




Impact of Sarcopenia on Head and Neck Cancer Treatment: A Review of Literature

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Abstract

The overall outcome of head and neck cancer (HNC) patients undergoing any treatment modality may significantly depend upon their general nutritional condition. Poor nutritional status leading to sarcopenia may be a negative prognostic factor in determining the outcome of HNC patients. PubMed database was searched to identify studies published between 2015 and 2022. All studies reporting the index for sarcopenia as well as its effect on HNC were included. This narrative review was conducted to specifically evaluate the impact of sarcopenia on HNC patients undergoing surgery/ free flap reconstruction/ adjuvant treatment. In oncology, computed tomography assessment of skeletal mass at C3 and L3 is the most suitable index to detect sarcopenia. From the articles yielded, the prevalence rate of sarcopenia ranges from 6 to 70% worldwide. Indian population presents with a significantly higher rate of 31.5% sarcopenia HNC patients. Sarcopenic patients have an increased propensity for surgical site infections, as high as 24.6% owing to the reduced skeletal muscle mass. These patients are also prone to have frequent breaks during radiation treatment of more than 1 week and increased chemotherapy-related toxicities. Further, sarcopenic individuals tend to have higher Ryle's tube dependency of more than 90 days. Sarcopenic patients undergoing surgery have a poor overall survival (OS) and disease-free survival (DFS). In terms of hazards ratio, sarcopenic patients have 1.96 times poor OS and 2.00 times poor DFS when compared to normal individuals who undergo HNC surgery. Sarcopenia is an indispensable part of cancer ailment and it is an independent factor negatively influencing DFS and OS. Thus, nutritional strategy needs to be developed to mitigate sarcopenic effects, especially in the Indian population in preoperative setting.

Keywords

- ▶ sarcopenia
- ▶ head and neck cancer
- ▶ chemotherapy
- ▶ radiation
- ▶ overall survival
- ▶ sarcopenic index

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Introduction

Head and neck cancer (HNC) is one of the most common malignancies in India, predominantly affecting the males.^{1,2} In 2020, India estimated nearly 1,35,929 (10.3%) new oral cavity cancer cases as per the Globocan data.³ Surgery has been the mainstay treatment modality and well-established standard of care for HNC.^{4,5} However, surgical procedures are lengthy and result in deformities, often followed by reduced food intake leading to nutritional deficiencies and weight loss. Additionally, a shift in paradigm has been observed for the treatment of locally advanced HNC cases utilizing radiotherapy (RT) and concurrent chemotherapy in adjuvant setting.^{6,7} Nonetheless, adjuvant treatment leads to remarkable toxicities such as nausea, vomiting, mucositis, dysphagia, and dermatitis, making maintenance of adequate nutrition a challenge.⁸ Thus, knowing nutritional status is highly essential prior to such intense treatment regime during the management of HNC. Given the emerging impact of sarcopenia in the overall survival (OS) of HNC patients, this review was aimed to analyze the mechanism of action and assess the effect of low skeletal muscle mass (SMM) on surgical and postoperative complications in head and neck oncology patients. In this study, we intended to review the literature for incidence of sarcopenia in HNC, mechanism of action, prognostic impact of sarcopenia on various treatment procedures including surgery, radiation, and chemotherapy.

Materials and Methods

PubMed database was searched to identify studies reporting the outcome of sarcopenia in HNC patients. All articles published from January 2015 to March 2022 were searched for this narrative review. The subsequent search terms were used: "Sarcopenia," and "HNC" in conjunction with "surgery," "free flap reconstruction," "postoperative complications," "overall survival," "disease free survival," or "adjuvant treatment," "chemotherapy," "sarcopenia index." Boolean operators (NOT, AND, OR) were also used in succession to modify the search. Additionally, the references of all studies were also searched individually for any additional publications. Only studies in English language, full text publications, and those establishing the impact of sarcopenia in HNC in terms of surgery, OS, disease-free survival (DFS), adjuvant radiation, and chemotherapy were deemed eligible to be included in this review. Case reports, pediatric studies, and any cancer apart from HNC were excluded. The literature search was screened by two authors (HS and KBT) and any differences were sorted in consultation with third author (MB). Each study was assessed for aforementioned inclusion criteria. The data was extracted by two different authors (HS and KBT) independently. The extracted data included first author, study designs, index to measure sarcopenia, and the criteria assessed.

What Is Sarcopenia?

Sarcopenia is defined as advanced and generalized loss of skeletal muscle with compromise in muscle strength as well

as physical function.^{9,10} Nutritional status, including muscle mass, may play a crucial role in determining the overall response of the patient to the subjected treatment. Current literature in general has demonstrated sarcopenia to be a positive predictor of increased postsurgical complication.⁹ Sarcopenia, also referred as loss of SMM, has been defined as an independent risk factor of both surgical and adjuvant treatment outcomes of cancer patients.¹⁰ The definition proposed by European Working Group on Sarcopenia in Older People is most popular and stresses on physical strength, mass, and strength of the muscle.¹¹ The frequency of sarcopenia in patients with HNC reported in literature is as high as 71%, which may vary depending on geographic region and index used to calibrate sarcopenia.¹² Indian population itself presents with a sarcopenic prevalence of alarmingly high as 31.5%.^{13,14}

Reports of sarcopenia causing higher incidence of postoperative complications is well documented, and attributes significantly to chemotherapy related toxicity, longer hospital stays and lower survival outcomes.¹⁰ However, data on sarcopenic patients undergoing HNC management is lacking.^{9,10,15} In the few studies that highlighted the relationship of sarcopenia on survival of HNC patients was only guided radiologically assessed low SMM was used to define sarcopenia.¹⁵

Mechanism of Action

Tumor microenvironment, a recent concept consists of inflammatory markers involving inflammatory cells, cytokines and chemokines which induces carcinogenesis.¹⁶ The exact pathogenesis of sarcopenia and its influence on the survival outcomes of HNC patients remains to be elucidated. Cancer progression is characterized by systemic inflammatory response (SIR), which tremendously exerts catabolic effects on the host metabolism to cause muscle breakdown leading to SIR cascade is characterized by cachexia and local inflammation.¹⁷ This SIR in turn leads to further muscle breakdown and increased release of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and transforming growth factor beta receptor.¹⁸ Hence, we focused to provide with a simple flowchart (**Fig. 1**) to understand the factors conducive to cancer progression as well as those associated with sarcopenia, thereby suggesting the interlinking negative synergetic prognosis factor in the survival outcomes of HNC patients.

How to Measure Sarcopenia

Till date, there is no consensus on a specific sarcopenic assessment method that can be incorporated in routine clinical practice. Therefore, we extrapolated the most common indices used from the literature for determining the SMM. Various tools for sarcopenia case finding and for measurement of muscle strength, muscle mass, and physical performance in clinical practice and in research are described in **Table 1**, while various studies stating the cutoff values of the indices used in the literature are described in **Table 2**.¹⁹⁻²⁸

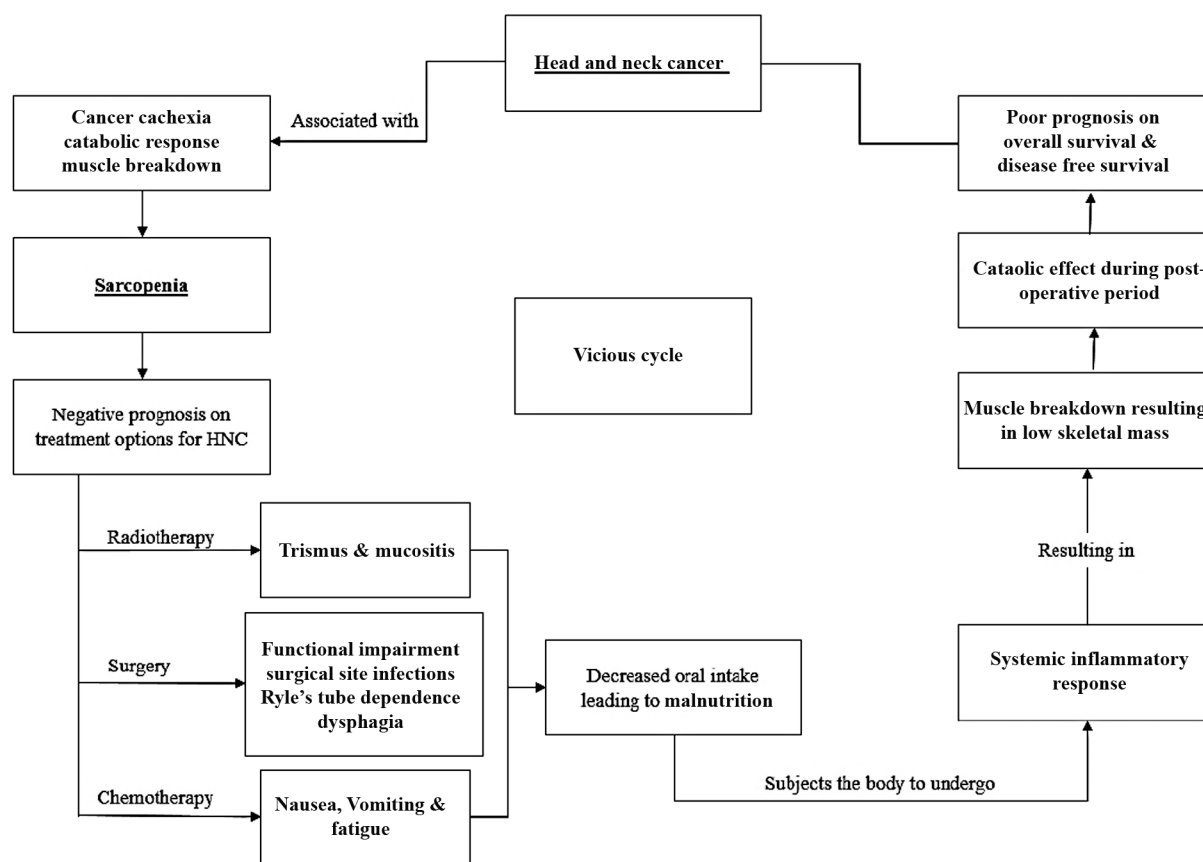


Fig. 1 Inter-relation of sarcopenia on treatment of head and neck cancers (HNC).

Table 1 Various indices to measure sarcopenia

Index criteria	Types of index
Questionnaire	SARC-F, SarQoL
Muscle strength	Grip strength, Chair stand test
Muscle quantity	ASMM by DXA, SMM with BIA, ultrasound assessment of muscle
Physical performance	Gait speed, SPPB, TUG
Specific biomarkers	Creatine dilution test
Radiographic measurement	Lumbar muscle cross-sectional area by CT or MRI, C3 vertebra SMI Mid-thigh muscle measurement, psoas muscle measurement

Abbreviations: ASMM, appendicular skeletal muscle mass; BIA, bio-electrical impedance analysis; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; SARC-F, strength, assistance walking, rise from a chair, climb stairs, and falls; SarQoL, sarcopenia quality of life; SPPB, short physical performance battery; TUG, timed-up and go test.

Analyzing the study characteristics, we observed that third cervical vertebra C3, followed by third lumbar vertebra L3, were the two frequent sites for assessing computed tomography (CT)-defined sarcopenia; and this goes in consistency with the findings of Takenaka et al in 2021.²⁹ The most accurate explanation for utilizing these two indices would be that, CT scan usually forms the investigation of choice for assessing

primary and neck node metastasis thus it can further be used to assess sarcopenia. However, CT image is sensitive enough to assess muscle quantity and muscle density identifying sarcopenia.²⁹ Collectively with the stated facts, we recommend skeletal muscle index at 3rd lumbar vertebra (SMI-L3) and skeletal muscle index at 3rd cervical vertebra (SMI-C3) methods ideal for the assessment of sarcopenia in patients with HNC.

Preoperative Effect of Sarcopenia in HNC Patients

The nutritional support of HNC patients represents a uniquely challenging cohort. Various factors such as the inherent biology of oral cancers, the tumor size, hindrance in proper swallowing, poor socioeconomic status, and the lack of social support all contribute the malnourished status of the patients.³⁰ Body mass index (BMI) less than 20 kg/m² and recently laboratory measurements such as total serum protein, hemoglobin, transferrin, prealbumin, retinol-binding protein, neutrophil-lymphocyte ratio, and other inflammatory markers have been routinely used to analyze the preoperative status of HNC patients.³¹

It is imperative to optimize the preoperative nutritional balance in such patients before ablative surgery. Dietary counseling must be mandatory to maintain appropriate nutritional intake, thereby preventing progression of the patient to loss of lean muscle mass.³⁰ Further, surgery alters the anatomy of enteral route and compromises the swallowing efficiency. RT and chemotherapy also produce

Table 2 Indices to measure sarcopenia with their cutoff values

Sr. no.	Author	Year	Variable	Index	Cutoff Value
1	Malmstrom et al ¹⁹	2016	Questionnaire	SARC-F	Score ≥ 4 –better outcome
2	Dodds et al ²⁰	2014	Muscle strength	Grip strength	<27 kg for men <16 kg for women
3	Studenski et al ²¹	2014	Muscle quantity	ASMM by DXA	<20 kg for men <15 kg for women
4	Yamada et al ²²	2017	Muscle quantity	SMM with BIA	6.8 kg/m ² for men 5.7 kg/m ² for women
5	Cruz-Jentoft et al ¹¹	2010	Physical performance	Gait speed	≤ 0.8 m/s
6	Pavasini et al ²³	2016	Physical performance	SPPB	≤ 8 point score
7	Bischoff et al ²⁴	2003	Physical performance	TUG	≥ 20 s
8	Shanakaran et al ²⁵	2018	Specific biomarkers	Creatine dilution test ^a	37 \pm 10 kg for men 23 \pm 4 kg for women
9	Jung et al ²⁶	2020	Radiographic measurement	SMI at L3	52.4 for male 38.5 for female
10	van Rijn-Dekker et al ²⁷	2020	Radiographic measurement	SMI at C3	42.4 for male 30.6 for female
11	Yoshimura et al ²⁸	2020	Radiographic measurement	PMI	6.05 for male 5.097 for female

Abbreviations: ASMM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry; PMI, psoas muscle index; SARC-F, strength, assistance walking, rise from a chair, climb stairs, and falls; SMI, skeletal muscle index; SPPB, short physical performance battery; TUG, timed-up and go test.

^aMuscle mass from D3-Crn enrichment with spillage correction by 24 h D3-Cr subtraction.

adverse effects such as mucositis, xerostomia, odynophagia, altered taste sensations, and nausea-vomiting, which exaggerate the poor nutritional intake of patients.³⁰ Hence, establishment of enteral route for access of adequate nutrition without reliance on oral intake is crucial. Preoperative placement of nasogastric tube or percutaneous endoscopic gastrostomy can significantly mitigate the problem of nutritional rehabilitation.

Preoperative Recommendation for Mitigation of Effects of Sarcopenia

Preoperative carbohydrate loading with ingestion of an 800 mL of 12.5% carbohydrate drink on the night before surgery followed by 400 mL on the morning of the procedure, consistent with Enhanced Recovery After Surgery Group, has been recommended.^{30,31} Also, HNC patients tend to have immunosuppression that in turn increases the rate of post-surgical complications. Arginine is known to be an essential amino acid when body undergoes metabolic stress.³⁰ Therefore, provision of arginine-supplemented immunonutrition and additional supplementation with omega-3 fatty acids has gained acceptance and should be encouraged.

Effect of Sarcopenia in Surgical Outcomes Intraoperatively

Surgical site infection (SSI) can be defined as an infection in a surgical wound within 30 days postoperatively. It can lead to increased hospital stay, higher cost, and delayed adjuvant therapy after surgical management of HNC patients. The

reported frequency of SSI after head and neck oncology surgery in healthy patients varies between 3 and 41% in numerous published studies.³²

Literature suggests a significant relation between SMM and the prognosis of HNC patients undergoing free flap reconstruction. Makiguchi et al in a retrospective analysis in 2019 investigated the SSI rate in 122 patients with sarcopenia.³³ Makiguchi et al reported 30 patients (24.6%) suffered with recipient site SSI and the authors concluded that lower SMM was an independent significant risk factor in such patients.

Further, Alwani et al stated that the definition of sarcopenia should be constantly evolving.⁹ However, the measurement of SMM remains the integral part. Additionally, he also noted that sarcopenic patients had higher frequency of blood transfusion; and they were more susceptible to prolonged ventilation.

Effect of Sarcopenia Postoperatively on Free Flap Reconstruction

Ansari et al in 2019 aimed to identify role of SMM on intraoperative and postoperative complications, as well as on survival rates in 78 patients who underwent mandibular reconstruction with free fibula flaps (FFF) in oral cancer resection.¹⁰ They suggested that sarcopenia tends to increase the complication rates in patients with FFF and subjects them to severe postoperative complications (Clavien Dindo grade III-IV). The frequently encountered complications are flap congestion (38.5%), partial skin paddle necrosis (23.1%), dehiscence (15.4%), and complete flap failure rate of 7.7%.

After introspecting the study, we can understand that among these four major complications, dehiscence may be the sole complication that could be directly related to sarcopenia; rest all are outcomes of vascular compromise. Furthermore, comparing the rate of wound dehiscence in using FFF in healthy patients would have given more insight on independent impact of sarcopenia on HNC. Lodders et al reported a 10.5% rate that is evidently lower in contrast to dehiscence rate noted in sarcopenic patients.³⁴ Another study with level IV evidence by Alwani et al, retrospectively determined the clinical impact of sarcopenia on postoperative outcomes in 168 patients receiving autologous free tissue reconstruction for HNC.⁹ Fistula formation, wound disruption, and longer intensive care unit stays signify that sarcopenia has a negative prognostic factor in surgical outcomes with HNC patients. The authors put forward a possible hypothesis for this correlation, suggesting that skeletal muscles produce myokines that exert antineoplastic effect. Myocyte apoptosis in sarcopenic patients cause depletion of SMM, which in turn causes a reduction in myokine-mediated antineoplastic activity that makes them vulnerable to adverse postoperative events.

Effects of Sarcopenia on Adjuvant Therapy

Surgery has been the established treatment modality and best standard of care for early HNC.

However, concurrent chemoradiotherapy (CRT) have now led to a shift in the paradigm for the treatment of locally advanced HNC. The addition of chemotherapy improves the survival rate, but it is not without added toxicities.⁸ With the impact of existing sarcopenia in such patients, the OS outcomes become questionable. The exact relation between effect of sarcopenia and occurrence of adverse effects of adjuvant therapy has yet not been elucidated distinctly. It can be understood that radiation induced fatigue is responsible for the increased toxicity of radiation therapy in sarcopenic patients. This is known to be associated with increased levels of proinflammatory cytokines, including TNF- α and IL-6, which leads to increased adverse effects. Ganju et al in 2019 reviewed the effect of sarcopenia on 246 HNC patients receiving concurrent chemo radiation.⁸

Sarcopenia was associated with worse OS and progression-free survival as 37% patients experienced chemotherapy delays of more than 1 week and 14% had radiation treatment breaks more than 1 week. They estimated that patients with age more than 65 years, BMI less than 30, and sarcopenia predicted for prolonged break from radiation and concluded that sarcopenic patients receiving concurrent chemoradiation are more likely to require frequent breaks during radiation treatment. Furthermore, these patients also suffer from increased chemotherapy-related toxicity such as mucositis, dysphagia, and nausea/vomiting than their nonsarcopenic counterparts. On multivariate analysis, these patients were 2.15 times more prone for above-mentioned toxicities than the normal patients. So, it can be noted that larger breaks in such patients could further lead to slower tumor depletion and increased chances of recurrence.

Additionally, tackling sarcopenia can lead to optimization of the condition of patients with HNC before adjuvant therapy to prevent long-term functional swallowing impairment, such as feeding tube dependency. Karsten et al in 2019 analyzed that sarcopenia led to prolonged (>90 days) feeding tube dependency in 61 HNC patients.³⁵ The extent of tumor and treatment disrupts normal swallowing physiology, followed by loss of muscle mass and function due to poor nutritional intake. Due to reduction in swallowing muscle activity, nonuse of atrophy of these muscles is inevitable, which is associated with further development of dysphagia and gets exaggerated by loss of muscle mass in sarcopenia. Thus, it can be safely concluded that sarcopenia may lead to Ryle's tube dependency patients with HNC treated with primary CRT.

Effect of Sarcopenia during Follow-Up of Head and Neck Cancer Patients—(Overall Survival and Disease-Free Survival)

Takenaka et al in a meta-analysis in 2021 studied the prognosis of sarcopenia in patients with HNC treated with surgery versus radiation.¹² In total 18 studies enrolling 3,233 patients were included which yielded that sarcopenia was associated with poor OS, DFS and disease-specific survival (DSS) in both surgery and RT groups with sarcopenia affecting more in surgery group. The hazards ratios for OS, DFS, and DSS were 2.50, 2.59, and 2.96, respectively, for surgery group and 1.63, 1.56, and 2.67, respectively, in the RT group. Another meta-analysis by Surov and Wienke in 2021 analyzed the influence of sarcopenia on clinical outcomes in 7,704 patients with head and neck squamous cell carcinoma (HNSCC) from 27 clinical studies, most frequently affecting nasopharynx (47.1%).³⁶ The study showed that the cumulative prevalence of sarcopenia is 42.0%; and it is an independent risk factor of OS and DFS attributing to hazard ratio of 1.96 and 2.00, respectively, in patients with HNSCC who underwent curative therapy. Sarcopenic patients predicted lower OS undergoing definitive chemotherapy and/or radiation, and primary surgery with hazard ratio of 1.95 and 2.21, respectively.

A retrospective analysis by Lee et al in 2020 investigated the impact of sarcopenia and systemic inflammation on survival in 174 oral squamous cell carcinoma (OSCC) patients.¹⁸ The skeletal muscle index was assessed at the C3 vertebra and the modified Glasgow scale was used to evaluate the systemic inflammation. The authors concluded that sarcopenia and systemic inflammation may significantly exert a negative synergistic prognostic impact in advanced-stage OSCC patients.

Another retrospective study by Stone et al in 2019 aimed at studying the mortality rate associated with sarcopenia in 260 HNC patients.³⁷ They suggested that sarcopenia can be considered as an apt marker for malnutrition than other conventional assessments, such as BMI, albumin level, or prealbumin level. The authors defined sarcopenia using previously determined thresholds of less than 52.4 cm²/m² for men and less than 38.5 cm²/m² for women. They analyzed

that at 5 years, the OS was 36.5% in patients with sarcopenia and 60.5% in patients without sarcopenia, implying sarcopenia to be a significant negative predictor of long-term OS in HNC patients. Sarcopenia has more deteriorating impact on geriatric HNC patients (≥ 70 years old). Charki et al in 2019 conducted a retrospective study on 85 elderly HNSCC patients and investigated SMM and muscle function as a combination contributing to sarcopenia.¹⁵ The study concluded that sarcopenia is associated with impaired OS in such patients with median OS of 12.07 months, compared to 13.60 months in nonsarcopenic individuals. Similarly, in a prospective setting by Jung et al in 2020 evaluated the impact of sarcopenia on postsurgical and oncological outcomes in 190 older adult patients with HNC.²⁶ They concluded that on multivariate analysis in elderly patient who underwent curative treatment for HNC had 3.2 times higher early complication especially those who were sarcopenic and 4.5-fold increase in mortality over a period of 5 years.

Sarcopenia in Indian Population with Head and Neck Cancer

HNC is the sixth most common cancers worldwide, while in India it is the most common cancer in males.³⁸ A study involving 18,363 older adults (aged 65 years and older) from three European, three Asian, two African, and one South American country demonstrated higher sarcopenia prevalence rates in older Indians (17.5%) as compared to the other eight countries assessed (12.6–16.7%).³⁹ After India, Mexico reported with 16.7%, China with 15%, Russia with 14%, and Spain with 13.8%. The probable reason can be attributed to the fact that Indians have a reduced BMI, higher percentage body fat and reduced SMM and strength in comparison to the western population.¹³ Additionally, according to the 2021 Global Hunger Index, India ranks 101 out of the 116 countries, with a score of 27.5, which is a serious level of hunger. This data enables to understand the impending hunger levels in India, which disposes the majority of HNC patients to develop sarcopenia.

With the prevalent data of foreign literature suggesting higher incidence of sarcopenia in Indian HNSCC patients, it becomes prudent to tackle this setback and develop potentially feasible approaches to reduce the burden. India's greater population warrants universal health screening programs and relevant questionnaire or index to identify sarcopenia and lastly develops stringent measures to address these patients for better outcomes especially those with HNC.

Conclusion

Sarcopenia is characterized by depletion of SMM, strength, and function and is associated with an adverse effect on the prognosis of patients with cancer.

Sarcopenia is an indispensable part of cancer cachexia and is a predictor of poorer outcomes in HNC. It can be established that patients with sarcopenia have worse OS and DFS. Additionally, it has a negative prognostic effect on free flap-

related complications, followed by the increased incidence of postoperative SSIs. When analyzing the effect on concurrent CRT in patients with locally advanced HNSCC, sarcopenia proves to cause greater toxicity and increased treatment breaks. Further, studies assessing SMM and providing information for its nutritional strategy are the need of the hour. Universal index to measure this deleterious prognostic factor and eventually to establish if sarcopenia must be part of a selection plan for surgical treatment of HNC patients warrants larger studies. Furthermore, recommendations for monitoring and surveillance strategies in managing outcomes of sarcopenia in HNSCC patients are yet to be established.

Recommendation

From this review, we would like to highlight few important factors associated with sarcopenia that affect the overall outcome of a HNC patient.

We suggest the CT assessment of skeletal mass at C3 and L3 as the most suitable index for diagnosis of sarcopenia in HNC. Maintaining the preoperative nutrition is equally crucial after analyzing the SMM of these patients. BMI and presurgical albumin levels indicate the nutritional status of the patient. Proper diet with nutritional supplements needs to be incorporated as strategy in wholesome management of HNC patients.

Essentially, a number of complications arise intraoperatively in sarcopenic patients. Such comorbidities warrant higher care level in terms of blood transfusion, prevention of SSI, and prolonged intensive care unit support. Sarcopenia also increased the postoperative complications in patients who have undergone free flap reconstruction, thereby severely exerting a negative effect on the survival outcomes of the patient. Further, the exaggerated side effects of adjuvant therapy and the need for longer radiation breaks predispose the sarcopenic patients to a higher risk of tumor relapse.

With the above-mentioned statements, it can be established that sarcopenia has an impaired overall effect on HNC patients, subjecting them to suboptimal healing and increased mortality.

Conflict of Interest

None declared.

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