Chapter 7
The Impact of Nutrition on Patient Outcomes

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Introduction

Head and neck cancer patients, of which up to two-thirds are malnourished at the time of diagnosis [1], face unique challenges that can directly affect their outcomes. Physicians tend to overestimate malnutrition and underestimate weight loss in the oncology patient population while patients routinely underestimate the degree of their own malnutrition [2].

Many patients are not psychologically prepared for the effect of treatments on oral intake [3]. Patients interviewed while undergoing treatment for head and neck cancer routinely consider taking an oral diet to be "a full time job" and "a struggle," often longing "to eat real food" [3]. Many patients view feeding tubes as personal failures and can be subject to widely differing opinions by providers, further complicating their view on this treatment modality [3].

The etiology of malnutrition is frequently multifactorial in head and neck cancer patients. Due to tumor location, tissue loss as a result of surgery, and side effects from adjuvant therapies, mechanical swallowing may be difficult. In addition to dysphagia, patients may experience odynophagia, trismus, globus sensation, and frank aspiration [1]. Poor dentition or tumor bulk may limit mastication. Diet may be constrained by these physical issues but also impacted by alcohol and tobacco

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intake. Over half of patients with head and neck cancer experience depression during treatments, which may further impact nutrition [4].

Malnutrition can be defined as a "subacute or chronic state of nutrition, in which a combination of varying degrees of overnutrition or undernutrition and inflammatory activity have led to a change in body composition and diminished function" [5]. Development of malnutrition has several adverse physical and psychosocial effects including impaired immune response, impaired wound healing, reduced functional status leading to inactivity and inability to work, reduced strength of respiratory muscles, electrolyte disturbances, depression, loss of libido, and poor self-image. In the clinical setting, there are three etiology-based diagnoses for malnutrition and their definitions are based on the presence or absence of inflammatory response. "Starvation-related malnutrition" is defined as chronic starvation without inflammation as seen in anorexia nervosa. "Chronic disease-related malnutrition" refers to chronic inflammation of mild to moderate degree as seen in pancreatic cancer, sarcopenic obesity, and organ failure. "Acute-disease or injury-related malnutrition" refers to disease or injury states with a marked inflammatory response as seen in burns, trauma, and major infection.

Validated Tests for Malnutrition

The exact prevalence of malnutrition in oncology patients is difficult to assess due to lack of standards for nutrition screening in oncology patients as well as lack of consensus on the validity of these screening tools. However, it is estimated that greater than half of cancer patients experience weight loss at diagnosis. Oncology patients are at risk for malnutrition not only due to the disease process itself but also because of consequences of treatment. It is further estimated that as many as 57% of head and neck cancer patients experience significant weight loss before initiating treatment while between 75% and 80% of patients will experience further weight loss once treatment begins [6].

In order to support a diagnosis of malnutrition, The Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition (ASPEN) have developed clinical characteristics based on energy intake, interpretation of weight loss, body fat loss, muscle mass wasting, fluid accumulation/edema, and reduced grip strength. A minimum of two of these six proposed characteristics must be present to support diagnosis of non-severe (moderate) or severe protein-calorie malnutrition [7].

Malnutrition in the context of acute illness or injury is diagnosed by less than 75% of estimated energy requirement for greater than 7 days (moderate malnutrition) and less than 50% of estimated energy requirement for greater than or equal to 5 days (severe malnutrition). In the context of chronic illness, moderate and severe malnutrition may be diagnosed by less than 75% of estimated energy requirement for greater than or equal to 1 month. Clinicians may estimate energy needs and compare them to estimates of recent intake by obtaining a detailed nutrition history

via assessment methods such as food diaries, food frequency questionnaires, and 24-hour dietary recalls. Inadequate intake may then be reported as percentage of estimated energy and protein needs over a defined time period.

Weight change and percent weight loss from baseline are also important indicators of malnutrition. Moderate acute illness or injury-related malnutrition may be diagnosed by percent weight loss of 1–2% in 1 week, 5% in 1 month, and 7.5% in 3 months while severe acute illness or injury-related malnutrition may be diagnosed by greater than 2% weight loss in 1 week, greater than 5% weight loss in 1 month, and greater than 7.5% weight loss in 3 months. In the context of chronic illness, moderate protein-calorie malnutrition may be diagnosed as follows: 5% weight loss in 1 month, 7.5% weight loss in 3 months, 10% weight loss in 6 months, and 20% weight loss in 1 year. Severe chronic illness-related malnutrition is defined as greater than 5% weight loss in 1 month, greater than 7.5% weight loss in 3 months, greater than 10% weight loss in 6 months, and greater than 20% weight loss in 1 year.

A nutrition-focused physical exam will aid in the assessment of moderate to severe subcutaneous fat loss as well as muscle loss. Exam results coupled with percent weight change or reported reduced energy intake may together support a malnutrition diagnosis. Common areas for assessment of fat loss are the orbital region: a hollow look around the eyes characterized by prominent depressions and loose skin may be indicative of the significant fat loss seen in severe protein-calorie malnutrition as compared to the slightly bulged under-eye fat pads one may find in a well-nourished individual. The upper arm region (i.e., triceps and biceps) and the thoracic and lumbar regions (ribs, lower back) are other common exam areas for assessment of fat loss. To assess muscle loss, the temporalis muscle, clavicle region (i.e., pectoralis major, deltoid, trapezius muscles), and anterior thigh soft tissues (quadriceps muscles) are commonly examined. Examples indicative of severe protein-calorie malnutrition may include protruding, prominent clavicles as well as a square appearance of the shoulder to arm joint (deltoid wasting) [8] (Fig. 7.1).

Both the prevalence of malnutrition in oncology patients and the current discrepancies in diagnosis justify the need for validated nutrition assessment and screening tools in clinical practice. Increased use of these screening tools may facilitate diagnosis and result in a more proactive approach in treatment of malnutrition where patients are captured earlier in cancer treatment course when they are only at risk for its development, and nutritional interventions have more significant results (i.e., pre-cachexia). As implied by its name, the scored Patient-Generated Subjective Global Assessment questionnaire (PG-SGA) uses information generated directly by the patient to create an additive score based on prognostic indicators (weight loss, functional status, and nutrition impact symptoms that restrict intake) that define the degree of malnutrition. This further generates a nutritional triage recommendation based on results. The tool's additive score allows for rapid and systematic risk assessment, and repeated assessments/changes in score throughout treatment course allow for continued measure of the effects of nutrition interventions. This makes the PG-SGA a multiuse instrument in that it serves as a nutrition screening tool, assessment tool, interventional triage, and an instrument to measure success of interventions

Fig. 7.1 (**a**) Malnourished appearance, supraclavicular wasting, and prominent clavicle due to high tumor burden in patient with squamous cell carcinoma of the neck. (**b**) Severe malnutrition evidenced by muscle and skin atrophy in right arm/forearm
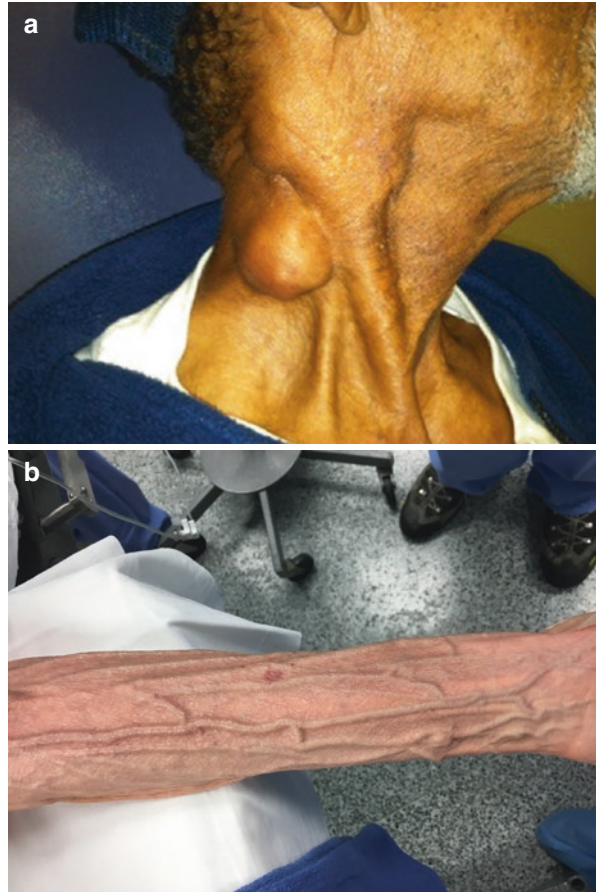
(Fig. 7.2). It has been applied in a variety of clinical settings for catabolic conditions beside oncology; examples include AIDS patients, geriatric patients, lung transplant patients, and dialysis patients. The Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics has accepted the PG-SGA as the standard for nutrition assessment in the oncology population. Other advantages associated with use of the PG-SGA include involvement of both patient and clinician and its reliance on readily available data. It does not rely on laboratory tests, making it an inexpensive tool.

The first portion of the questionnaire is to be completed by the patient while the second half is completed by the clinician (i.e., doctor, nurse, dietitian, therapist). The four boxes on the first page of the screening tool are organized into the following categories: Weight, Food Intake, Symptoms, and Activities and Function. The fact that the patient independently completes these portions saves clinician time while emphasis on patient involvement empowers him/her to identify the root causes of nutritional issues. Box 1 – Weight History and Box 3 – Symptoms have

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

History: Boxes 1 - 4 are designed to be completed by the patient.
[Boxes 1-4 are referred to as the PG-SGA Short Form (SF)]

Patient Identification Information

1. Weight (See Worksheet 1)

In summary of my current and recent weight:

I currently weigh about _____ pounds
I am about _____ feet _____ inches tall

One month ago I weighed about _____ pounds
Six months ago I weighed about _____ pounds

During the past two weeks my weight has:

☐ decreased (1) ☐ not changed (0) ☐ increased (0)

Box 1 ☐

2. Food intake: As compared to my normal intake, I would rate my food intake during the past month as

☐ unchanged (0)
☐ more than usual (0)
☐ less than usual (1)

I am now taking

☐ normal food but less than normal amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritional supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0) Box 2 ☐

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply)

☐ no problems eating (0)
☐ no appetite, just did not feel like eating (3)
☐ nausea (1)
☐ constipation (1)
☐ mouth sores (2)
☐ things taste funny or have no taste (1)
☐ problems swallowing (2)
☐ pain; where? (3) _____
☐ other (1)**
**Examples: depression, money, or dental problems

☐ vomiting (3)
☐ diarrhea (3)
☐ dry mouth (1)
☐ smells bother me (1)
☐ feel full quickly (1)
☐ fatigue (1)

Box 3 ☐

4. Activities and Function:
Over the past month, I would generally rate my activity as:

☐ normal with no limitations (0)
☐ not my normal self, but able to be up and about with fairly normal activities (1)
☐ not feeling up to most things, but in bed or chair less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3)
☐ pretty much bed ridden, rarely out of bed (3)

Box 4 ☐

The remainder of this form is to be completed by your doctor, nurse, dietitian, or therapist. Thank you.

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Additive Score of Boxes 1-4 ☐ A

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Additive Score of Boxes 1-4 (See Side 1) ☐ A

Worksheet 1 – Scoring Weight Loss
To determine score, use 1-month weight data if available. Use 6-month data only if there is no 1-month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point score in Box 1 of PG-SGA.

Weight loss in 1 month	Points	Weight loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10- 19.9%
3-4.9%	2	6- 9.9%
2-2.9%	1	2- 5.9%
0-1.9%	0	0- 1.9%

Numerical score from Worksheet 1 ☐

5. Worksheet 2 – Disease and its relation to nutritional requirements:
Score is derived by adding 1 point for each of the following conditions:

☐ Cancer
☐ AIDS
☐ Pulmonary or cardiac cachexia
☐ Chronic renal insufficiency
☐ Presence of decubitus, open wound or fistula
☐ Presence of trauma
☐ Age greater than 65

Other relevant diagnoses (specify) _____
Primary disease staging (circle if known or appropriate) I II III IV Other _____

Numerical score from Worksheet 2 ☐ B

6. Worksheet 3 – Metabolic Demand
Score for metabolic stress is determined by a number of variables known to increase protein & caloric needs. Note: Score fever intensity or duration, whichever is greater. The score is additive so that a patient who has a fever of 38.8 °C (3 points) for < 72 hrs (1 point) and who is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points.

Stress	none (0)	low (1)	moderate (2)	high (3)
Fever	no fever	> 99 and < 101	≥ 101 and < 102	≥ 102 °F
Fever duration	no fever	< 72 hours	72 hours	> 72 hours
Corticosteroids	no corticosteroids	low dose (< 10 mg prednisone equivalents/day)	moderate dose (≥ 10 and < 30 mg prednisone equivalents/day)	high dose (≥ 30 mg prednisone equivalents/day)

Numerical score from Worksheet 3 ☐ C

7. Worksheet 4 – Physical Exam
Exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle, & fluid. Since this is subjective, each aspect of the exam is rated for degree. Muscle deficit/loss impacts point score more than fat deficit/loss. Definition of categories: 0 = no abnormality, 1+ = mild, 2+ = moderate, 3+ = severe. Rating in these categories is not additive but are used to clinically assess the degree of deficit (or presence of excess fluid).

Muscle Status					
temples (temporalis muscle)	0	1+	2+	3+	
clavicles (pectoralis & deltoids)	0	1+	2+	3+	
shoulders (deltoids)	0	1+	2+	3+	
interosseous muscles	0	1+	2+	3+	
scapula (latissimus dorsi, trapezius, deltoids)	0	1+	2+	3+	
thigh (quadriceps)	0	1+	2+	3+	
calf (gastrocnemius)	0	1+	2+	3+	
Global muscle status rating	0	1+	2+	3+	

Fat Stores
orbital fat pads 0 1+ 2+ 3+
triceps skin fold 0 1+ 2+ 3+
fat overlying lower ribs 0 1+ 2+ 3+
Global fat deficit rating 0 1+ 2+ 3+

Fluid status
ankle edema 0 1+ 2+ 3+
sacral edema 0 1+ 2+ 3+
ascites 0 1+ 2+ 3+
Global fluid status rating 0 1+ 2+ 3+

Point score for the physical exam is determined by the overall subjective rating of the total body deficit.
No deficit score = 0 points
Mild deficit score = 1 point
Moderate deficit score = 2 points
Severe deficit score = 3 points
Again, muscle deficit/loss takes precedence over fat loss or fluid excess.

Numerical Score for Worksheet 4 ☐ D

Total PG-SGA Score (Total numerical score of A+B+C+D)

Clinician Signature _____ RD RN PA MD DO Other _____ Date _____

Global PG-SGA Category Rating (Stage A, Stage B or Stage C)

Worksheet 5 – PG-SGA Global Assessment Categories

Category	Stage A Well-nourished	Stage B Moderate/suspected malnutrition	Stage C Severely malnourished
Weight	No weight loss OR recent non-fluid wt gain	Moderate (≤5% in 1 month (≥10% in 6 months) OR Progressive weight loss	Severe (>5% in 1 month (>10% in 6 months) OR Progressive weight loss
Nutrient Intake	No deficit OR Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms (NIS)	No deficit OR significant recent improvement allowing adequate intake	Presence of NIS (Box 3 of PG-SGA)	Presence of NIS (Box 3 of PG-SGA)
Functioning	No deficit OR Significant recent improvement	Moderate functional deficit OR Recent deterioration	Severe functional deficit OR Recent significant deterioration
Physical Exam	No deficit OR chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of muscle mass &/or muscle tone on palpation &/or loss of SQ fat	Obvious signs of malnutrition (e.g., severe loss muscle, fat, possible edema)

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage). First line nutrition intervention includes optimal symptom management.

Triage based on PG-SGA point score
0-1 No intervention required at this time. Re-assessment on routine and regular basis during treatment.
2-3 Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and lab values as appropriate.
4-8 Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms (Box 2).
≥ 9 Indicates a critical need for improved symptom management and/or nutrient intervention options.

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Fig. 7.2 Patient-Generated Subjective Global Assessment questionnaire (PG-SGA)

additive scores whereas Box 2 – Food Intake and Box 4 – Activities and Function are not additive; the highest point score should be used.

The professional component includes sections covering diagnosis, age, metabolic stress, and physical exam. It also includes a section for scoring of weight loss. Pertinent components of metabolic stress known to either increase energy/protein needs or negatively affect muscle mass and functional status include fever, sepsis, and corticosteroid use. The physical exam component includes subjective assessment of patient fat, muscle, and fluid status and evaluation of degree of deficit with 0 being indicative of no deficit, 1+ indicative of mild deficit, 2+ indicative of moderate deficit, and 3+ indicative of severe deficit.

The Global Assessment, total numerical score, and nutritional triage recommendations follow. The Global Assessment is divided into a grading system where A = well nourished, B = moderately malnourished or suspected malnutrition, and C = severely malnourished. The numerical score is used for development of nutritional triage recommendation. This point score is based on all data gathered from patient to clinician portion of the assessment tool. A score greater than 9 indicates critical need for improved management of nutrition-related symptoms including pharmacologic intervention, nutrition education, and/or nutritional intervention in the form of nutritional supplements or enteral/parenteral intervention. The numerical PG-SGA score and PG-SGA category score are related but serve as independent triage systems. The numerical score provides specific guidelines called Nutritional Triage Recommendations that indicate the level of medical nutrition therapy needed whereas the categorical assessment with A, B, or C rating allows the clinician to have a clear overall picture of the patient's status. Recent data have shown that the PG-SGA has the potential to predict clinical outcomes, including survival rates, postoperative complications, quality of life, and length of stay. Moreover, a recent review demonstrated that the PG-SGA as well as the PG-SGA Short Form (Boxes 1 through 4) encompasses all domains in the current conceptual definitions of malnutrition as proposed by ASPEN (American Society for Parenteral and Enteral Nutrition) and ESPEN (European Society for Clinical Nutrition and Metabolism) [9].

The PG-SGA is available in multiple languages including Portuguese, Danish, Dutch, English, German, Italian, Norwegian, and Thai. The need remains for greater number of high-quality PG-SGA translations as this allows for capture of a wider patient population as well as for international benchmarking [9]. The PG-SGA shows great promise for use in clinical settings, especially in multidisciplinary outpatient clinics where various staff members can be involved in tool distribution and collection of data.

The malnutrition screening tool (MST) is another item used to screen and identify patients who are at risk for malnutrition. It can be used for adults in both the inpatient and outpatient setting, and the two parameters used for nutritional screening are weight loss and reduced appetite. It is a very simple tool to use in that a cutoff score of only two or higher is needed to determine that an individual is at risk, and this score is based off of two questions.

The tool's first prompt asks patients if they have recently lost weight without trying. Answer no is equal to zero points whereas answer unsure or yes is equal to

two points. This first question further prompts patients to provide information on the extent of weight loss, that is, greater amount of weight loss is equivalent to a higher point score (0–4 for recent weight loss). Two to 13 pounds is classified as one point, 14–23 pounds is equal to two points, 24–33 pounds equals three points, and 34 pounds or greater represents a maximum of four points. If a patient is unsure exactly how much weight they have lost, this is also a possible answer equal to two points. The final weight loss score is additive based on both the initial question and its prompt.

The second prompt asks if the patient has been eating poorly due to decreased appetite with answer options no and yes and a score of zero to one, respectively. Once this process is complete, the weight loss and appetite scores are added to generate a final MST score that determines risk. A score of zero or one is categorized as not at risk, "eating well with little to no weight loss." An MST score ≥2 is consistent with an at-risk patient, "eating poorly and/or recent weight loss." Recommendation based on this result is formal nutrition assessment and implementation of pertinent nutrition interventions within 24–72 hours depending on the risk. The MST is to be completed within 24 hours of admission and again weekly during same admission. Medical staff, nursing staff, and dietetics staff may all provide and complete the screening tool for patients. Current practices suggest that nursing staff may complete this form as part of an admission personal health history questionnaire, thereby triggering tasks for dietitians who will receive nutrition assessment referrals for any patient with a score of 2 or greater.

As previously mentioned, the malnutrition screening tool's low cutoff score allows for the capture of a large patient pool, reducing the likelihood that malnourished patients are overlooked early in their admission or treatment course. The short format of this screening tool also makes it more realistic for use as a routine inpatient screening tool when compared to the PG-SGA. The fact that it does not require calculations potentially increases compliance of nursing staff with screening practices. A recent study comparing assessment of nutritional status of PG-SGA to the MST at The Royal Marsden Hospital found that the MST had a sensitivity of 66% and a specificity of 83% [10]. However, this tool has been shown to have better sensitivity in the outpatient oncology setting for patients undergoing both radiation and chemotherapy. It was also found to have good sensitivity in older adult residential settings [10].

A possible drawback of this large patient pool and low cutoff score is that dietitians may receive referrals for the wrong reasons despite a fair specificity percentage of 83% (normally nourished patients referred). Patients may misunderstand and respond positively to questions of recent weight loss even though this weight loss may have been purposeful, decreasing available clinician time for those patients who truly do fall into high-risk categories. Moreover, the MSTs short format does not allow for specification between degrees of malnutrition. A score of 2 or higher simply identifies a patient at risk for malnutrition, but further assessment is needed to determine whether the patient is moderately or severely malnourished. The MST could potentially be used to determine which patients require a more extensive nutrition assessment while a form such as the PG-SGA would be appropriate to generate more specific information for treatment [10].

Additional tools that have been utilized for assessment of malnutrition include the Onodera's prognostic nutritional index (O-PNI), which has been shown to predict adverse events associated with radiation therapy in head and neck cancer patients [11].

Functional Testing

An assessment of overall functional status has been shown to serve as a marker of malnutrition in addition to the other factors discussed earlier. Lower handgrip strength as measured by the handgrip dynamometer has been shown to correlate with higher PG-SGA scores (indicating malnutrition) in adult head and neck and lung cancer patients.

Bioelectrical impedance analysis is a newer method of assessing body composition [12]. It can be used to assess changes in fat and lean mass as well as fluid shifts experienced by patients, particularly in states of acute illness including the perioperative period as well as those brought on by malignancy and during its treatments. This has been well established in the evaluation of GI, lung, and urological cancers and has now been established as an effective tool in the nutritional assessment of head and neck cancer patients. This modality measures body parameters such as resistance, reactance, and fat-free mass index by recording a voltage change in the applied current to soft tissues. While this method does require specialized equipment, it has been shown to document the impact of malnutrition on survival in the head and neck patient population.

Biomarkers

Biomarkers at all stages of treatment have been popularized recently because they represent an objective indicator for diagnosis, prediction, and response to treatment. Changes in objective predictors of malnutrition such as prealbumin and albumin have not been associated with more frequent adverse events in patients with head and neck cancer undergoing nonsurgical therapy with radiation [11]. Conversely, preoperative hypoalbuminemia (i.e., <3.5 mg/DL) was independently associated with reduced 5-year overall survival, disease-specific survival, and disease-free survival in patients undergoing surgery for head and neck cancer [13]. In one study the risk of poor outcomes was sixfold higher than in patients with normal preoperative albumin [14]. Patients with postoperative complications have a lower preoperative albumin on average than those who do not experience complications [15]. In a study of 233 patients with Stage 3 or 4 head and neck cancer undergoing surgery with free flap reconstruction, postoperative hypoalbuminemia (i.e., <3.5 mg/DL) was independently associated with higher risk of postoperative wound infection [13, 16]. In

addition, hypoalbuminemia 2 months after treatment was associated with reduced overall survival, disease-specific survival, and disease-free survival [14].

Micronutrients may impact outcomes as well as studies show that many head and neck cancer patients are deficient [17]. Vitamin D deficiency and insufficiency is common in head and neck cancer patients [18]. Low vitamin D level is associated with increased risk of head and neck cancer, specifically laryngeal and hypopharyngeal subsites, in smokers, and increased rate of recurrence in all patients [19, 20]. In a study of patients undergoing radiation with or without chemotherapy, low vitamin D levels lost twice as much muscle mass than patients with normal levels during treatment [18]. Pre-treatment Vitamin D insufficiency also correlates well with incidence of mucositis [18].

Underlying inflammation that contributes to poor outcomes can be identified in the pre- and perioperative setting with other laboratory studies. In a study of 100 patients undergoing free flap reconstruction for head and neck cancer, postoperative pro-calcitonin, C-reactive protein (CRP), and leukocyte count did not predict poor flap perfusion in the perioperative setting [21]. However, other studies have looked at preoperative CRP and demonstrated a higher risk of complications. Specifically, a preoperative CRP greater than 10 mg/L was associated with greater risk for postoperative complications (odds ratio = 2.01) and was an independent predictor of complications on multivariate regression [15].

CRP and albumin can be combined to calculate a modified Glasgow Prognostic Score (mGPS) [22]. High CRP (>1 mg/dL) and low albumin (<3.5 g/dL) are each a point for a score of 2. High CRP without hypoalbuminemia is a score of 1. Normal CRP and albumin are a score of 0. Patients with an mGPS of 1 or 2 had significantly worse disease-free and overall survival compared to patients with a score of 0 in patients with stage III or IV head and neck cancer [22]. This finding was consistent when even more stringent parameters were used to measure elevated CPR (CPR > 0.3 mg/dL) [23]. mGPS correlated more with 5-year outcomes than tumor or node classification, site, age, or sex [22]. The hazard ratio for high mGPS was 2.4 compared to tumor (T) classification of 1.58 for overall 5-year survival [22]. In patients undergoing concurrent chemoradiation for head and neck cancer, an mGPS of 1 or 2 experienced significantly worse recurrence-free and overall survival compared to patients with an mGPS of 0 with median follow-up time of 39 months [24].

Enteral Nutrition in Head and Neck Cancer Patients

Enteral nutrition (EN) is a method of feeding that utilizes the gastrointestinal tract to deliver energy and nutrients in a manner which bypasses the oral cavity. Tube feeding refers to liquid food mixture known as formula that delivers macronutrients (protein, carbohydrate, and fats), micronutrients (vitamins and minerals), and free water through a feeding tube into either the stomach or small intestine. A patient may need a feeding tube for several different reasons which result in an inability to

maintain volitional intake. Surgery, inability to eat by mouth due to trauma to the head/neck, altered mentation, dysphagia due to stroke, significantly decreased appetite, or respiratory failure that requires mechanical ventilation via endotracheal tube all result in such a scenario. The major advantage of EN over parenteral nutrition is that is maintains the functional integrity of the GI tract. Therefore, candidates for EN support include individuals with functional GI tract whose disease makes oral intake inadequate, impossible, or unsafe due to risk of aspiration. For individuals who cannot maintain volitional intake and who do not have a functional GI tract (i.e., short bowel syndrome, bowel obstruction, intractable vomiting or diarrhea, GI fistula), parenteral nutrition (PN) is used as it bypasses the normal digestive process. PN is intravenous administration of nutrition including protein, carbohydrates, fats, vitamins, minerals, and electrolytes. Compared to EN, it does not preserve the gut's functional integrity, it is more expensive, and is associated with greater infectious complications.

According to the 2002 "Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients," nutrition support should be initiated in patients with inadequate oral intake for a time period of 7–14 days or in patients where inadequate oral intake is expected for 7–14 days [25]. EN is also indicated in the malnourished patient who is expected to be unable to eat for greater than 5–7 days. In the critically ill patient population, early enteral feeding is recommended; this is defined as initiation within 24–48 hours of ICU admission [26]. Early EN in this patient population is associated with more rapid weaning from mechanical ventilation, improved wound healing, decreased length of stay, and reduced complications overall [26]. ASPEN guidelines state that the previously mentioned clinical benefits from EN are derived through achievement of 50–65% of calorie goal during the first week of hospital admission. Although a universal definition for effective delivery of EN has not been established, it is reasonable to define this as an infusion of >90% estimated energy needs [27].

The choice of route of enteral access is based on several different factors including disease, gastrointestinal function, and estimated duration of nutrition support. Options for short-term placement (<4 weeks) include feeding tube placement through the nose or mouth into the stomach or post-pyloric placement into the small bowel (nasogastric tube, orogastric tube, nasoenteric tube). Nasogastric tubes are less invasive but are only used if the estimated time frame of need is <1 month as these feeding tubes are smaller in diameter and more likely to malfunction. They are also susceptible to accidental displacement.

When nutritional support is estimated to last for a period of greater than 4–6 weeks, gastrostomy, gastrojejunostomy, or jejunostomy feeding tubes are utilized. There are also several delivery methods for enteral nutrition that are appropriate for a variety of clinical situations. Tube feeds may be administered either via continuous or cyclical infusion, intermittent drip, or bolus method. Disease status and comorbidities, location of feeding tube tip, and expected tolerance are all factors to consider when determining best delivery method for a patient. Location of care will also play a role in determining delivery method (i.e., critical care unit,

ambulatory patient in home setting, etc.). A single method or a combination of methods may be employed.

Continuous infusion via pump (also known as around-the-clock) is the preferred delivery method for patients who are critically ill, intubated, at risk for developing refeeding syndrome, are being fed through a jejunostomy tube (due to lack of stomach reservoir capacity), or those who are unable to tolerate larger formula volumes as seen with bolus or intermittent gravity drip. Cyclic feeding is similar to continuous infusion in that feedings are provided via a pump, but this is delivered in less than a 24-hour period. They are often used at night, for example, for an 8–12 hour timeframe, to provide supplemental nutrition while a patient is asleep.

Intermittent feedings can either be delivered via pump or gravity drip; in this method of feeding enteral nutrition is administered over a period of 20–60 minutes every 3–6 hours. Bolus or gravity drip feedings are similar to meals; they provide a set formula volume at specific time intervals (i.e., three times a day) throughout the day. They are frequently delivered over a short time period (i.e., 240 mL formula administered over a 10 minute period three to six times a day). The advantages of the bolus delivery method are many: they are more physiologic, they are less expensive as no pump is required, and they allow for greater mobility [28]. Outpatients often prefer this modality for home, and it is important to establish tolerance to this feeding method prior to discharge when possible [28].

Estimating Nutritional Needs

When estimating nutritional needs for patients on EN, many factors are considered such as extent of surgery, disease stage, presence of comorbidities, age, gender, and level of physical activity. General guidelines for "normal" weight patients estimate 25–30 calories per kilogram actual body weight per day and 1.0–1.5 g pro/kg [29]. The needs of a hypermetabolic or malnourished patient, as seen in high tumor burden or poor oral intake, may increase up to 30–35 calories per kilogram per day and 1.5–2.5 g pro/kg/day [29]. The severely malnourished patient at risk of refeeding syndrome generally receives supplementation at 15 calories per kilogram with gradual advancement to full-calorie goal over the following days of hospital admission.

Adjustments to EN may be appropriate over the treatment course. In the setting of poor wound healing, lack of expected weight gain, or unintentional weight loss, EN needs may be re-estimated and increased. While the enteral formula chosen will depend on the factors previously mentioned, standard polymeric formulas of 1.5 calories per milliliter are generally well-tolerated and frequently used. In the postoperative setting, extensive resections may require specialized higher protein formulas for wound healing or standard formulas with high protein modulars (protein powder or liquid protein supplements). Patients with very high calorie needs or those with complaints of early satiety or GI fullness may use 2 calories per milliliter formula for high calorie provision with less volume.

Perioperative Nutrition

Preoperative nutrition recommendations state that patients with severe nutritional risk should receive appropriate nutrition support for at least 10 days before surgery for improved outcomes even if this means delay of surgery [30].

Weight loss greater than 10% before surgery is associated with increased complications [12]. The peri- and postoperative period represents a critical time period for intervention to improve outcomes. Early postoperative tube feeding defined as within 24 hours is indicated for patients whose surgical excisions make them unable to resume early oral nutrition. High-dose protein and energy provision (30–35 calories per kilogram body weight) are generally appropriate for this population save for special cases such as reduced renal function, etc. The ESPEN Guidelines on Nutrition in Cancer Patients state that optimal nitrogen supply ranges for repletion, and postoperative wound healing ranges between a minimum of 1 g pro/kg of body weight and a target range of 1.2–2.0 g/kg/day to induce protein anabolism. Recommendations for patients with acute or chronic renal failure state that protein provision should not go higher than 1.0–1.2 g pro/kg/day.

Immunonutrition

Immunonutrition is defined as the potential to modulate the activity of the immune system by interventions with specific nutrients. In this practice, specific nutrient compositions are utilized to modify body inflammatory and immune responses. It is of most interest in the context of critically ill and surgical patients as both of these patient populations tend to have suppressed immune systems and need alternate means of nutrition support through EN or PN. Many enteral nutrition formulas already are made with some combination of these potentially immune-modulating ingredients.

Head and neck cancer patients often are malnourished at the time of diagnosis, and the postoperative period tends to be followed by a period of immunocompromise and immune suppression that results in increased risk of morbidity and mortality. Surgery induces catabolic stress to the body, which stimulates inflammation, depletes nutrient reserves, and thereby impairs the body's normal immune response, increasing the risk for complications after surgery. The rationale of immunonutrition is that using dietary compounds associated with improved immune function during this time frame will reduce negative surgical outcomes such as infection and poor wound healing. Immune-enhanced enteral nutrition formulas that provide basic macronutrients and micronutrients also contain amino acids arginine and glutamine, lipids, that is, omega-3-fatty acids, vitamin E, prebiotics and probiotics, and ribonucleic acids.

At this time, there are no strong evidence-based recommendations or formulas for enteral based immunonutrition [31]. This is attributed to the high degree of

variation in ingredients and concentrations by current manufacturers, thereby making it difficult to isolate which of the ingredients mentioned is responsible for the improved immune status and surgical recovery; it is likely that not one single ingredient is responsible but rather the synergistic effect of more than one. The amino acid arginine is a precursor to polyamines and proline, which play important roles in tissue regeneration and wound healing. Omega 3 fatty acids have been associated with attenuation of the inflammatory response.

Strategies and products to deploy immunonutrition remain in their nascent stages without long-term data. The main approach for preoperative nutrition optimization remains the use of standard oral supplements such as Ensure® or Boost®. The standard oral supplements tend to be more accessible for patients due to lower price point and improved taste, thereby resulting in higher rates of compliance among patients. Recent review of the literature found no statistical differences from the standard oral supplement to the immunonutrition supplements. Other studies have shown a trend towards shorter hospital stay and lower infection rates with the use of preoperative immunonutrition. Further research with a larger series must be conducted to clarify better guidelines and recommendations for optimal preoperative nutrition paradigms.

Other Factors That Contribute to Malnutrition in Head and Neck Cancer Patients

Chemoradiation (CRT) in the treatment of head and neck cancers has known adverse side effects that drastically disturb the patient's nutritional status [32]. Nausea, mucositis, dysphagia, dysgeusia, xerostomia, and thickened saliva are common side effects seen during and after treatment that affect the functional ability to swallow and limit the patient's desire to eat [29]. Over half of the patients were unable to maintain sufficient oral intake during treatment and required enteral feedings. Even for the patients maintaining nutrition completely by mouth, many required supportive care with meals including special preparation or consistency precautions [33].

Mucositis in head and neck cancer patients receiving CRT occurs most often in the oral cavity and/or the pharynx. The Common Terminology Criteria for Adverse Events (CTCAE version 4) rates mucositis from grade 1 with mild symptoms and minimal pain related to inflammation to grade 5 or death. A large percentage of patients will experience some degree of mucositis during treatment. Even grade 1 or 2 can be debilitating to obtaining proper nutrition, especially when compounded with any of the other common side effects. Grade 3 mucositis, which is defined as inflammation and ulceration leading to severe pain interfering with oral intake, is reported to occur in 21–80% of patients [33]. During the seventh and final week of CRT, over half of the patients with oral or pharyngeal mucositis need supportive care with meals through speech pathology or enteral feeding. Of note, patients with T3 or T4 tumors have four times the incidence of grade 3 mucositis than those with T2 tumors [33].

These toxicities typically manifest around week 2 of CRT and peak at week 7, the final week of treatment. Less than a quarter of patients tolerated a full diet by mouth at week 7 [33]. Functional improvement gradually occurs following the final week of treatment. However, over 75% of patients report experiencing dysgeusia 12 weeks post-treatment. A third of these patients have an altered diet secondary to dysgeusia [33]. Dysgeusia is the abnormal taste of food, which can be affected by decreased smell (CTCAE v4). Patients complain of altered taste, unpleasant tastes, or even a loss of taste. The impact of this toxicity on nutrition is profound. Over 95% of head and neck cancer patients receiving CRT experience diet-altering dysgeusia [33]. Symptoms last long after treatment is over, affecting nutrition months following chemoradiation.

Taste can be affected by saliva production because chemical signals cannot reach receptors [34]. Taste and smell can be impacted by smoking, older age, and medications, particularly cyclophosphamide, folic acid antagonists, methotrexate, and platinum agents [34]. Up to 70% of patients with cancer have alterations in taste and smell [34]. The University of Pennsylvania Smell Identification Test can be used to objectively detect smell [34]. Physicians underestimate taste and smell changes in patients undergoing oncologic treatment [34]. Patients frequently describe smell alterations as "rancid" and taste alterations as "bitter, chemical, and nauseating" [34]. Increased or decreased taste and smell sensation are associated with certain chemotherapies and radiation treatments as little as 15–30 Gy and can lead to food aversion [34].

Prophylactic PEG Tube Placement

Patients with head and neck cancer often require tube feeding due to issues with maintenance of oral intake. Treatment modalities including chemotherapy, radiation, and surgery often exacerbate these issues with side effects including dysphagia, mucositis, stomatitis, nausea, and altered taste. The establishment of a steady source of nutrition that bypasses the oral cavity helps improve functional and nutritional status as well as patient tolerance to treatment. Head and neck cancer patients generally have normal GI function and are candidates for EN.

Prophylactic PEG tube placement prior to initiation of chemotherapy or radiation is likely to lead to reduced incidence of protein-calorie malnutrition [35]. PEG or other gastrostomy tubes are most often used in this population, and post-pyloric feeding tubes are usually only employed in the case of intolerance to gastric feeds. A number of factors have been associated with need for enteral nutrition during radiation treatment including nodal disease, bilateral neck radiation, age, and regional or free flap reconstruction [36].

Caution must be exercised when utilizing EN during treatment to avoid enteral dependence without active effort of swallowing. Patients who are non-compliant with speech and swallow rehabilitation exercises or those with advanced-stage disease are at particular risk as avoidance of activation of the

pharyngeal constrictors can worsen atrophy and scarring and lead to a higher likelihood of long-term feeding tube dependence [29]. Furthermore, esophageal stricture may contribute to dysphagia and PEG tube reliance for years after treatment is finished [29].

Cachexia

Cachexia is a multisystem condition primarily characterized by loss of skeletal muscle mass that may not improve with nutritional support that affects 30% of patients with head and neck cancer at the time of treatment [37]. Cancer cachexia is associated with poorer outcomes, poorer response to treatment, and poor quality of life after diagnosis in head and neck cancer patients [38]. A consensus group defined cancer cachexia as >5% weight loss over 6 months, or >2% weight loss and either body mass index (BMI) <20 kg/m^2 or evidence of sarcopenia [39]. As such it remains a clinical diagnosis; however, certain tests can provide an indication as to whether a patient is cachectic.

A cardinal feature of cancer cachexia is muscle wasting. Decreased skeletal muscle fiber size and protein expression in animals with cancer cachexia compared to those without cancer cachexia has been consistently demonstrated [40–42]. Skeletal muscle index can quantify presence of muscle wasting in patients with cancer based on calculations previously described on abdominal computed tomography (CT) imaging of the lumbar spine area [37, 43, 44].

Underlying systemic inflammation is another marker of cancer cachexia. Elevated inflammatory markers in tissue in mice have been demonstrated with cancer cachexia [45]. However, systemic inflammation has not been studied extensively in patients with head and neck cancer and cancer cachexia compared to those without cancer cachexia. However, a recent study demonstrated that the Glasgow Prognostic Score, calculated from albumin and C-reactive protein, correlated with outcomes in head and neck cancer patients with cachexia [22]. In addition, a particular genotype (TNF-α −1031 T/C) associated with the TNF-alpha cytokine may be more frequently found in patients with cachexia [46].

Several treatments are currently undergoing testing in clinical trials, but currently there are no drugs approved for the treatment of cachexia by the Federal Drug Administration [47].

References

  1. Alshadwi A, et al. Nutritional considerations for head and neck cancer patients: a review of the literature. J Oral Maxillofac Surg. 2013;71(11):1853–60.
  2. Gyan E, et al. Malnutrition in patients with cancer: comparison of perceptions by patients, relatives, and physicians-results of the NutriCancer2012 study. JPEN J Parenter Enteral Nutr. 2018;42(1):255–60.

3. Alberda C, et al. Nutrition care in patients with head and neck or esophageal cancer: the patient perspective. Nutr Clin Pract. 2017;32(5):664–74.
4. Buchmann L, et al. Psychosocial distress is prevalent in head and neck cancer patients. Laryngoscope. 2013;123(6):1424–9.
5. Soeters PB, Schols AM. Advances in understanding and assessing malnutrition. Curr Opin Clin Nutr Metab Care. 2009;12(5):487–94.
6. Lees J. Incidence of weight loss in head and neck cancer patients on commencing radiotherapy treatment at a regional oncology centre. Eur J Cancer Care (Engl). 1999;8(3):133–6.
7. White JV, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). J Acad Nutr Diet. 2012;112(5):730–8.
8. Huhmann MB, August DA. Review of American Society for Parenteral and Enteral Nutrition (ASPEN) clinical guidelines for nutrition support in cancer patients: nutrition screening and assessment. Nutr Clin Pract. 2008;23(2):182–8.
9. Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: role of the Patient-Generated Subjective Global Assessment. Curr Opin Clin Nutr Metab Care. 2017;20(5):322–9.
10. Shaw C, et al. Comparison of a novel, simple nutrition screening tool for adult oncology inpatients and the Malnutrition Screening Tool (MST) against the Patient-Generated Subjective Global Assessment (PG-SGA). Support Care Cancer. 2015;23(1):47–54.
11. Kono T, et al. Pre-therapeutic nutritional assessment for predicting severe adverse events in patients with head and neck cancer treated by radiotherapy. Clin Nutr. 2017;36(6):1681–5.
12. van Bokhorst-de van der Schueren MA, et al. Assessment of malnutrition parameters in head and neck cancer and their relation to postoperative complications. Head Neck. 1997;19(5):419–25.
13. Tsai MH, et al. Clinical impact of albumin in advanced head and neck cancer patients with free flap reconstruction-a retrospective study. PeerJ. 2018;6:e4490.
14. Lim WS, et al. Pretreatment albumin level predicts survival in head and neck squamous cell carcinoma. Laryngoscope. 2017;127(12):E437–42.
15. McMahon JD, et al. Postoperative complications after major head and neck surgery with free flap repair--prevalence, patterns, and determinants: a prospective cohort study. Br J Oral Maxillofac Surg. 2013;51(8):689–95.
16. Danan D, et al. Prognostic value of albumin in patients with head and neck cancer. Laryngoscope. 2016;126(7):1567–71.
17. Nejatinamini S, et al. Head and neck cancer patients do not meet recommended intakes of micronutrients without consuming fortified products. Nutr Cancer. 2018;70(3):474–82.
18. Nejatinamini S, et al. Poor vitamin status is associated with skeletal muscle loss and mucositis in head and neck cancer patients. Nutrients. 2018;10(9):E1236.
19. Fanidi A, et al. Circulating vitamin D in relation to cancer incidence and survival of the head and neck and oesophagus in the EPIC cohort. Sci Rep. 2016;6:36017.
20. Yokosawa EB, et al. Vitamin D intake and survival and recurrence in head and neck cancer patients. Laryngoscope. 2018;128(11):E371–6.
21. Koerdt S, et al. Perioperative serum levels of procalcitonin, C-reactive protein, and leukocytes in head and neck free flaps. Int J Oral Maxillofac Surg. 2017;46(6):699–705.
22. Nakayama M, Tabuchi K, Hara A. Clinical utility of the modified Glasgow prognostic score in patients with advanced head and neck cancer. Head Neck. 2015;37(12):1745–9.
23. Hanai N, et al. The high-sensitivity modified Glasgow prognostic score is superior to the modified Glasgow prognostic score as a prognostic predictor for head and neck cancer. Oncotarget. 2018;9(97):37008–16.
24. Chang PH, et al. Glasgow prognostic score after concurrent chemoradiotherapy is a prognostic factor in advanced head and neck cancer. Chin J Cancer Res. 2017;29(3):172–8.
25. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr. 2002;26(1 Suppl):1SA–138SA.

26. Seron-Arbeloa C, et al. Enteral nutrition in critical care. J Clin Med Res. 2013;5(1):1–11.
27. Alberda C, et al. Energy requirements in critically ill patients: how close are our estimates? Nutr Clin Pract. 2002;17(1):38–42.
28. Martin K, Gardner G. Home enteral nutrition: updates, trends, and challenges. Nutr Clin Pract. 2017;32(6):712–21.
29. O'Neill JP, Shaha AR. Nutrition management of patients with malignancies of the head and neck. Surg Clin North Am. 2011;91(3):631–9.
30. Bertrand PC, et al. Preoperative nutritional support at home in head and neck cancer patients: from nutritional benefits to the prevention of the alcohol withdrawal syndrome. Curr Opin Clin Nutr Metab Care. 2002;5(4):435–40.
31. Talwar B, et al. Nutritional management in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130(S2):S32–40.
32. Arribas L, et al. Nutritional changes in patients with locally advanced head and neck cancer during treatment. Oral Oncol. 2017;71:67–74.
33. Moroney LB, et al. Helical intensity-modulated radiotherapy with concurrent chemotherapy for oropharyngeal squamous cell carcinoma: a prospective investigation of acute swallowing and toxicity patterns. Head Neck. 2018;40(9):1955–66.
34. Spotten LE, et al. Subjective and objective taste and smell changes in cancer. Ann Oncol. 2017;28(5):969–84.
35. Beaver ME, et al. Predictors of weight loss during radiation therapy. Otolaryngol Head Neck Surg. 2001;125(6):645–8.
36. van der Linden NC, et al. Indicators for enteral nutrition use and prophylactic percutaneous endoscopic gastrostomy placement in patients with head and neck cancer undergoing chemo-radiotherapy. Nutr Clin Pract. 2017;32(2):225–32.
37. Couch ME, et al. Cancer cachexia update in head and neck cancer: definitions and diagnostic features. Head Neck. 2015;37(4):594–604.
38. Kwon M, et al. Prevalence and clinical significance of cancer cachexia based on time from treatment in advanced-stage head and neck squamous cell carcinoma. Head Neck. 2017;39(4):716–23.
39. Fearon K, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489–95.
40. Barreto R, et al. Cancer and chemotherapy contribute to muscle loss by activating common signaling pathways. Front Physiol. 2016;7:472.
41. Bonetto A, et al. Differential bone loss in mouse models of colon cancer cachexia. Front Physiol. 2016;7:679.
42. Pin F, et al. Growth of ovarian cancer xenografts causes loss of muscle and bone mass: a new model for the study of cancer cachexia. J Cachexia Sarcopenia Muscle. 2018;9(4):685–700.
43. Chamchod S, et al. Quantitative body mass characterization before and after head and neck cancer radiotherapy: a challenge of height-weight formulae using computed tomography measurement. Oral Oncol. 2016;61:62–9.
44. Mourtzakis M, et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997–1006.
45. Tsoli M, et al. Depletion of white adipose tissue in cancer cachexia syndrome is associated with inflammatory signaling and disrupted circadian regulation. PLoS One. 2014;9(3):e92966.
46. Powrozek T, et al. Relationship between TNF-alpha -1031T/C gene polymorphism, plasma level of TNF-alpha, and risk of cachexia in head and neck cancer patients. J Cancer Res Clin Oncol. 2018;144(8):1423–34.
47. Couch ME, et al. Cancer cachexia update in head and neck cancer: pathophysiology and treatment. Head Neck. 2015;37(7):1057–72.