found factors like node-positive status, oral intake difficulty, concomitant chemo-radiotherapy, primary tumor sites like nasopharynx, and hypopharynx tumor site were significantly associated with malnutrition. A systematic review [21] published much prior (in 2013) analyzed the effect of nutritional interventions like individualized dietary counseling, oral nutritional supplements (ONS), nasogastric (NG) tube feeding, and percutaneous endoscopic gastronomy (PEG) on nutritional status, quality of life (QoL), and mortality in HNSCC patients receiving radiotherapy or chemo-radiotherapy. They found beneficial effects on nutritional status and QoL for individualized dietary counseling only; ONS, NG tube, and PEG tube feeding were not consistently associated with benefit.

The detrimental effects of treatment for HNSCC on the nutritional status of a patient may vary according to the oncological treatment. Early-stage HNSCC is usually treated with single-modality treatment like surgery or radiotherapy, whereas locally advanced HNSCC is treated with a multi-modality treatment like surgery followed by radiotherapy or chemo-radiotherapy or radical chemo-radiotherapy, depending on the location of primary tumor. Some patients, with locally advanced HNSCC, receive a single-modality treatment with a palliative intent. Nutritional parameters of a single-modality treatment and multi-modality treatment groups were compared in the present study. At completion of treatment, we found that the ECOG performance status and mean weight were not different in both groups. But the mean reduction in weight was 4.75% more, mean reduction in BMI was 1.28 kg/m^2 more, and median increase in SGA score was 7 points more in the multi-modality group as compared to those of a single-modality group (all statistically significant).

Similar findings were noted in both node-negative and node-positive cohorts. In a prospective study published in the year 2020 [22], patients undergoing a single-modality treatment with radiotherapy for HNSCC were followed up for nutritional status and nutrition impact factors. Similar to the present study, they used a SGA score and found that 56% patients were malnourished at baseline and this increased to 100% after completion of treatment, and the mean weight loss was 4.53 ± 0.41 kg, 7.39%. They also reported taste changes and dry mouth in 100% patients. Another study published in the same year compared the health-related QoL in 19 HNSCC patients undergoing multi-modality treatment with chemo-radiotherapy. They found that well-nourished patients had fewer QoL issues like pain, sticky saliva, fatigue, chewing difficulty, appetite loss, and social eating as compared to malnourished ($p < 0.05$). They found a statistically significant association (but weak strength, $r = -0.37$, $p = 0.012$) between global QoL score and SGA score [23]. A randomized controlled trial [24] on HNSCC patients receiving radiotherapy compared nutritional counseling alone versus ONS along with nutritional counseling. ONS resulted in smaller weight loss (mean 1.6 kg, 95%CI 0.5–2.7, $p = 0.006$), improved QoL and higher protein-calorie intake, and reduced need for plan changes in oncological treatment (HR = 0.40, 95%CI 0.18–0.91, $p = 0.029$). The QoL of a patient is inter-related with psychological distress; an RCT aimed to improve the nutritional status of HNSCC patients receiving radiotherapy, using the psychological technique "Eating as Treatment" (EAT) program, delivered by the dietitians. The control group had 151 patients and the intervention group, 156. SGA score was used to assess the primary end point, nutritional status. Intervention group had better SGA score, less percent weight loss, less treatment interruptions, lower depression scores, and higher QoL [25]. This RCT demonstrated effectiveness of psychological intervention (EAT) in improving nutrition in HNSCC patients undergoing treatment. The negative impact of treatment usually continues in the survivorship period too. In a qualitative study, 31 HNSCC survivors were interviewed to acquire a comprehensive understanding of their lived experience of chronic Nutrition Impact Symptoms (NIS) burden [26]. It was interesting to note that they found at least one or more chronic NIS in all survivors, but before treatment 40% were unaware of the potential for chronically persistent NIS. The present study highlights the need for supportive therapies in cancer care, especially nutritional services. Low- and middle-income countries like India face disparities in health care systems with regard to these supportive care services. There are limitations in availability of nutrition specialists, cancer dieticians, and even nutritional supplements in low-cost cancer centers, where a majority of cancer patients are treated.

In 2016, "Nutritional management in head and neck cancer: United Kingdom National Multidisciplinary Guidelines" was published [27]. The following recommendations were made regarding treatment of HNSCC:

- The multidisciplinary team should include a specialist dietitian.
- Nutritional assessment should be performed using a validated tool before starting treatment and at regular intervals.
- High-risk patients should be referred for early dietary intervention.
- Appropriate nutritional support and malnutrition treatment should be offered without delay.
- They recommended SGA and patient-generated SGA as validated tools for nutritional assessment.
- Pre-treatment nutritional assessment should be offered.
- Patients well-nourished pre-treatment should receive regular dietary assessment and intervention.
- They recommended energy intake of a minimum 30 kcal/kg/day and protein intake 1.2 g/kg/day.
- Enteral nutrition to be started in the food intake is < 60% of the estimated energy expenditure.
- Gastrostomy is recommended over NG tube if long-term (4 weeks) tube feeding is anticipated.
- Nutritional interventions like dietary counseling and diet supplements should be offered up to 3 months after treatment.
- QoL parameters related to nutrition should be estimated pre-treatment, during treatment, and post-treatment at regular intervals.

In conclusion, HNSCC patients may be malnourished at presentation, and the nutritional status deteriorated in a vast proportion of patients during treatment. Node-positive patients had a higher burden of malnutrition at diagnosis, and higher worsening of nutritional parameters during treatment as compared to node-negative patients. A higher decline in nutritional status was seen in patients receiving a multi-modality as compared to a single-modality treatment. Thus, node-positive HNSCC patients receiving a multi-modality treatment have the highest burden of malnutrition.

Author contribution All the authors contributed to the study conception and design. Material preparation, and data collection and analysis were performed by Anshika Arora, Sunil Saini, and Meenu Gupta. The first draft of the manuscript was written by Anshika Arora and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

Data availability Available.

Code availability SPSS version 22.

Declarations

Ethics approval Ethics committee approval number: SRHU/HIMS/ETHICS/2018/115.

Consent to participate A written informed consent was obtained from all participants.

Consent for publication Consent for publication was obtained from the Institutional Research Committee.

Conflict of interest The authors declare no competing interests.

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Annexure-7

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Certificate of Oral Presentation

THIS ACKNOWLEDGES THAT

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COMPLETED AN ORAL PRESENTATION FOR THE

4th Annual UTRGV Research Symposium

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Title of Presentation:

Association of Nutritional Status with Failure to Complete Planned Treatment in patients with HNSCC- a prospective cohort study in a Tertiary cancer centre in Northern India

Subhash Chauhan, Ph.D.

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Scientific Committee Chair- 2021 UTRGV Research Symposium
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Role of Nutritional status and Systemic immunity in treatment outcome of Head & Neck Squamous Cell Carcinoma- A prospective cohort study at a tertiary cancer centre in Northern India
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