

Nutritional support in oral cancer patients: An updated review

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التغذية مشكلة منتشرة عند مرضى سرطان الفم، الذين يعانون من كبت المناعة أيضاً. هذان الأمران لهما أهمية للمريض وللطبيب الممارس، بسبب تأثيرهما على نوعية الحياة والتكهن بعاقبة المرض. ومن هنا يجب على كافة مرضى سرطان الفم الخضوع إلى تقييم والفهم الغذائي من قبل مختص قبل إجراء أي معالجة. هناك دليل قوي على أهمية البدء بالدعم الغذائي الباطني قبل المعالجة إلى أن يتمكن المريض من تحصيل المتطلبات الغذائية اللازمة عن طريق الفم بعد المعالجة. تهتم البحوث الحالية بموضوع التغذية المناعية مثل غلوتامين، أرجينين، W-3 أحماض دهنية متعددة غير مشبعة وبعض العناصر النادرة. أفضل طريقة لإعطاء الدعم الغذائي هو عن طريق الإطعام الباطني غالباً بواسطة أنبوب موضوع في ثقب المعدة بواسطة المنظار الجلدي.

Malnutrition is a common problem in oral cancer patients who also suffer from immunosuppression. These sequelae are significant to patients and their clinicians since they affect the quality of life of the patient and the prognosis of the disease. Therefore, oral cancer patients who will undergo surgery should have proper preoperative assessment of their nutritional status. There is strong evidence on the benefit of commencing enteral nutritional support preoperatively until patients can meet their nutritional requirements unaided postoperatively via the oral route. Currently, there is research interest on the role of immunonutrients like glutamine, arginine and polyunsaturated fatty acids, trace elements in decreasing morbidity and improving the outcome of treatment in oral cancer patients. The best route of providing nutritional support is by enteral feeding mostly via percutaneous endoscopic gastrostomy tube.

Introduction

Oral cancer is recognised globally as one of the ten commonest forms of malignant diseases. Although its incidence varies greatly around the world, it is known to account for almost 3% of all cancers in the western world. Squamous cell carcinoma accounts for about 90% of oral malignancies and tobacco smoking is recognised as the most important aetiological factor.¹ Despite recent advances in the management of oral cancer, the five-year survival rate of patients remains relatively unchanged at around 50%.²

About half of all cancer patients experience cachexia - a body wasting syndrome.^{3,4} Oral cancer per se and its treatment modalities directly affect the function of the upper part of the digestive tract, therefore hindering normal food intake. This could explain why weight loss is more profound in oral cancer patients compared to other cancer patients. Malnutrition associated with malignancy has a substantial prognostic value; it reduces survival rate and increases postoperative morbidity including delayed wound healing, break down of wounds and postoperative infections.^{5,7}

Malnutrition in Oral Cancer Patients

Malnutrition is more prevalent in patients with cancer of the proximal gastrointestinal tract⁸ and there are reports that malnutrition is present in 30-

59% of head and neck cancer patients at the time of diagnosis.^{5,9-12} Significant malnutrition eventually leads to severe wasting (cachexia) which accounts for 30-50% of deaths in patients with gastrointestinal tract cancers.⁴ Cachexia is a complex syndrome characterised by progressive tissue depletion and decreased nutrient intake. It is manifested clinically by anorexia and inexorable weight loss. It cannot be explained by decreased nutrient intake and increased resting energy expenditure only. Dysfunctional metabolic activities, hormonal and cytokine-related abnormalities, seem to play a significant role.¹³ Factors like circulatory tumour-produced catabolic factors in concert with certain cytokines like, tumour necrosis factor- α (TNF- α), interleukin-6 (IL-6) and interferon- γ (INF- γ) are known to produce lipolysis and increased protein degradation.^{3,14} Malnutrition from oral cancer could therefore be due to several factors:

- Impairment of nutritional intake due to pain, dysphagia, tongue tethering and the tumour itself causing poorly fitting dentures which in turn affects the ability to masticate.
- Radical surgery compromises oral function, mastication and swallowing. In addition, postoperative complications such as infection, oro-cutaneous fistula and wound dehiscence can further restrict oral feed.¹⁵

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- Radiotherapy has short-term and long-term undesirable effects on the olfactory and secretory functions, the digestive tract and the mucous membranes. Chemotherapy causes mucositis, induces nausea, vomiting, anorexia and/or diarrhoea. These local and systemic effects can lead to nutritional impairment.^{8,6}

Importance of Nutritional Support

Nutritional support is indicated for patients who cannot have adequate nutrition by diet alone. Nutritional support for a malnourished patient:

- Encourages growth, tissue healing and maturation of collagen.⁵
- Enhances T-cell function and immunity by improving macrophage and polymorph mobility, and power to neutralize ingested bacteria. In severe malnutrition, patients develop lymphopenia.¹⁷
- Restores muscle bulk and function, preventing any compromise in ventilatory function which could otherwise lead to atelectasis and bronchopneumonia as a result of mucous retention.¹⁸
- Maintains by enteral feed, gut mucosal integrity, preventing a possible gram-negative bacterial sepsis.¹⁹

Nutritional Assessment

All oral cancer patients should be assessed preoperatively by a dedicated dietician with regards to nutritional status and this should be an integral part of the multidisciplinary team approach in managing such patients. The following are some sources of information used to assess nutritional status:

- History: Premorbid weight, recent loss of weight, loss of appetite, ability to swallow and ability to have three meals a day. Weight loss of 10% or more of the usual body weight in less than 6 months is an indication for nutritional support and a significant parameter to establish the prognostic value of malnutrition in head and neck cancer patients.²⁰
- Assessment of food intake including the calculation of the calorie-nitrogen ratio consumed using dietary recall and dietary record.¹⁵

- Examination: Measurement of the current height and weight (compared to the population's norms for age and sex), muscle wasting or weakness and peripheral or dependent oedema. Measurement of skin fold thickness or midarm muscle circumference can be added to the examination.
- Weight Index (WI): Measured as the actual weight (kg) divided by the reference weight for height, a WI <0.80 is considered to indicate malnutrition.²¹
- Body Mass Index (BMI): Calculated as the body weight (kg) divided by the square of the height in meters, normal values are ≥ 20 .
- Dynamometry: Dynamometer is a device used to measure hand grip strength of the non-dominant arm. It is a useful, non-invasive indicator of skeletal muscle mass and a predictor of postoperative complications.²²
- Biochemistry tests: Risk factors combining several parameters including albumin, prealbumin, transferrin and retinol binding protein measurements are a useful biological markers for malnutrition.^{8,23}

Nutritional Requirements

Patients with upper gastrointestinal tract cancer frequently suffer from protein-calorie malnutrition for the reasons mentioned previously. In addition, postoperatively patients are usually hypermetabolic as a result of normal neuroendocrinological response to injury which redistributes endogenous macronutrients, causing further depletion of body fat stores and lean body mass.^{24 25} Total energy expenditure is the sum of resting energy expenditure, energy needed to maintain body temperature and energy expenditure based on the individuals level of activity or in case of malnourished patients the energy required to replenish the depleted store. The average energy requirement for a normal healthy adult is 25 kcal/kg/day, this figure could go as high as 35 kcal/kg/day for a catabolic patient. Therefore energy requirements are rarely more than 2200-2400 kcal per 24 hours for surgical patients to achieve positive energy balance, and this is what is aimed for in this group of patients.

Nitrogen (protein) and fat supplements constitute the core of nutritional support. Glutamine, a nonessential amino acid and the

most abundant amino acid in the free amino acid pool of the body, promotes nitrogen retention. Studies using glutamine as the main source of nitrogen demonstrated a reduction in clinical infection, shorter hospital stay and maintenance of intestinal integrity in patients.²⁶ The use of medium chain triglycerides instead of total dependence on long-chain triglycerides in supplemental feeds is proving beneficial in providing a safe, calorically rich nutrient and a source of essential fatty acids. The use of long-chain triglycerides has been linked to disturbances in liver function tests. Adding medium-chain triglycerides to the feeding regimen achieved a progressive increase in lymphocyte count, a decrease in serum aspartate transaminase and a significant improvement in nitrogen balance.²⁷⁻²⁹

Finally, a recent review of randomized controlled trials for gastrointestinal tract cancer cases showed a decrease in morbidity in malnourished patients who started nutritional support preoperatively and continued in the postoperative period compared to those who received postoperative nutritional support only, also the hospital stay was shorter.³⁰ However, because of the failure in getting consistently significant benefits in terms of entirely curtailing protein catabolism, researchers are looking at possible role for anabolic agents in this regard, for example the combined use of insulin and glucose infusion. This was shown to decrease protein loss in the critically ill. However, this is not without harm and further trials are needed.²⁵

Immunonutrients

Malnutrition, smoking, alcohol abuse, age and serum inhibitory factors affect the immune system in oral cancer patients.^{15,31} In addition, major surgery and other modalities of treatment are associated with severe derangement in the host's defence mechanisms, making the patient susceptible to postoperative infections.^{24,32} Patients with advanced or recurrent disease usually suffer a greater degree of immunological derangement than patients who have minimal disease. That is why the concept of immunonutrients' or the immune-enriched diet' has been introduced as a mean of reversing the immunosuppression state associated with this disease and the effectiveness of immunonutrients has been demonstrated by randomized trials.^{30,33}

Recent investigations have concentrated on the ability to modulate metabolic and immune response via specifically modulated enteral diets. The nutrients included glutamine, arginine, ω -3 polyunsaturated fatty acids and ribonucleotides.²⁴ Evidence is building on their potential pharmacological action on the immune system. Plasma glutamine and arginine were found to be low in upper gastrointestinal tract patients postoperatively. Therefore glutamine supplement was shown to increase plasma glutamine levels and up regulated human immune cell number and function, possibly by stimulating lymphocyte proliferation. Arginine, a semi-essential amino acid in healthy people becoming essential in catabolic states, has been found to improve phagocytosis ability and respiratory burst of polymorphonuclear cells. In addition, increasing the ratio of ω -3 polyunsaturated fatty acids in the diet decreased the production of immunosuppressive prostaglandins, like PGE₂, therefore potentiating immune function.^{24,34,35} Also the trace element selenium has been shown to enhance cell mediated immunity by encouraging lymphocytes to respond to stimulation with mitogens and to destroy tumour cells. The importance of this is highlighted by the finding that the plasma selenium levels are significantly lower in patients with head and neck cancer compared with healthy individuals.³² Finally, prospective studies have demonstrated the benefits of starting an enteral immune-enriched diet, in the preoperative period compared to a standard one, on malnourished patients. The improved immune response was shown by an increase in the peripheral total lymphocyte count.^{24,30}

Routes for Feeding Oral Cancer Patients

Feeding oral cancer patients can be accomplished via enteral or parenteral routes.

Enteral

Oral feeding Tube feeding:

- Nasogastric/duodenal/jejunal
- Cervical pharyngostomy
- Cervical oesophagostomy
- Gastrostomy: surgical, percutaneous endoscopic gastrostomy (PEG) or percutaneous radiographic gastrostomy

- Jejunostomy: surgical or needle catheter jejunostomy

Parenteral

Central

Peripheral

Enteral Nutrition

Enteral nutrition should be used whenever the gastrointestinal tract is functioning. The feeds come in two main forms:

- Polymeric diet: This is usually based on milk proteins with added polymerized sugars and fat. It is indicated for most patients.
- Elemental diet (pre-digested): This is composed of free amino acids, oligopeptides, monosaccharides, simple glucose polymer mixture and triglycerides. It is relatively expensive and has no nutritional superiority over the polymeric diet and the high osmolality is known to cause diarrhoea.

Both types contain vitamins, minerals and may contain immunonutrients, fibres and/or stool softeners. Enteral feed is administered by continuous infusion either by gravity feed or more commonly by a peristaltic pump. A continuous overnight feed followed by disconnection during the daytime may be the optimal technique, giving the patient the freedom to move during the day. All enteric feed should be started slowly, usually 50ml/hr, gradually increasing the volume over few days in order to minimize nausea, colic and diarrhoea until the set target is reached, usually at a rate of 125ml/hr overnight. As the patient slowly commences oral feed, the enteral feed is reduced until ultimately enough nutrients are taken by mouth, then supplemental feed can be stopped. Usually the oral cancer patient is totally dependent on the supplemental enteral feed for 10 days postoperatively. The advantages of enteral feed include cost, ease of administration, assurance of adequate calorie delivery and more importantly maintenance of integrity and immunological function of the gastrointestinal tract.³⁵ Some of the reported complications include malposition and blockage of the feeding tube, diarrhoea (in about 10% of cases), bloating, nausea, cramps, regurgitation, pulmonary aspiration, problems with the giving sets and implantation of squamous cell carcinoma from the upper aerodigestive tract to the PEG exit site has been reported.^{36,37}

Total Parenteral Nutrition (TPN)

Intravenous nutrition was first introduced in 1968.³⁸ It is absolutely indicated in the malnourished or potentially malnourished patients with non-functioning and/or non-accessible gastrointestinal tract. TPN can be delivered via large veins or by the use of the peripheral route which is being recently encouraged for short-term use, to avoid the risks associated with using central lines. However with the latter, some precautions have to be taken to reduce the risk of thrombophlebitis.³⁹

Parenteral nutrients like those taken by the mouth should be complete and balanced. Macronutrients consist of energy sources consisting of carbohydrates (glucose) and lipid emulsions. The nitrogen sources at present are l-amino acids. Micronutrients are electrolytes, trace elements and vitamins.

Complications should occur in less than 5% of the TPN cases and they are mostly operator dependent (Table 1). These potential complications along with others like involuntal changes affecting the gut mucosa. A more complicated set up and the need for careful monitoring make enteral route of feeding the desirable method whenever there is a need for supplemental nutrition.

Table 1. Potential complications of total parenteral nutrition

Insertion related	Air embolism Arterial puncture Arrhythmias Catheter embolus Haemo/hydrpericardium Haemothorax Pneumothorax Neurological injuries
Late	Catheter infection/sepsis Luminal occlusion Catheter displacement Central venous thrombosis
Metabolic	Hyper/hypoglycemia Hypophosphataemia Hyper/hypocalcemia Hyper/hypokalaemia

Route of Choice in Oral Cancer

Since the introduction of PEG in 1980⁴⁰ it has been getting more and more popular among surgeons treating oral cancer patients and is becoming increasingly recognised as the technique of choice for indefinite administration of enteral nutrition. PEG has advantages over both nasogastric (NG) and total parenteral nutrition. Postoperative swallowing disorders and mucositis secondary to radiotherapy reduce the tolerance for NG tubes and longstanding intravenous catheters carry the risk of infection and thrombosis. In addition, patients on PEG feed can be discharged early from hospital and lead reasonable life at home since complications associated with its insertion, maintenance and use are uncommon⁴¹ Also PEG is more acceptable socially than NG tube feeding.

Patient Monitoring

An important part of nutritional support is monitoring the patient. Whether it is enteral or parenteral, a close eye should be kept on the patient's weight, calorie-nitrogen ratio, a record of daily diet and fluid balance charts if necessary.⁸ Continuous supervision of patients by a dedicated dietitian from the moment the disease is diagnosed is essential in limiting weight loss.⁴² Patients on TPN require a more elaborate monitoring system.

Conclusion

There is no doubt that oral cancer patients are predisposed to malnutrition and immunosuppression. The nature and site of the disease, the ablative surgery and radiotherapy compromise the nutritional status of patients, rendering them susceptible to postoperative complications. Nutritional support via enteral feeding is the preferred approach whenever possible as it has lesser complications. PEG is proving to be the method of choice for delivering nutritional support. Research on immunonutrients has been encouraging so far. Whether the enhanced immunologic responsiveness demonstrated could actually affect morbidity and mortality in these patients remains the issue.

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