CHAPTER-5

DISCUSSION

5.1 Baseline parameters

In this study majority patients were male (88.2%); usually, men are at higher risk for HNSCC as compared to women. The median age(SD) was 56.32±13.27 years in the present study, but in the published literature, at the time of diagnosis median age for HPV negative HNSCC was 66 years, whereas, for HPV positive oropharyngeal cancer it was ~53 years and Epstein–Barr virus-associated nasopharyngeal cancer it was ~50 years.[215,216] A prospective study found mean age to be 63.5±11 years (range 32 to 89); 72.5% patients were male and the commonest subsite was oropharynx (43.7%).[75] Sanz et al. found the mean age 62.6 years for female but it was 68.8 years for male.[217] Various Indian studies reported sixth decade to be the commonest age for HNSCC (31.13%).[218-220] In our study the patients were a decade younger. The reason for increased prevalence seen in the younger males in Indian subcontinent could be early onset of habits like oral tobacco along with lime and betel quid and even early tobacco smoking. The sample size estimation in the present study was performed for correlation keeping in mind the main objectives of the study.

Fesinmeyer et al. analyzed 5086 HNSCC patients from “Surveillance, Epidemiology, and End Results” (SEER) data; 66.7% were male, larynx 39.4%, nasal cavity 4.8%, oral cavity 28.6%, pharynx 18.7%, salivary gland 8.3%, mean age diagnosis was 75.1±6.4 (SD) years; Charlson score 0 (21.7%), 1 (28.8%), 2 (19.3%) and ≥3 (30.2%).[221] Overall, 60.5% patients had nodal disease, with 39.6%, 75.2%, 71.3%, 83.8%, and 61.4% in subsites larynx, nasal cavity, oral cavity pharynx and salivary gland, respectively.

In our study, 61.2% patients were T3/4 stage, commonest subsite was oral cavity followed by orophaynx and larynx, probably due to high rate of oral tobacco usage in this part of the country. Majority patients had ECOG PS of 0 or 1 (77%). The node positive (N+) cohort differed from node negative (N-) cohort, as there were significantly higher proportion of T3/4 patients, subsite oropharynx tumors and poorly differentiated tumors. The baseline factors like age, gender, ECOG PS were similar in both the cohorts.

5.2 Nutritional profile during treatment

The significance of starting nutritional screening early has been made abundantly clear in various guidelines that have consistently advised screening the patients for nutritional risk once the cancer is diagnosed, and that this should be followed by a full nutrition assessment if the risk was present.[222,223] It is noteworthy that no sinlge parameter could be used to define malnutrition in the adults; thus, presence of ≥2 of the following parameters has been recommended to diagnose malnutrition[224] –

- Inadequate calorie intake
- Loss of weight
- Loss of muscle mass
- Loss of subcutaneous fat
- Edema which could be generalized or localized may occasionally disguise weight loss
- Reduced functional status (as measured by handgrip strength)

Bhattacharjee et al. found the pre-treatment mean weight (±SD) was 40.3±6.7kg and mean BMI (±SD) was 15.9±2.2 in HNSCC patients.[106] They also noted that HNSCC patients were consuming only around 1685 kcal via their regular diet, but the recommendation for calorie intake for an average 60 kg man and moderate activity is about 2425 kcal/day. In the present study, pre-treatment weight of patientswas 57.75±11.77kg and mean BMI was 21.58±4.2 kg/m^2, with no significant differences in mean between the two groups, i.e.,node positive (N+) and node negative (N-) for these two parameters.

Langius et al. studied 1340 HNSCC patients and noted that 70% patients experienced no pre-treatment weight loss, ≤5% weight loss was noted in 16% patients, >5 to 10% weight loss in 9% patients and ≥10% weight loss in only 5% patients.[207] In the present study, the median pre-treatment weight loss was 6% in N+ and zero in N- cohorts; the proportion of patients with ≥10% pre-treatment weight loss was higher in the N+ when compared to N- cohorts (28.4% and 13.7% respectively, p=0.034), overall being 21.7%. A study published in

2009 noted >50% patients with advanced HNSCC had marked impairement of nutrition and also significant unintentional weight loss at diagnosis.[225]

Prevalence of malnutrition was noted to be higher in older as compared to younger patients and in advanced stage as compared to early stage in some studies.[211,226] A study found that upto 80% HNSCC patients were malnourished, mainly due to the lifestyle and risk factors linked to this disease.[73] In the present study, 22.3% patients had low BMI, 21.7% had ≥10% pre-treatment weight loss, and 47.1% had ≥40 pre-treatment SGA score; thus the prevalence of malnutrition at diagnosis was found to be 21.7% to 47.1%.

In their prospective study on 229 HNSCC, Sandra et al. noted that at baseline, 11.9% patients had malnutrition according to the GLIM criteria; 12.3% in patients aged <70years, and 9.3% in those ≥70years (p=0.501); 10.2% male, 14.3% female (p=0.389); 13% orophayrnx, 11.9% oral cavity, 14.3% larynx, and 2.9% other tumor subsites (p=0.379). Of these, 7.5% were Stage I/II and 16.8% were Stage III/IV (p=0.029).[75] In the present study, it was observed that the malnutrition rate was higher in N+ cohort as compared to N- cohort (34.2% versus 58%, p=0.015) (as defined by low pre-treatment SGA scores of ≥40). Advanced stage (III-IV) has been shown to be significantly associated with malnutrition pre-treatment and at subsequent follow-ups even in various other studies, and also strongly associated with critical weight loss in patients with HNSCC.[227,228]

A study from Switzerland found that patients with oral SCC with malnutrition experienced significantly poorer QOL scores, specially, with regard to physical function in comparison to well-nourished patients.[210] In 2016 detailed guidelines for nutritional management in HNSCC patients were published from the United Kingdom.[229] A summary of the recommendations is outlined below-

- A dietitian specialist should be part of multidisciplinary team.
- Screening should be done using validated tools for nutrition at initial diagnosis and thereafter at frequent intervals during different stages of cancer treatment.

- Patients with increased nutritional risk need to be referred to specialist dietitian for starting timely nutrition intervention.
- Patient should be offered treatment and suitable nutritional support for the malnutrition without delay.
- The validated assessment tools suggested are- PG-SGA or SGA for nutritional status.
- Patients should be offered a pre-treatment assessment of nutrition.
- One should aim for energy and protein intake- 30 kcal/kg/day and 1.2 g protein/kg/day respectively if receiving RT or CRT.
- Nutritional support to be commenced if there is malnutrition or if it is likely that patient may have no intake for >7 days.
- Gastrostomy should be considered if >4 weeks tube feeding is anticipated.
- The pre-operative patients at higher risk for malnutrition to be offered nutritional treatment 10 to 14 days before any major surgery and the surgery could be delayed.
- In the post-operative period, tube feeding should be initiated within 24 hours.
- When oral diet is found inadequate, the patients should be offered prophylactic tube feeding.
- The patient should be offered nutrition intervention, in terms of dietary counseling with or without supplements, for at least 3 months post-treatment.
- QOL parameters like swallowing and nutritional assessment to be done at diagnosis as well as at regular intervals after completion of the treatment.
- Disease free patients who have finished their rehabilitation should be advised on healthy eating as part of wellbeing clinic.

Arends et al. noted that cancer patients were at increased risk for developing malnutrition during oncological treatment; this was as high as 90%.[222] Malnutrition seen during oncological treatments can be defined as-

"An acute, subacute or chronic state of nutrition, in which a combination of varying degrees of overnutrition or undernutrition with or without inflammatory activity have led to a change in body composition and diminished function".[230]

During treatment of HNSCC, 75-80% patients experienced weight loss and 30-50% severe loss of weight.[130] In the present study, at the end of treatment, weight loss was 9.17%; ≥10% weight loss was observed in 45.3% patients, the mean reduction in BMI was 2.09 and proportion of patients with low BMI was 43.4%; low MUAC was 30.8% and high SGA score was 87.4%. The median SGA score increased from 39 pre-treatment to 50 post-treatment (all p values significant).

Singh et al. in their prospective observational study, aimed to evaluate the weight loss along with the alterations in BMI for the period of CRT with nutritional supplementation and active diet counseling in 128 HNSCC patients.[231] The primary end point was weight loss and change in BMI during the treatment, the secondary end points were completion of expected treatment during time frame expected, rate of NG tube feed, intra-venous support, and duration of admission to hospital. They found a significant reduction in mean weight and BMI pre- and post-treatment (53.86 kg to 48.30 kg, p=0.001; 21.52 to 19.18, p=0.0003 respectively), with 11% weight loss during treatment, 14 patients required NG tube feeds, 23 patients required admission for intravenous/parenteral nutrition and the median hospital stay was three days in this study. Conclusion derived by the authors was that significant loss of weight and reduction in BMI during the CRT in HNSCC patients. They also recommended a regular assessment of nutrition status and active nutritional interventions in every patient in order to better the compliance for treatment.

In the present study, the mean weight reduced from 57.83 (±11.79 SD) at pre-treatment to 52.22 (±10.51 SD) at post-treatment (p=0.000); mean BMI reduced from 21.59 (±4.19 SD) to 19.54 (±3.79 SD) (p=0.000) in the overall group. The changes in weight, BMI, MUAC, ≥10% reduction in weight and SGA score were greater in N+ cohort as compared to the N- cohort.

The effect of single versus multi-modality treatment on the nutritional status of the patients was also evaluated.

Surgery is an important modality of treatment in HNSCC and can be ablative resulting in changes of function in the affected areas (such as cranial nerves, soft tissue, bone and teeth). Decline of sensory functions (such as, alteration insmell and taste) or the mechanical functions (such as, chewing, facial, and neck movements) may occur due to extensive surgery.[232,233] "Enhanced Recovery after Surgery" (ERAS) protocols should be implemented so as to minimize the risk of malnutrition after major surgery. ERAS protocols have been proven to hasten time to consume solid food after the surgical procedures.[234] RT is administered localized to a specific site and causes direct cell damage (including even the healthy cells) in the area. As a result, there is damage to structures that are involved with consuming food. Effects on the salivary glands further reduce the capacity for adequate early digestion process and changes in the perception of taste for different foods. In HNSCC patients RT may also reduce the desire to eat food. It has been noted in studies that presence of severe mucositis during RT was found to be linked to increased weight loss, reduction of nutritional status and energy.[235] The use of "intensity-modulated" RT (IMRT) was associated with reduced RT related toxicities.[236,237]

Some patients require combination of RT and chemotherapy (CRT), with the commonly used chemotherapy being weekly cisplatin.[238] Many authors have noted that concurrent use of chemotherapy results in an increase in toxicities related to RT, like oral mucositis.[225,235] Many investigators have reported a weight loss of 10% or more (from the pre-treatment weight) in HNSCC patients, through CRT treatment.[239-241] In the present study, we compared the change in weight, BMI, SGA score, and other anthropometric parameters in patients with single versus multi-modality treatment. Overall, the mean reduction in weight (±SD) being 6.26% (±8.3) and 11.01% (±7.82) in patients with single and multi-modality treatment respectively (p=0.000). Percentage of patients with ≥10% weight loss during treatment was 28.5% and 56.3% in single and multi-modality treatment respectively (p=0.002). The mean fall in BMI was also significantly more with multi-modality treatment (2.57 versus 1.29;

p=0.000). The median rise in the SGA score was 6 and 13 with single and multi-modality treatment (p=0.000). These findings were similar in the N- and N+ cohorts.

One of the adverse effects of poor nutrition in HNSCC patients could be on the oncological outcomes, which includes reduced treatment response that this could also result in prolonged periods of treatment. Malnutrition is also associated with reduced recovery after RT and CRT, contributes to a significantly reduced physical strength and QOL.[242] It is seen to increase mortality rates (by 10–20%) particularly related to malnutrition and not to cancer itself.[222,243] The management or prevention of malnutrition by minimizing treatment related toxicities needs to be initiated at the biggening of treatment. Some studies in Europe hospitals noted that as few as 30% to 60% cancer patients with risk of poor nutrition were given any nutrition support (such as oral, enteral, or parenteral supplements).[68,70] Gyan et al. reported that cancer patients and their relatives frequently underestimated the presence of malnutrition even when the physicians recognized it.[244] In the present study, malnutrition (defined as low BMI, or low MUAC, or SGA score ≥40) was found in 47.2%, 34.3% and 58% patients overall, N- and N+ cohorts pre- treatment; this rate increased to 87.4%, 79.5% and 94.2% respectively at completion of treatment.

A prospective observational study aimed to evaluate alterations in NIS and nutritional/functional status during RT in HNSCC patients.[245] They followed 50 patients before, during, and at end of RT, and the nutritional parameters were collected. Using the PG-SGA, they found that the proportion of patients with malnutrition increased from 56% at baseline to 100% post-treatment, with mean (SD) weight loss 4.53 (± 0.41)kg (7.39%) at the end of RT.Nutritional parameters like muscle, fat mass, BMI, dietary and protein intake significantly decreased (p<0.0001).

In a study on 71 HNSCC patients undergoing treatment, it was seen that 25/71 (37.5%) patients had weight loss of <5%, 18/71 (29.6%) patients 5-10% and 24/71(35.8%) patients were >10% from the baseline weight. They found that the weight loss correlated significantly

with the PS (p=0.02), number of admissions to hospital (p=0.005), and infections episodes (p=0.035). The patients with >10% weight loss had a shorter OS and PFS (p=0.0481).[113]

Sandra et al. noted in their prospective study on HNSCC that according to tumor subsite, the prevalence of malnutrition after 7 weeks of starting treatment was 52% oropharynx, 46.3% oral cavity, 14.3% larynx, and 29.4% in other subsites; according to stage- Stage I,II 33.8%, Stage III, IV 53.7%; according to treatment modality- surgery alone 22.2%, RT± surgery 33.3%, CRT± surgery 67.2%.[75] After 3 months of completion of treatment, 11.5% males and 23.1% females (p=0.038), 7.1% Stage I,II and 25.6% Stage III, IV (p<0.001), surgery alone 0%, RT± surgery 12.4%, CRT± surgery 17.2% (p=0.035), grade I,II mucositis 13.6% and grade III,IV 60% had malnutrition. The proportion of patients underweight at the 3 months follow-up was 12.5%. The highest rate of malnutrition was seen at 7 weeks post-treatment (42.4% patients). In this study the mean weight reduced from 83.1 kg (±17.3 SD) pre-treatment to the lowest value of 77.6 kg (±15.1 SD) at 6 months follow up post-treatment.

Ottosson et al. compared loss of weight during and after 2 different schedules of RT.[246] They found that weight loss was multi-factorial; the factors significantly predictive for weight loss were obesity, primary site, and no tube feeding during RT. They found the maximum weight loss at 5 months post-treatment. More patients receiving accelerated fractionation RT required tube feeding as compared to the conventional fractionation RT.

It is projected that >90% of HNSCC survivors who underwent CRT have one or more nutrition impact symptoms (NIS) in months and years post-treatment. A systematic review by Sylvia et al. looked at the presence of NIS and the associated outcome in HNSCC survivors post-CRT.[91] Fifteen studies with 849 patients were included in the analysis. Functional impairments like xerostomia, dysphagia, trismus, salivary issues, oral pain, and mucositis have been studied in this patient population. The authors concluded that the NIS negatively influenced HNSCC survivors even after the acute treatment phase. These symptoms were associated with reduced nutrition and QOL. Interventions are required to improve the survivor's eating difficulties even after the treatment completion.

Widespread research has acknowledged the harmful impact of HNSCC treatment on the patient's nutrition; however, there are few studies addressing the patient's experiences. A qualitative study described the HNSCC patient's experience of nutritional situation and the perception of nutritional support from the time of diagnosis to post-treatment phase.[247] Data collection was performed by individual interviews after RT with 10 patients (aged 49-70 years). Patients experienced undergoing surgery as a poor starting point of nutritional for the adjuvant RT. During RT, ever-increasing side effects made the patients customize the meals to recover the food intake. About mid-way through RT, patients experienced almost no food intake and this led to admission to hospital and starting of tube feeding. All patients were recommended ONS, but the oral supplements sooner or later became unbearable to consume. When RT finally finished, the patients felt unenthusiastic about the continual side effects of RT that prevented them from resuming normal eating. The patients missed structured information regarding the side effects of RT and contribution of a dietitian as they reflected on the treatment period. They concluded that wide-ranging nutritional issues experienced by HNSCC patients during RT need early nutrition assessment and improvement in individually modified nutritional support.

Various strategies have been used to improve nutrition status of HNSCC patients undergoing oncological treatment. A study published in 2020 noted that pre-habilitation exercises for swallowing under the guidance of a speech pathologist may improve the swallowing function.[248] A retrospective study published in 2019 included 152 HNSCC patients treated with surgery, RT or CRT.[249] The patients were grouped according to the gastrostomy status into prophylactic and non-prophylactic groups. The clinical and nutrition outcomes were assessed at 6 weeks after start of treatment. Prophylactic gastrostomy was performed in 41 patients; whereas, 111 patients received no nutrition support. There was worse pre-treatment BMI, more severe malnutrition and increased oral intake problems with prophylactic gastrostomy. They found that the patients without prophylactic gastrostomy had worse outcome like- hospital readmissions ($p=0.042$), dysphagia, weight loss at 6 weeks ($p<0.0001$), severe malnutrition and a poorer state of health ($p=0.001$). The complication

rate for gastrostomy in this study was 4.9%, with 5.9-9.3% as the usual rate of complication in the reported literature. They concluded that prophylactic PEG had benefits for reducing hospital admissions, weight loss at 6 weeks, severe malnutrition, dysphagia and poor state of health. In this study they also noted that node-positive status, CRT, oral intake problems, and tumor sites like hypopharynx and nasopharynx were factors significantly predictive for malnutrition.

The following table gives details of proposed nutritional assessment in HNSCC patients-

Table 5.1 Proposed nutritional assessment in HNSCC patients planned for treatment

Clinical evaluation	Chewing and swallowing dysfunction, Dentition, Weight loss history Other medical illness compromising nutrition,e.g., Diabetes Mellitus
Detailed diet history	24 hour recall of diet intake, Change in appetite, Amount of fluid intake Change in amount of diet, Change in texture of diet, Reporting of early satiety Time taken to complete the meal, Gastrointestinal alteration of function Oral care regime
Calculation of nutrient requirements (National Collaborating Centre for Acute Care 2006)	Energy-25-35 kcal/kg/day, Protein- 0.8-2.0 g/kg/day, Fluid- 30-35 mL/kg/day Vitamins and minerals- as per daily recommendations
Anthropometry	Weight, Height, History of loss of weight, % change in weight Calculate BMI, MUAC, Hand grip strength
Social support and information	Caregiver support, Financial aspects, Access to type of meals required, eg. Tube feeds, Smoking and alcohol intake
Tools for nutritional assessment	SGA, PG-SGA, MUST (for surgical patients)
Frequency of nutritional assessment	Pre-treatment, At regular intervals during treatment Regular intervals on follow up 6 months to 2 years
(MUAC- mid-upper arm circumference, BMI- body mass index, SGA- subjective global assessment, PG-SGA- patient generated SGA, MUST- malnutrition universal screening tool)	

Nutritional support is to be recommended in the following clinical scenarios-

- BMI less than 18.5 kg/m^2
- Unintentional loss of weight more than 10% over 3 to 6 months
- BMI less that 20 kg/m^2 with unintentional loss of weight over 3 to 6 months
- Minimal dietary intake for more than 5 days

• Increased nutrition requirements as a result of catabolism.

5.3 Systemic immunity profile during treatment

HNSCC is an aggressive tumor in nature, it induces the production of certain cytokines and growth factors that are involved in regulation of expression of genes that control tumor growth, cancer cell survival, and tumor chemo-sensitivity.[250] This dysregulation of the host inflammatory response is thought to be responsible for perpetuation of the malignant phenotype and the cause of significant immune-suppression.

In the present study, there was significant reduction in TLC counts, absolute neutrophil, and lymphocyte counts at the end of the treatment. But the mean %neutrophil count increased from 65.2% to 71.5% and mean %lymphocyte count reduced from 23.9% to 15.3%. The median NLR was 3 (2-4 IQR), 3(2-4.13 IQR) and 3(2-4 IQR) in the overall, N- and N+ cohorts pre-treatment; this increases to 5(3.8-8.4 IQR), 4.5(3.02-8.23 IQR) and 6.08(4.8-7.8 IQR) at the end of treatment in the respective cohorts. All p values were significant. When comparing patients having received either single or multi-modality treatment, the post-treatment NLR was same in the overall group, but significantly higher in patients with single modality treatment in the N+ cohort (8 versus 5.82, p=0.042). This could be explained by the fact that the patients with node positive advanced stage cancer underwent treatment with single modality palliative intent.

Bruixola et al. in their retrospective study included 145 HNSCC patients who were planned for multi-modality treatment with induction chemotherapy and thereafter CRT.[59] In this study 52.6% patients had an NLR <2.6 and 47.4%, NLR ≥2.6 at baseline. Agarwal et al. evaluated pre-treatment NLR in 189 Indian HNSCC patients and found the mean NLR in their patients population was 3.4±3.13 (SD).[201] This finding is similar to our study. Kuss et al. evaluated the pattern of the absolute counts and %lymphocyte subsets in peripheral blood samples of 146 patients and 54 controls.[251] Absolute counts and % of $CD3^+$, $CD4^+$,and $CD8^+$ T cell subsets were established using flow cytometry. They found that HNSCC patients had significantly reduced absolute $CD3^+$, $CD4^+$, and $CD8^+$ T cell counts as compared to the

normal controls, but there was no difference in the %T cell subsets in the two groups. Patients with active cancer had significantly lesser $CD3^+$ and $CD4^+$ T cell absolute counts as compared to recovered patients with no disease at time of sample collection. They also found that, neither the TNM stage nor the subsite of disease was associated with changes in the absolute T cell counts, and the lowest $CD4^+$ T cell absolute counts were found in patients with recurrent cancer. Discussion about systemic immunity is carried out in greater detail in further sections. NLR was used to assess systemic immunity after due discussion in the Departmental Research Committee meeting prior to submission of study protocol.

5.4 Association between nutrition and NLR

In a recent publication, Xu et al. had found cancer cachexia in 10/153 (6.54%) patients, the study group being with p16 negative SCC of unknown primary in head and neck.[146] They found that elevated NLR was significantly associated with the rate of cancer cachexia. The proportion of patients with cancer cachexia was 1.9%, 4.5%, and 18.2% in patients with NLR of 1.4-3.7, 3.7-6, and ≥6 respectively (p=0.008). In the present study, association between patients nutritional parameter's groups and NLR was tested using three methods, comparison of median NLR value, proportion of patients with NLR ≤3, >3 and ≤6, >6, and finally calculation of correlation coefficient.

In the present study, pre-treatment the median NLR was not different with variables like PS, weight, BMI. The median NLR was significantly higher in N+ cohort with pre-treatment weight loss of ≥10% (3.93 versus 2.79; p=0.024), low MUAC (5.55 versus 2.44; p=0.001) and high SGA score (4.3 versus 2; p=0.022). Post-treatment, the median NLR was significantly higher only with variable PS >2 (6.34 versus 4.67; p=0.004) in the overall group.

In the present study, there was significant association between PS of the patient and NLR in the overall and the N- cohort pre-treatment. No association was found between NLR and nutrition parameters like weight, % pre-treatment weight loss, MUAC or SGA score in the N- cohort pre-treatment (Table 4.19). But, a statistically significant association of NLR was noted with ≥10% versus <10% pre-treatment weight loss (NLR<3 in 44% versus75.8%

patients; p=0.015; RR= 2.478), low MUAC (NLR<3 in 30.8% versus73% patients; p=0.006; RR= -3.253) and ≥40 versus <40 SGA score (NLR<3 in 54% versus 83.8% patients; p=0.010; RR= 2.935) in the N+ cohort pre-treatment (Table4.20).

The linear correlation between NLR and various nutrition parameters was calculated using parametric Pearson's coefficient and non-parametric Spearman's coefficient. In pre-treatment, a mild to moderate correlation was discovered between all nutrition parameters and NLR in overall group, but no linear correlation was found in the N- cohort. In the N+ cohort there was mild to moderate but statistically significant linear correlation between PS, weight, % pre-treatment weight loss, MUAC, BMI, and SGA score.

Post-treatment, the NLR was found to be associated with only weight (p=0.018; RR=-2.689) in the N- cohort and PS (p=0.014; RR=1.911) in the N+ cohort. Similarly, significant correlation was found between weight and NLR in the N- cohort and PS and NLR in the N+ cohort.

The results from the present study suggest an association between the nutritional status and the systemic immunity marker NLR only in the patients with nodal metastasis but not in node negative HNSCC patients.

In cancer patients, systemic inflammation hampers utilization of nutrients and encourages catabolism, leading to breakdown of muscle. It has been noted that fortification of foods with even calorie or proteinfailed to decrease systemic inflammation. Certain recent nutrition strategies advocate considering fortification with ingredients that have anti-catabolic and inflammation reducing properties. Some studies had pointed out that ONS with high dose leucine or added essential amino acids may help in improving synthesis of muscle protein even when inflammation was present, although results were not completely consistent.[252,253] More research is required in this specific area to substantiate roles of addition of EAA and leucine to the nutrition in management of cancer patients.

Fish oil (contatining long-chain omega 3 fatty acids) has been recently suggested to have a role in the recovery of oral intake, appetite, lean body mass, and body weight in advanced cancer patients at malnutrition risk.[222] The mechanism by which fish oil downregulates cancer cachexia related systemic inflammation is under investigation. Results of an RCT in advanced colorectal cancer patients, who daily consumed 2 g of fish oil during theinitial 9 weeks of treatment with chemotherapy, demonstrated that the time to tumor progression was significantly more for patients consuming the fish oil.[254] Although further studies are required to corroborate the proposed improvements in clinical outcome, fish oil still shows potentialas an important part of the overall nutritional management in cancer patients.

Immune-modulatory agents like nucleotides and arginine are also under study as immune supporting components in an enteric feed formula in patients undergoing surgery or RT. When immune-modulatory enteric feeds were used in patients who were undergoing surgery for cancer, a positive trend towards enhanced immune response as well as reduced post-operative infections was seen in a study.[255] Another study in patients receiving RT also demonstrated an enhance in immune cell responses in the group receiving immune enhancing enteric therapy.[256]

5.5 Complications and failure to complete all planned treatment

The oral cavity is extremely susceptible to the direct and indirect harmful effects of chemotherapy and RT. In certain severe cases, treatment toxicities like oral mucositis may cause interruption in active oncological treatment; thus, having an adverse impact on the patient's prognosis.[257]

In the present study 23.6%, 23.3%, 23.9% developed Grade III complications in overall, N- and N+ cohorts respectively (p=1.000). Delay or interruption of treatment occurred in 6.2% and 4.9% patients respectively with no significant differences in N- or N+ cohorts. But default was observed to occur at a much higher rate in N+ cohort as compared to the N- cohort (18.2% versus 4.1%; p=0.006).

The intensity and dose of radiation and modality CRT were found to be linked to higher risk for admissions during HNSCC treatment. In a study, around 60% of HNSCC patients receiving CRT, 45% only RT were admitted for treatment related.[258] Paccagnella et al. also noted that oral health related adverse effects were usually a reason for patients' hospitalizations or unplanned visits to the emergency department during oncological treatment.[259] Givens et al. remarked that patients required an emergency medical care for adverse effects like dehydration, gastrointestinal upsets, and malnutrition related symptoms; and nearly 10% HNSCC patients receiving CRT were hospitalized for severe oral mucositis alone.[260]

In the present study we found that higher rates of Grade III complications were associated with subsite hypopharynx (p=0.010) and cT4 stage (p=0.015) in N- cohort only. No disease, patient, nutrition, or systemic immunity parameter was found to be significantly associated with severe treatment related toxicity.

There is clinical evidence to suggest that the duration and dose of RT correlates with cancer control and patient survival.[261,262] Inadvertent breaks in RT have associated with worse tumor control for the subsites like pharynx, larynx, and oral cavity.[263,264]

In the present study 13.04%, 4.1% and 20.5% patients in the overall, N- and N+ cohorts respectively failed to complete all planned treatment (p=0.002).When we looked for association between patients baseline, disease and treatment factors associated with failure to complete all planned treatment (*FailureTxCompletion)*, we found in N+ cohort single modality treatment was associated with higher rates of *FailureTxCompletion* as compared to multi-modality treatment (34.5% versus 13.56%; p=0.028; RR=3.35). This could be explained by the fact that N+ patients were planned for single modality treatment with a palliative intent only and had probably other medical and cancer related morbidities. Other parameters like age, gender, tumor subsite, cT stage, and PS were not found to be associated with *FailureTxCompletion.*

It was interesting to note that we found only poor nutritional status in N+ cohort and only raised NLR in N- cohort were associated with *FailureTxCompletion* (Table-4.27a,b). In N+ cohort the mean weight, mean BMI, median MUAC were significantly lower and median SGA scores significantly higher in patients who had *FailureTxCompletion*. In N- cohort the median pre-treatment NLR was significantly higher in patient with *FailureTxCompletion* (10 versus 3, p=0.045); 0%, 1.9%, and 25% patients with NLR ≤3, >3 and ≤6, and >6 had *FailureTxCompletion* (p=0.035) respectively.

ROC curves were plotted for numerical variables like pre-treatment BMI, % weight loss, SGA score, and NLR for cut-off points with high specificity to predict *FailureTxCompletion.* In the N+ cohort BMI cut-off ≤17 had a specificity of 92.9% (AUC 0.667; SE 0.078; 95%CI 0.514-0.819); pre-treatment % weight loss cut-off ≥10.5% specificity of 80%, ≥18% specificity of 91.4% (AUC 0.661; SE 0.083; 95%CI 0.499-0.823); SGA score cut-off ≥50.5 specificity of 81.4%, ≥56.5 specificity of 95.7% (AUC 0.695; SE 0.084; 95%CI 0.53-0.861). In the N- cohort, pre-treatment NLR cut-off ≥5.99 had specificity of 87%, ≥6.5 specificity of 91.3% (AUC 0.841; SE 0.114; 95%CI 0.616-1).

A large SEER based study aimed to find out factors associated with early discontinuation or interruption of treatment in HNSCC patients receiving RT.[265] They analyzed 5086 HNSCC patients above 65 years age; 39.5% patients were node negative and 60.5% node positive. Incomplete RT or interruption occurred in 39.8%, 45.9%, 28%, 56.8%, and 49.7% patients overall, with RT only, with surgery+ RT, with chemo+RT and with chemo+surgery+RT respectively in this study (much higher than the present study). Presence of N+ disease was associated with a reduction in the chances of completing the RT (finding similar to our study). Patients with pharyngeal, oral and laryngeal subsites, who received CRT, were found to have lesser chance of completing expected course of RT without interruptions. The authors attributed this reduced chance of completing RT to treatment related toxic effects of chemotherapy drugs (the common side effects were nausea, vomiting, neutropenia, mucositis, thrombocytopenia, anemia, and neuropathy). Rosenthal also noted that the toxic

effects of chemotherapeutic agents may result in patients taking prolonged breaks between or during treatments.[266]

Bertrand et al. demonstrated that 7 to 10 days of pre-operative nutrition showed significant benefit in post-operative QOL and 10% reduction in post-operative infections.[267] Van Bokhorst-de van der SM et al. found that patients having lost ≥10% of the ideal body weight were at raised risk for post-operative complications.[119]

A study published in 2012 evaluated the organizational efficiency, clinical outcomes and acceptability of dietitian led HNSCC clinic.[268] Two patient cohorts were studied and analyzed with a pre- and post-test design (98 patients before and 100 patients after the dietician led clinic was introduced). These 2 groups were contrasted for the frequency of any dietitian intervention, enteral feeding, weight loss, hospital admissions, and medical follow up needs after treatment. They found that nutrition management in a dietician led clinic was associated with reduction in nutrition related hospital admissions (12% to 4.5%;p=0.0029), un-planned NG tube insertions (75% to 39%;p=0.02), improvement in switch to oral diet post RT (68.3% to 76.7%;p=0.10) and reduction in review by radiation oncologist at 2 weeks post RT (32% to 15%;p=0.009). The authors concluded that dietician led clinic for HNSCC patients was associated with improvement in efficiency of nutrition management and offered a reasonable model of care.

Bossola in a narrative review defined the role of nutrition interventions in prevention and treatment of the malnutrition in HNSCC patients who were undergoing CRT, and also the impact of the nutrition interventions on toxicity related to CRT and patient survival.[269] Nutritional counseling and ONS could be used to enhance the dietary intake and to reduce the therapy associated loss of weight and interruption of RT. However, the author also noted that there seemed to be insufficient evidence to establish the optimal mode for enteral feeding. Prophylactic feeds through NG tube or PEG were commonly used to prevent loss of weight, reduce hospitalizations and dehydration, and reduce treatment interruptions. They also found that when comparing ‘reactive feeding’ to ‘prophylactic feeding’, there were no

benefits for nutritional outcomes, interruptions of RT, and survival. They concluded that further prospective RCTs were needed to identify better nutrition intervention in HNSCC patients undergoing CRT.

Zheng et al. noted in their review article that nutritional status of HNSCC patients was extremely important for the tolerance of RT and recovery.[270] Malnutrition could lead to low protein, anemia, reduced immunity and various other problems; and is a significant clinical factor that affects progression of tumor and overall treatment. They also noted that other recent studies had revealed early nutrition intervention could improve oral mucositis and the nutritional status of HNSCC patients.

Fesinmeyer et al. aimed to identify factors that were associated with early discontinuation or interruption of RT in HNSCC patients because they believed that interruption or early discontinuation of treatment increased risk for relapse of disease and poorly influenced the survival.[221] Using the SEER data base, they recognized 66 years or older Medicare beneficiaries diagnosed with HNSCC from the year 1997 to 2003. For each patient, they evaluated timing and the duration of RT using the Medicare claims data base. They carried out analyses with logistic regression to find out the association between clinical/tumor characteristics and the early interruptions and/or discontinuation of RT. The main outcome of this study was “completion of un-interrupted RT”. They found that a considerable proportion of patients had interruptions and/or incomplete RT (39.8% overall). Overall, 70.4% of patients who had undergone surgery completed RT without interruptions as compared to only 52% of patients with no prior surgery (p=0.001) for all tumor sites. They found the following factors to be associated with reduced chances of completing RT—presence of co-morbidity, CRT, and regional disease (node positive).

5.6 Nutrition factors associated with early PFS and OS

In the present study, patients were followed up for 6 months PFS and OS, with median follow up of 182 days (range 0 to 640), loss to follow-up was low (4.3% patients). The 6

months PFS was 63.98%, 76.7%, and 53.4% (p=0.000); 6 months OS was 85.1%, 91.8%, and 79.5% (p=0.009) in overall, N- and N+ cohorts respectively.

The following variables were found to be significantly associated with poor 6months PFS on multivariate analysis—cT3/4 v/s cT1/2 stage PFS 53.1% v/s 78.6% (HR 4.06; 95%CI 0.53-21.22; p=0.021); single v/s multi-modality treatment PFS 52.2% v/s 69.5% (HR 2.67; 95%CI 1.46-4.97; p=0.001); failure to complete planned treatment PFS 26.3% v/s 68.1% (HR 2.88; 95%CI 1.32-6.29; p=0.008); ≥40 pre-treatment SGA score PFS 52.1% v/s 72.6% (HR 1.83; 95% CI 1.08-3.09; p=0.025); pre-treatment NLR ≤3, >3≤6, >6 PFS 72.6%, 48.7%, 35.3% (HR 1.28; 95%CI 0.55-2.97; p=0.559) and post-treatment NLR ≤3, >3≤6, >6 PFS 72%, 71.7%, 50.8% (HR 2.54; 95%CI 1.3-4.92; p=0.006) (Figure 4.12).

In N- cohort, baseline factors like PS, age, gender, tumor subsite, grade and modality of treatment were not found to be associated with 6 month PFS. Factor associated with worse 6 months PFS were- cT3/4 versus cT1/2 stage (65.8% v/s 88%; RR=4.03; HR 3.24; 95%CI 1.05-9.9; p=0.040), low post-treatment weight (p=0.045), low post-treatment BMI (p=0.031), SGA score ≥40 versus <40 (70.69% v/s 100%; p=0.035), deranged post-treatment NLR >6 v/s >3 and ≤6 v/s ≤3 (55% v/s 89.66% v/s 75%; HR 4.76; 95%CI 1.29-17.5; p=0.019).

In N+ cohort, baseline factors like age, gender, tumor subsite, cT stage, and grade were not associated with 6 months PFS. The following factors were found to be associated with worse 6 months PFS- single versus multi-modality treatment (15.38% v/s 67.24%; RR=11.1; HR 3.53; 95%CI 1.8-6.85; p=0.000), failure to complete planned treatment (26.3% v/s 68.1%; RR=4; HR 2.1; 95%CI 0.97-4.52; P=0.008), ≥10% pre-treatment weight loss (33.33% v/s 58.33%; p=0.033; RR=0.033), low pre-treatment MUAC (15.39% v/s 57.75%; p=0.006; RR=0.113), pre-treatment SGA score ≥40 versus <40 (41.67% v/s 63.89%; p=0.050; RR=2.48), pre-treatment NLR ≤3, >3≤6, >6 (72.6%, 48.7%, 35.3%; HR 1.28; 95%CI 0.55-2.97; p=0.036), post-treatment low weight (p=0.037), low post-treatment MUAC (p=0.029) and high post-treatment SGA score (p=0.036).

A study published in 2015 reported treatment outcomes and factors predictive of rates of hospitalizations, treatment completion and OS in older patients with locally advanced HNSCC treated with CRT.[271] They analyzed 129 patients with a follow up of 27 months (range 1.7 to 125 months); the completion rate of CRT was 84%; at 4years the OS and DSS were 56%, and 75% respectively; hospitalization occurred in 36% patients. On multivariate analysis, a low PS and weight loss >5% were found to be predictive of death. PS and type of chemotherapy was predictive of treatment completion and hospitalizations.

Langius et al. studied 1340 HNSCC patients and found the 5 year OS to be 65%.[207] They found that gender was not associated with the OS, but alive patients were significantly younger 60.0±11.7 (SD) years versus 64.1±12.1 (SD) years ($p<0.001$); the mortality rate was higher in tumor subsites hypopharynx (70%), oral cavity (42%), and lowest in subsite larynx (26%)($p<0.001$); mortality was higher in patients with cT3/4 stage versus cT1/2 stage ($p<0.001$); mortality rate was higher with PS 2/3 versus 0/1 (62% v/s 24%; $p<0.001$).

In the present study, development of distant metastasis during first 6 weeks follow up occurred in 0 and 1.21%, 6 weeks to 3 months follow up in 1.39% and 1.33%, 3 to 6 months follow up in 1.47% and 3.03% patients in N- and N+ cohorts respectively (all differences statistically significant). Thus, distant metastases were seen to occur at a higher rate in node positive cohort as compared to the node negative cohort.

Various studies have noted the incidence for distant metastasis varied from 3 to 52% in HNSCC.[272,273] This vast range may be attributed mainly to the varied study populations and the study designs, along with the timing of diagnosis of distant metastasis. Some articles study distant metastasis at the time of initial diagnosis of primary tumor, whereas, some at follow-up after treatment completion and others were autopsy studies. Patients with distant metastasis usually receive treatment with palliative intent and sadly nearly 90% are dead within 12 months of diagnosis of distant metastasis.[274] Age was found to be predictive of distant metastasis in 3 studies, however one study concluded that patients with older age[275] and two studies concluded patients with younger age[276,277] to be a at higher risk for distant

metastasis.In a study with large cohort of nearly 2000 HNSCC patients, age <45 years was significantly associated with distant metastasis.[276]

A study published in 2021 aimed to evaluated factors like age and others for prediction of distant metastasis in patients with HNSCC. In this study, out of 1413 HNSCC patients, 9.3% developed distant metastasis. Most common sites for distant metastasis were lung (51.1%), bone (19.1%) and then liver (11.5%). On multivariable analysis it was identified that male gender (HR=1.95, 95%CI 1.23–3.10) hypopharynx subsite (HR=3.28, 95%CI 1.75–6.14), advanced Tstage (HR=1.61, 95%CI 1.09–2.38), poorly differentiated tumor (HR=2.49, 95%CI 1.07–5.78), nodal metastasis (HR=5.35, 95%CI 3.25–8.79) and the presence of extra-nodal extension of metastasis (HR=3.06, 95%CI 1.39–6.72) were independent risk factors for distant metastasis in this study; but there was no relation with age.[277]

A retrospective study analyzed 130 advanced stage, N+ HNSCC patients with palpable neck disease (N1to N3). They found that histological evidence of nodal metastasis, extra-nodal extension and ≥3 positive nodes were predictors for distant metastasis development.[278] In this study, other factors like gender, age, primary site, history of RT, tumor grade and perineural invasion were not found to be associated with a greater risk for distant metastasis. In yet another study, development of distant metastasis was not associated with age; but the T and N stage were found to be strongly associated.[273] Takes et al. also found that advanced tumor stage and poorly differentiated tumors were significant independent predictors of distant metastasis in HNSCC patients.[279] Many studies have noted that the subsite hypopharynx seemed to have the highest risk or distant metastasis.[275,276,280]

In the present study, factors associated with poor 6 month overall survival on multivariate analysis were cT3/4 v/s cT1/3 stage OS 77.1% v/s 96.4% (HR 2.47; 95%CI 1.16-5.23; p=0.018), single v/s multi-modality treatment OS 77.4% v/s 89.5% (HR 5.56; 95%CI 1.75-17.69; p=0.004; RR=2.48), failure to complete planned treatment OS 52.6% v/s 89.1% (HR 7.31, 95%CI 2.13-25.11; p=0.002; RR=7.35), pre-treatment SGA score≥40 OS 80.8% v/s

88.1% (HR 2.97; 95% CI 0.92-9.57; p=0.068), high post-treatment NLR ≤3, >3≤6, >6 OS 92%, 93%, 75% (HR 7.94; 95% CI 2.83-27.8; p=0.001).

In N- cohort, the following factors were associated with poor 6 month OS- cT3/4 stage, failure to complete planned treatment; post-treatment change in weight (median decrease 8.5 v/s 5 kg, p=0.043), high SGA (median score 57 v/s 48, p=0.044), change in SGA (median increase>9, p=0.049) and high NLR (mean 13.84 v/s 5.6, p=0.005). On multivariate analysis none of the factors reached statistical significance due to small number of events (only 6 events (8.2%)).

In N+ cohort, the following factors were associated with poor 6 month OS; single v/s multi-modality of treatment OS 53.9% v/s 89.7% (HR 17.47; 95%CI 2.63-116.03; p=0.003; RR=7.41), failure to complete planned treatment OS 56.3% v/s 83.8% (HR 6.16; 95%CI 1.14-33.4; p=0.035; RR=4.03); ≥10% pre-treatment weight loss (p=0.038; RR=3.4); pre-treatment PS≥3 (p=0.005; RR=7.75), high SGA score ≥40 OS 40.8 v/s 83.3 (HR 15.8; 95%CI 1.88-132.84; p=0.011; RR=1.67) and high NLR ≤3, >3, ≤6,>6 OS 87.5%, 68.4%, 44.4% (HR 5.15; 95%CI 1-27; p=0.050); post-treatment PS≥3 (p=0.051; RR=4.13) and high NLR ≤3, >3≤6,>6 OS 100%, 90.3%, 70.7% (HR 10.99; 95%CI 2.17-55.6; p=0.004). On multivariate analysis only cT3/4, single modality treatment, failure to complete planned treatment, pre-treatment PS≥3, high SGA, high NLR and post-treatment high NLR were found to be significantly associated with poor 6months OS.

Capuano et al. reported that for advanced stage (III/IV) HNSCC patients who were treated with multi-modality treatment, *pre-treatment weight loss* was the most important independent predictor for survival.[281] Nutritional deficits and malnutrition have been found to have a major negative impact on morbidity, mortality, and QOL.[205] In 2015 a study from Canada noted that, in patients with cancer who were weight stable and had a BMI ≥25 kg/m^2,the survival was longest; while, in patients with a high % weight loss and associated lower BMI, the survival was shortest.[206]

In published literature a critical weight loss of ≥5% during the treatment was found to be associated with poorer survival outcomes.[29,207] In this study the authors noted that 70% patients had no weight loss, 16% patients ≤5% weight loss, 9% patients <5–10% weight loss and 5% patients ≥10% weight loss. The 5 year OS rates for above groups being 71%, 59%, 47%, and 42% (p=0.001); and DSS rated being 86%, 86%, 81%, and 71%, respectively (p=0.001). After adjusting for the known confounders, ≥10% weight loss pre-treatment with RT remained to be significantly associated with poorer OS (HR1.7; 95% CI 1.2–2.5;p=0.002) and DSS (HR 2.1; 95% CI 1.2–3.5;p=0.007). In this study, 5 year OS and DSS rates in patients with critical loss of weight during the RT were significantly lower as compared to patient without critical loss of weight during the RT (62% and 82%, p=0.01 v/s 70% and 89%, p=0.001). This demonstrates the significance of optimal nutrition during treatment to reduce the weight loss. They also found highest mortality in patients having undergone CRT and least in patients having undergone surgery+CRT (43% v/s 23%, p=0.01). As a reflection of nodal burden, highest mortality was found in patients with bilateral nodal RT and least in patients with no nodal RT (43% v/s 21%, p<0.001).

A study from France noted that as compared to well nourished cancer patients the malnourished patients had higher requirement of antibiotic treatments (36% v/s 23%; p<0.0001) and significantly longer length of stay. The patients with severe malnutrition were at 4 times higher risk of 2 months mortality as compared to well nourished patients.[202]

Mick et al. studied a group of patients with advanced stage (III and IV) HNSCC treated with multi-modality treatment.[212] They found that the most important independent predictor for survival was pre-treatment weight loss. A study published in 2013, retrospectively evaluated the role of pre-treatment weight loss in locoregional failure in 140 patients HNSCC patients receiving CRT.[213] They found that the pre-treatment Ideal Body Weight Percentage (IBW%) was significantly different statistically in patients who had disease progression as compared to those with no progression of disease (p=0.02), yet was not a independent predictor for progression. Median pre-treatment IBW% was lower in the group with disease progression (101.5 v/s 118). In this study there was severe weight loss (~ 9 %) from baseline by the end

treatment in both the groups. The authors concluded that pre-treatment weight was a crude indicator of the nutrition status and may carry a prognostic value in HNSCC patients undergoing definitive CRT; insufficient nutritional status in the patients had been associated with poorer clinical outcomes and reduced QOL.

A meta-analysis in 2020 aimed to examine the effects of nutritional interventions, physical exercise and combining these during RT for HNSCC patients on the body composition, physical function and nutrition status.[282] Thirteen RCTs were identified and analysis included 858 HNSCC patients. They found statistically significantly positive effect of nutritional intervention and physical exercise but no effects observed in the studies when combined interventions were used.

Improvement in the nutritional status of patients has been linked to improvement in aspects of QOL.[283,284] A systematic review was performed to examine effect of nutrition interventions on the nutritional status, QOL and mortality in HNSCC patients receiving RT or CRT.[29] Effects of individualized diet counseling, in 4 out of 10 studies, demonstrated significant benefits in nutrition status and QOL as compared to no nutrition counseling or a general nutrition advice by nurse ($p<0.05$). There were 3 studies on ONS, but the results were not consistent about any effect of ONS on nutrition status as compared to no ONS. A study showed the beneficial effects of NG tube feeding on nutrition status as compared to ONS ($p<0.04$),one demonstrated the benefit of PEG feeding (as compared to NG tube feeding) on the nutrition status after RT ($p=0.001$). Importantly, 2 studies demonstrated that a prophylactic PEG feeding was *'not superior'* over tube feeding as and when required. They concluded that there were favorable effects of individualized diet counseling on the nutrition status and QOL as compared to no or standard counseling; the findings related to the effects of ONS and various tube feedings were still inconsistent.

The recent publications on early nutritional intervention (ENI) in HNSCC patients undergoing treatment are enumerated in Table 5.2. The major findings noted were significant reduction in % weight loss, decreased unplanned admissions, improved global QOL, decreased

interruptions/delays in treatment, reduction of drop in serum hemoglobin and albumin levels, significant reduction in Grade III toxicities related to the treatment and reduction in emergency visits.

Table 5.2 Recent publications on *Early Nutritional Intervention* for HNSCC patients undergoing treatment.

Publication	Year	Number		Rx	Outcome parameter			P value
		ENI	CG		Variable studied	ENI	Controls	
Piquet et al.[285]	2002	45	45	RT	Loss of weight	3.5±0.7%	6.1±0.7%	<0.01
					Unplanned admission	0%	18%	<0.01
Isenring et al.[283]	2004	29	31	RT	Loss of weight	0.4 kg	4.7 kg	<0.001
					Global QOL	favorable		0.009
Paccagnella et al.[259]	2010	33	33	CRT	Loss of weight	2.4±8.2%	9.6±8.1%	0.008
					CT/CRT break	30.3%	63.6%	0.007
					Days of delay in CRT	4.4±5.2	7.6±6.5	0.038
					Unplanned admission	16.1%	41.4%	0.03
Wang et al.[286]	2012	35	23	CRT	Loss of weight (kg)	5.64± 2.54	8.77± 1.61	<0.001
					Albumin change (g/L)	−4.79± 3.69	−7.1± 3.39	<0.001
					Hemoglobin loss (g/L)	−12.9± 19.8	-14.8 ± 24	<0.001
					Grade III oral mucositis	17.9%	50%	0.012
Meng et al.[287]	2019	46	32	CRT	CT/CRT break	10.9%	25%	0.017
					Days of delay in CRT	2.2±1.8	3.1±3.2	0.033
					Unplanned admission	13%	31.3%	0.009
					Grade III oral mucositis	13%	21.9%	0.028
Wei et al.[71]	2020	28	26	CT/ CRT	Loss of weight (kg)	5.64±2.54	8.77±1.61	<0.001
					Albumin change (g/L)	−4.79± 3.69	−7.1± 3.39	<0.001
					Hemoglobin loss (g/L)	−12.9± 19.8	-14.8± 24.5	<0.001
					Grade III oral mucositis	17.9%	50%	0.012
Kono et al.[288]	2020	32	61	CRT	Grade III oral	25%	70%	0.006

					mucositis			

(Rx- Treatment, ENI- Early Nutritional Intervention, RT- Radiotherapy, CT- Chemotherapy, CRT- Chemo-Radiotherapy, QOL- quality of life)

5.7 NLR cut-off to predict failure to complete planned treatment, early recurrence and death

In the present study, we found that pre-treatment NLR was not associated with treatment related Grade III complications, but was a significant predictor of failure to complete planned treatment in the node negative cohort and not in the node positive cohort. In the N- cohort, median pre-treatment NLR in patients who failed to complete versus who completed planned treatment was 10 v/s 3 (p=0.045); the failure to complete planned treatment rate in patients with ≤3, >3 to ≤6, >6 pre-treatment NLR was 0, 1.9% and 25% (p=0.035). On multivariate analysis we found that failure to complete planned treatment was a strong predictor of early disease progression and poor survival at 6 months.

A meta-analysis by Yu et al. evaluated the role of pre-treatment NLR from the peripheral blood sample in prognosis of HNSCC patients.[197] From the eligible cohort design studies 5475 patients were analyzed. The data on OS indicated increase in mortality risk in patients with high NLR (HR=1.84; 95%CI 1.53–2.23; p<0.001). On subgroup analysis of NLR cutoff values revealed a significantly increased mortality risk and shorter DFS in the patients with a high NLR as compared to patients with low NLR (HR=2.18; 95% CI1.46–3.24; p<0.001). The probability of recurrence was higher in patients with a high NLR (HR=1.63; 95%CI 1.09–2.45; p=0.017), probability of development of distant metastasis after treatment was also greater in patients with a high NLR (HR=1.92; 95%CI 1.36–2.72; p<0.001). They concluded that HNSCC patients that had an elevated pre-treatment NLR in the peripheral blood had worse prognosis and were prone to disease progression and even distant metastasis. Another meta-analysis by Takenaka et al. analyzed of 3770 HNSCC patients and concluded that a raised NLR predicted worse clinical outcomes.[48]

NLR values can be effortlessly obtained from the routinely collected peripheral blood samples and could be a predictor of prognosis in patients with HNSCC. In the present study,

the median pre- and post-treatment NLR were significantly higher in patients with disease progression at 6months versus patients with no disease progression (3.66 v/s 2.63, p=0.005 and 6.73 v/s 4.33, p=0.001 respectively), similar finding was noted in the N+ cohort and not in the N- cohort. The 6months PFS for patients with pre-treatment NLR ≤3, >3 to ≤6, >6 was 72.55%, 48.65%, 35.29% (p=0.001) respectively; post-treatment NLR≤3, >3 to ≤6, >6 was 72%, 71.67%, 50.82% (p=0.039) respectively. The median pre- and post-treatment NLR were also significantly higher in patients with mortality at 6 months (4 v/s 3, p=0.047 and 8.2 v/s 5, p=0.002 respectively), pre-treatment NLR was predictive for 6month OS only for the N+ cohort but post-treatment NLR for both N- and N+ cohorts. The 6month OS for patients with pre-treatment NLR ≤3, >3 to ≤6, >6 was 87.5%, 68.42%, 44.44% (p=0.007), respectively; post-treatment NLR≤3, >3 to ≤6, >6 was 92%, 93.33%, 75.41% (p=0.012), respectively

Various cut-offs have been used for NLR. Tables 5.3 a & b enumerate values used in different patient populations over the globe. The lowest and highest cut-off values were used in studies on Australian patients (NLR1.97 and 5.5).

Table 5.3a Various cut-off values of NLR used in geographically different patient populations of HNSCC (as studied in meta-analysis by Yalian Yu et al.[197])

Study	Ethnicity	Number of Patients	Outcomes Studied	Follow Up Duration months(range)	NLR Cut-Off Used
An et al.(2011)[289]	Asian	363	MFS,DSS	62 (2-91)	3.737
He et al.(2012)[290]	Asian	1410	PFS, OS	41 (2-60	2.747
Fang et al.(2013)[291]	Asian	226	DFS, OS		2.446
Perisanidis et al. (2013)[196]	Caucasian	97	DSS	>5 years or till death	1.97
Wong et al.(2016)[292]	Caucasian	140	DFS, OS	41 (2-103)	3.18
Li et al.(2015)[293]	Asian	363	DSS	14.7 (3.22-92.9)	2.818
Tu et al.(2015)[294]	Asian	141	DFS, OS	51 (5-102)	2.177
Song et al.(2015)[295]	Asian	146	OS	33.2 (2-128)	2.37
Salim et al.(2015)[296]	Caucasian	79	OS		2.936
Haddad et al. (2015)[198]	Caucasian	46	OS,RFS, FS	34 (13-47)	5.5
Rassouli et al. (2015)[297]	Caucasian	273	DFS	45 (42-48)	4.276
Selzer et al.(2015) [298]	Caucasian	318	OS		1.587
Sun et al.(2016) [299]	Asian	251	PFS, OS	50 (5-84)	2.68
Fu et al.(2016) [300]	Asian	420	CSS, OS		2.597
Nakahira et al.(2016) [301]	Asian	100	CSS	37.85 (4-92)	3.8
Charles et al.(2016) [302]	Caucasian	145	RFS, OS	29 (1.5-84)	5
Moon et al.(2016) [303]	Asian	153	RFS, OS	39.5 (4.7-62.6)	3.38
Rachidi et al.(2016) [304]	Caucasian	543	OS	64.4 (2-156)	4.398
Kim et al.(2017) [305]	Asian	104	PFS, OS	39 (4.8-82.5)	3
Arora et al. present study	Indian Asian	161	PFS, OS	6 (1-21)	≤3 >3≤6 >6
("OS-overall survival, PFS-progression-free survival, DFS-disease-free survival, DSS-disease-specific					

survival, MFS-metastasis-free survival, RFS-recurrence-free survival")

Table 5.3b Various cut-off values used for NLR and the Hazard ratio for Overall survival (as studied in meta-analysis by Yalian Yu et al.[197])

Study	Year	NLR cut-off for OS	HR	95%CI
He JR et al.[290]	2012	≥2.1<3	1.57	1.04-2.38
Fang HY et al. [291]	2013	≥2.1<3	2.04	1.04-4.02
Tu XP et al. [294]	2015	≥2.1<3	2.18	1.21-3.92
Song Y et al. [295]	2015	≥2.1<3	2.99	1.91-4.68
Salim DK et al. [296]	2015	≥2.1<3	1.03	0.55-1.94
Selzer E et al. [298]	2015	≥2.1<3	1.58	1.01-2.48
Wong BY et al. [292]	2016	≥3<4	2.01	0.71-5.67
Haddad CR et al. [198]	2015	≥4	1.95	0.42-8.96
Sun W et al.[299]	2016	≥2.1<3	1.87	0.89-3.94
Fu Y et al. [300]	2016	≥2.1<3	1.3	0.99-1.70
Moon H et al. [303]	2016	≥3<4	3.22	1.44-7.22
Kim DY et al. [305]	2017	≥3<4	1.52	0.93-2.48
Charles KA et al. [302]	2016	≥4	3.64	1.34-9.88
Rachidi S et al. [304]	2016	≥4	2.3	1.56-3.40
Arora et al.	**present study**	≤3 >3≤6 >6	5.15	1-27

(OS- overall survival, HR- hazard ratio, CI- confidence interval)

Yu et al. in their meta-analysis noted that with NLR cut-off 2.1 to <3 the HR for OS varied between 1.03 to 2.99; cut-off 3 to <4 HR varied between 1.52 to 3.22 and cut-off ≥4 HR varied from 1.95 to 3.64.[197]

ROC curves were plotted to get cut-off value with high specificity to predict disease progression at 6 months. In the overall group, the pre-treatment NLR cut-off ≥ 5.485 had a specificity of 92.9% (AUC 0.634; SE 0.048; 95%CI 0.54-0.729), in N- cohort cut-off ≥ 5.49 had specificity of 89.1% % (AUC 0.625; SE 0.084; 95%CI 0.459-0.79), in N+ cohort cut-off

≥4.160 had specificity of 93% (AUC 0.655; SE 0.062; 95%CI 0.535-0.776). The cut-off for post-treatment NLR were 10.4 (90.3% specificity), 10.04 (92% specificity) and 9.57 (90.7% specificity) in overall, N- and N+ cohorts respectively (Table 4.57, Figure 4.7).

For 6 months OS, in the overall group, pre-treatment NLR cut-off ≥6.08 had specificity of 91.7% (AUC 0.627; SE 0.071; 95%CI 0.487-0.766), in N- cohort cut-off ≥6.46 specificity of 89.4% (AUC 0.557; SE 0.146; 95%CI 0.27-0.844) and N+ cohort cut-off ≥4.39 specificity of 90.9% (AUC 0.660; SE 0.086; 95%CI 0.492-0.828). The cut-offs for post-treatment NLR were 11.04 (92.1% specificity), 11.04 (93.3% specificity) and 11.13 (91.9% specificity) in overall, N- and N+ cohorts respectively (Table 4.61, Figure 4.11).

Ding et al. noted that evidence suggested the early decrease in NLR was associated with favorable outcome and superior response rate, but a raise in NLR during the first weeks on treatment had the contradictory effect.[306]

Haddad et al. evaluated the role of pre-treatment NLR in 46 advanced HNSCC patients treated with CRT.[198] NLR was grouped as <5 v/s ≥5 above and below the median value. The primary end point was OS and secondary end points were loco-regional relapse free survival and metastasis free survival.Variables analyzed wereage, Eastern Cooperative Oncology Group performance status (0 v/s 1), gender, smoking (yes v/s no), Stage (III v/s IV), and NLR (<5 v/s ≥5 and <3.3 v/s ≥3.3). They found the median NLR to be 3.3 (IQR=0.4-22.8). At median follow up of 34 months (range 13 to 47 months), the 2-year OS, loco-regional relapse free and metastasis free survival for groups NLR <5 v/s ≥5 were 89% v/s 61% (p=0.017), 81% v/s 70% (p=0.17) and 84% v/s 64% (p=0.083) respectively. NLR ≥5 (p=0.025), ECOG 1 (p=0.025) and older age (p=0.01) were significantly associated with poor OS.

Agarwal et al. evaluated the role of pre-treatment PLR and NLR on OS in 189 Indian HNSCC patients.[201] The study population was as follows: mean age was 54.5±11.8 (SD) years, 42% underwent surgery + adjuvant CRT, remaining CRT, neo-adjuvant chemotherapy was given to 29.4% patients. Mean pre-treatment NLR was 3.4±3.13 (SD)

and PLR was 12.7±8.8 (SD). The cut-off using ROC analysis was 2.23 for NLR and 9.49 for PLR. Kaplan-Meir analysis on OS revealed significantly better survival (67.5% v/s 58%) in patients with <2.23 NLR compared to those with > 2.23 (p=0.02). Patients with <9.49 PLR were found to have a better OS (69% v/s 56%) compared to those with > 9.49 (p=0.005). Patients with a lower NLR also had better disease-free survival (44 v/s 33 months; p=0.03) and lower PLR also had better disease-free survival (44 v/s 33 months; p=0.004).

A systemic review and meta-analysis published in 2018 evaluated the role of pre-treatment NLR on OS in HNSCC patients.[199] Total of 24 articles that included 6479 patients, were analyzed. The combined HR for OS in patients with elevated NLR (range=2.04 to 5) was 1.78 (95%CI 1.53-2.07; p<0.0001). The HR for subsite specific cancer were as follows- oral cavity 1.56 (95%CI 1.23-1.98; p<0.001), nasopharynx 1.66 (95%CI 1.35-2.04; p<0.001), larynx 1.55 (95%CI 1.26-1.92; p<0.001) and hypopharynx 2.36 (95%CI 1.54-3.61; p<0.001). They concluded that elevated NLR was predictive of worse OS in HNSCC patients.

A systematic review and meta-analysis published in the same year evaluated the association between NLR and prognosis in HNSCC patients.[200] They used OS, DSS, DFS and PFS as the end points. For the quantitative analysis, 33 cohort studies with more than 10,072 patients were included. The pooled data showed that an elevated NLR was a significant predictor of poor OS and DSS. They concluded that elevated pre-treatment NLR was a significant prognostic marker HNSCC and also noted that NLR represented a straightforward and easily attainable marker which could be used to stratify patients into high-risk groups (Table5.4).

Table 5.4 Publications on association of NLR and clinical outcomes in HNSCC patients.

Study	Year	Study design	Number	NLR cut-off	Outcome measured	Findings(95%CI)	p value
Yu et al.[197]	2018	meta-analysis	5475	high NLR	OS	HR1.84(1.53-.23)	<0.001
					DFS	HR2.18(1.46-3.24)	<0.001
					Recurrence	HR1.63(1.09-2.45)	0.017
					Distant metastasis	HR1.92(1.36-2.72)	<0.001
Takenakaet al.[48]	2018	meta-analysis	3770	high NLR	worse clinical outcomes		
Ding et al.[306]	2019	cohort		early decrease in NLR	response favourable		
				increase in NLR	response unfavourable		
Haddad et al.[198]	2015	cohort	46	<5 v/s ≥5	2 year OS	89% v/s 61%	0.017
					relapse free survival	81% v/s 70%	0.17
					metastasis free survival	84% v/s 64%	0.083
Agarwal et al.[201]	2017	cohort	189	<2.23 v/s >2.23	OS	67.5% v/s 58%	0.02
Mascarella et al.[199]	2018	meta-analysis	6479	2.04 to 5	OS overall	HR1.78(1.53-2.07)	<0.001
					oral cavity	HR1.56(1.23-1.98)	<0.001
					nasopharynx	HR1.66(1.35-2.04)	<0.001
					larynx	HR1.55(1.26-1.92)	<0.001
					hypopharynx	HR2.36(1.54-3.61)	<0.001
Tham et al.[200]	2018	meta-analysis	10,072	high NLR	OS	poor	
					DSS	poor	
Study	**Yea**	**Study desig**	**Number**	**NLR cut-off**	**Outcome measured**	**Findings(95%CI)**	**p value**

	r	n						
Perisanidis et al.[196]	2013	cohort	97	>1.9	DSS		poor	
Bruixola et al.[59]	2018	cohort		≥2.6	OS		poor	
Arora et al. present study		cohort	161	pre-treatment NLR ≤3, >3≤6, >6in node negative cohort	failure to complete planned treatment	0, 1.9%, 25%		0.035
				pre-treatment NLR ≤3, >3≤6, >6	PFS	72.6%, 48.7%, 35.3%	HR 1.28 (0.55-2.97)	0.001
				post-treatment NLR ≤3, >3≤6, >6	PFS	72%, 71.7%, 50.8%	HR 2.54 (1.3-4.92)	0.039
				pre-treatment NLR ≤3, >3≤6, >6in node positive cohort	OS	87.5%, 68.4%, 44.4%	HR 5.15 (1-27)	0.007
				post-treatment NLR ≤3, >3≤6, >6	OS	92%, 93.3%, 75.4%	HR 7.94 (2.83-27.8)	0.012
(NLR-neutrophil/lymphocyte ratio, OS-overall survival, DFS-disease free survival, PFS-progression free survival, HR-hazard ratio)								

5.8 Low cost risk stratification model

The main prognostic and risk factors in HNSCC are stage, subsite and co-morbidities. In the past decade, high risk HPV has been recognized as a cause of and even a significant prognostic factor for patients with oropharynx cancer (better prognosis). Apart from the regular prognostic factors, nutritional status and systemic inflammation also play an important role in the prognosis of HNSCC. It has been noted the there still unmet need for improvement in predictive and prognostic factors in HNSCC at present.[59]

Various factors like tumor related, nutrition and treatment related may be predictors of malnutrition, making it important for the physicians to integrate above factors in the nutritional approach. It is important to note that despite the BMI at disease presentation, the unintentional pre-treatment weight loss of ≥10 % in the prior 6 months has been identified to be a significant factor leading to a range of problems including[309] –

- Increased infection risk

- Delay in wound healing
- Impaired cardiac and respiratory function
- Muscle weakness
- Poor QOL
- Depression
- Increase in risk for post-operative complications
- Reduction in response to RT and chemotherapy
- Increase in mortality rate

Xu et al. found in their study that both systemic inflammation and poor nutrition (≥6 NLR and cancer cachexia) were associated with a worse DSS (HR 2.54; p=0.01; and HR 2.12; p=0.001) in patients treated for unknown primarySCC head and neck.[146] Thus, there seems to be a need for a novel risk stratification model to predict disease outcomes in patients being treated for HNSCC.

Ye et al. aimed at building predictive nomogram models based on the pre-treatment hematological parameters and a risk stratified score system for HNSCC.[308] They used systemic inflammation indices (NLR, platelet count) and nutritional status index (serum albumin) to build the normogram. Total of 197 patients with hypopharyngeal, oropharyngeal and laryngeal cancers received multi-modality treatment between years 2012 and 2014 and were included in the analysis. A large number of patients were early stage (T1/2 - 60%, node negative - 53.6%) and larynx subsite (68%). They found that 5-year loco-regional recurrence was less for patients with the pre-treatment NLR<2.77 (p=0.004); 5-year loco-regional recurrence and cancer specific survival were reduced in patients with pre-treatment platelet count ≥248×109/L (p=0.031 and p=0.021). They used albumin, NLR and platelet counts to

build normograms to predict the 3 and 5 year loco-regional recurrence in patient subgroups likeT1/2 N-, T1/2 N+, T3/4 etc.

In the present study, we used factors significantly associated clinical outcomes (failure to complete planned treatment, 6months PFS and OS) to build novel low-cost risk stratification models and tested them on the study data for internal validation. The indices of strength of association like RR and HR and ROC cut-offs with high specificity were utilized to allocate points to each factor. Total score was calculated for each patient and they were stratified into low, medium and high risk for the clinical outcome in question (Tables 4.68, 4.70 and 4.72).

The factors used to in the risk stratification model to predict failure to complete planned treatment are –

- Pre-treatment weight in kg
- Pre-treatment BMI
- Pre-treatment % weight loss
- Pre-treatment MUAC in cm
- Presence of Bitot spots
- Pre-treatment SGA score
- Treatment modality (single or multiple)

Overall, 75%, 18% and only 6.8% patients were stratified as low, medium and high risk for failure to complete planned treatment. On internal validation using Chi-square test, 6.6% patients in low, 27.6% in medium and 45.5% in high risk group had failure to complete planned treatment(p=0.000). Similar findings were noted in the N+ cohort (10% patients in low, 35% in medium and 62.5% in high risk group had failure to complete planned treatment, p=0.001), but not in the N- cohort.

For the prediction of 6 months PFS, following factors were used for risk stratification model –

- Clinical T stage
- Modality of treatment
- Failure to complete planned treatment
- Pre-treatment NLR
- Post-treatment SGA score
- Post-treatment NLR

Using this novel model, overall, 45.2%, 45.9% and only 8.9% patients were stratified as low, medium and high risk for disease progressionrespectively. On internal validation using Chi-square test, 16.9% patients in low, 47.2% in medium and 85.7% in high risk group had disease progression(p=0.000) in the overall group. Similar findings were noted for both N- (10.5% patients in low, 33.3% in medium, and 60% in high risk group had disease progression, p=0.014), and N+ cohorts (24.2% patients in low, 57.1% in medium, and 100% in high risk group had disease progression, p=0.000).

For the prediction of 6 months OS, following factors were used for risk stratification model –

- Clinical T stage
- Modality of treatment
- Failure to complete planned treatment
- Pre-treatment ECOG PS
- Pre-treatment SGA score
- Pre-treatment NLR
- Post-treatment NLR

After applying this novel risk stratification model, overall, 57.3%, 30.6%, and only 12.1% patients were stratified as low, medium, and high risk for 6 months mortality respectively. On internal validation, 4.4% patients in low, 18.8% in medium, and 57.9% in high risk group had mortality (p=0.000). Similar findings were noted for the N+ cohort (5% patients in low, 20.7% in medium and 66.7% in high risk group had mortality, p=0.000), but not the N- cohort. The reason for non-significant findings in the N- cohort could be the low number of events 6/73 (8.3%) patients.

These novel low-cost risk stratification models need to be tested for external validity in geographically, ethnically and disease site wise different patient populations.