REVIEW

Nutritional Management During Neoadjuvant Therapy for Esophageal Cancer

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Patients undergoing neoadjuvant therapy for esophageal cancer are at a high risk for malnutrition due to the effects of chemoradiation, dysphagia, and malignancy induced cachexia. Preparation for esophagectomy requires careful assessment of nutritional risk and adequate supplementation as indicated. Supplementation via the enteral route is preferred to the parenteral route but requires feeding tube placement. Endoscopically placed silicone stents have also shown promise as a means to alleviate malnutrition and avoid invasive feeding tubes.


KEY WORDS: enteral nutrition; parenteral nutrition; esophageal stenting

INTRODUCTION

Nutritional management of the esophageal cancer patient is uniquely challenging. Patients with esophageal cancer are faced with the double threat of a catabolic state induced by the malignancy and a potential for dysphagia caused by an obstructing tumor. A recent study of 1,000 outpatients with cancer found that patients with esophageal malignancy had the highest median percentage weight loss among the primary tumor sites evaluated [1]. In fact, the rate of malnutrition in patients with esophageal cancer has been estimated to be as high as 78.9% [2]. In addition, patients that present with weight loss at the time of esophageal cancer diagnosis have a decreased over all survival [3,4]. Malnutrition becomes an even more significant issue among patients who are candidates for esophageal resection. The importance of adequate nutritional status prior to a major operation is well recognized [5]. Nutritional status and the effectiveness of the immune response are intimately connected. Evidence clearly indicates that malnourished patients that undergo major operations are predisposed to infectious complications and poor outcomes [5–7].

Furthermore, many centers now advocate a regimen of neoadjuvant chemoradiation prior to esophagectomy. Patients treated with multimodal therapy for esophageal cancer often have significantly worse nutritional parameters than those who only undergo resection [8]. The side effects of 5-fluorouracil and cisplatin, the most common chemotherapy regimen employed to treat esophageal cancer, include nausea, vomiting, and diarrhea. Also, therapy with radiation frequently causes esophagitis that further aggravates dysphagia. The incidence of esophagitis is reported as 15–28% depending upon the chemotherapy type and radiation dosing regimen used [9,10]. Malnutrition itself reduces the rate of patient tolerance of a complete chemoradiotherapy regimen [11]. This article reviews the assessment and nutritional management of esophageal cancer patients prior to surgical resection.

NUTRITIONAL ASSESSMENT

The first step in preoperative nutritional management should involve determining the degree of nutritional risk. The mere diagnosis of esophageal malignancy confers significant nutritional risk, but not all esophagectomy patients will require preoperative nutritional support. Odelli et al. [12] found that only about 30% of patients that were categorized as moderate risk (i.e., the presence of anorexia, dysphagia, or weight loss of 5–9%) eventually required nutritional support with enteral feeds.

The available techniques of nutritional assessment involve a combination of history and physical exam findings, biochemical markers, and anthropometric measurements. The most widely accepted standard for determining nutritional status is the subjective global assessment (SGA). The assessment group patients as category A (well nourished), B (moderately or suspected of being malnourished), or C (severely malnourished). The SGA relies on the physician subjectively grading the patient based on symptoms and a series of physical exam findings (Table I). The physician then forms an overall assessment (SGA). The assessment group patients as category A (well nourished), B (moderately or suspected of being malnourished), or C (severely malnourished). The SGA was developed to identify patients that were at risk for nutritionally associated complications following surgery, and its validity has been well studied [14]. Various SGA scoring systems are used to incorporate the subjective findings (Table I). The physician then forms an overall assessment based upon his or her subjective ratings [13].

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used less often because it is more costly and has no specific advantage over albumin or prealbumin.

Other mathematical indices of nutritional status that incorporate various laboratory values and patient parameters have been described. The prognostic nutritional index (PNI; 1.519 × serum albumin + 41.7 × current weight/usual weight) [21] is one of the few that has been studied in esophagectomy patients. Nozoe et al. [22] examined a series of 258 esophagectomy patients and found that preoperative albumin and PNI were significantly lower in patients that had post-operative complications. Han-Geurts et al. [8] also found a correlation between PNI and complications post-esophagectomy, but they noted that the measurement had a low predictive value.

Table III summarizes the parameters for nutritional assessment. Patients with severe malnutrition should have supplemental nutrition initiated prior to beginning multimodal therapy. Patients with moderate malnutrition have an increased likelihood of requiring nutritional support during the course of therapy [12]. Patients with minimal malnutrition can usually be managed with close observation and the support of a dietician.

**STRATEGIES FOR SUPPLEMENTATION**

A multidisciplinary approach to the care of the esophageal cancer patient may provide one of the most cost effective measures to improve nutritional outcome. Incorporating dietician support early in the process of evaluating esophageal cancer patients can help avoid invasive measures to manage malnutrition. Dietitians are beneficial in identifying patients who have nutritional risk factors [23], and dietary measures alone can help some patients maintain nutrition throughout the course of therapy. The adverse effects of neoadjuvant treatment are time limited. Patients that develop esophagitis develop symptoms 2–3 weeks into treatment and the symptoms usually resolve 1–2 weeks following treatment completion [24]. During this time patients may be able to cope with adverse effects of treatment with various eating strategies including frequent small meals and avoiding abrasive, spicy, or acidic foods [25]. Odelli et al. [12] noted in a retrospective review of esophageal cancer patients that adoption of a nutritional pathway and early intervention by a dietician resulted in decreases in weight loss, better rates of completion of radiotherapy, and fewer hospital admissions.

Dietitians can also guide the patient in the use oral nutritional supplements (ONSs). These supplements are commercially available protein and calorie rich drinks that are taken ad libitum along with meals. They provide a safe and noninvasive strategy to improve nutritional status in the setting of poor calorie intake. ONSs have not been shown to dramatically affect surgical outcomes, but they have been demonstrated to improve perioperative weight gain [26,27]. The main draw back of ONSs is their cost and lack of insurance reimbursement.

**THE IMPACT OF SUPPLEMENTATION**

Those patients that fail conservative measures will require some form of nutritional supplementation. Some have feared that nutritional supplementation might actually stimulate tumor growth. Though seen in some animal models, stimulation of tumor growth by either parenteral or enteral nutrition has never been clearly verified in humans [28]. Most data show that malnourished surgical cancer patients have the greatest benefit to supplemental nutritional support. Well-nourished cancer patients have failed to demonstrate any benefit to either total parenteral nutrition (TPN) or enteral nutrition (EN) during chemotherapy [29,30]. In contrast, the Veterans Affairs Cooperative Study revealed a benefit of parenteral nutrition supplementation in the subset of malnourished elective surgery patients. Malnourished patients who were to undergo thoracic or abdominal surgery were randomly assigned to receive one of two treatments: either TPN or EN.
Trend toward decreased survival [30]. Several evaluations of parenteral nutrition in the post-operative setting have found that enteral feeding is associated with fewer complications than controls (5% vs. 43%) and a similar rate of infectious complications leading to the conclusion that TPN should be limited to patients that are severely malnourished [31]. Amongst esophageal cancer patients, Sikora et al. performed a retrospective review of 30 patients that were unable to maintain oral diets but received TPN during neoadjuvant therapy. The TPN patients tolerated a higher total dose of chemotherapy and had surgical outcomes similar to those who were able to maintain oral diets [32].

The timing of nutritional support may also be a relevant factor. Many studies on nutritional supplementation have involved only providing supplementation in the post-operative setting. Daly et al. [33] noted a trend toward a decrease in major post-operative complications in esophageal cancer patients who were malnourished and received TPN prior to surgery when compared to those that did not receive TPN or only received TPN following surgery. Early detection of malnutrition is critical in patients with esophageal cancer. Delayed initiation of supplementation or supplementation only in the post-operative patient, may limit its ability to impact outcome.

The means of nutritional supplementation can impact outcome. Nutritional support with enteral nutrition for patients with esophageal cancer is generally viewed as superior to parenteral nutrition. Randomized studies comparing enteral to parenteral nutrition have shown that parenteral nutrition leads to greater rates of infection and a longer length of stay among hospitalized patients [34–36]. Also, several evaluations of parenteral nutrition in the post-operative setting have found that enteral feeding is associated with fewer complications and a more efficacious reversal of malnutrition [37,38]. In a meta-analysis of 29 randomized trials, Mazaki and Ebisawa [39] found the enteral nutrition compared to TPN reduced the risk of anastomotic leak, hospital stay, and infectious complications. Furthermore, the daily cost of TPN is about four times that of enteral nutrition [38]. In particular amongst cancer patients, TPN has failed to show improvement in chemotherapy induced toxicity [40]. One metaanalysis of studies using TPN in patients undergoing chemotherapy even showed a trend toward decreased survival [30].

**MECHANISMS FOR ENTERAL FEEDS**

The primary drawback of enteral feeding is that a route, often by surgical means, must be established for providing the feeds. Also, special considerations must be taken into account for patients undergoing treatment for esophageal cancer. The simplest means of giving enteral nutrition is via a nasogastric tube. Nasogastric tubes, however, are uncomfortable and unappealing cosmetically. They can lead to increased rates of aspiration pneumonia [41], and they can also significantly compound the symptoms of esophagitis. Because of this negative quality of life impact, many patients may not tolerate a nasogastric tube for the full length of time required for nutritional support.

The most common technique for providing enteral nutrition is by a feeding tube placed using either an open, laparoscopic, or percutaneous technique. Many patients that are able to eat upon initial presentation will eventually require supplementation during the course of neoadjuvant therapy [11,42]. As a result some centers advocate routine feeding tube placement in all patients undergoing multimodal therapy [43,44].

Most of the experience with feeding tubes in cancer patients comes from the use percutaneous endoscopic gastrostomy (PEG) tubes in patients with head and neck cancer. In this subset of patients, studies have revealed PEGs to be a safe and effective means of providing nutritional support [12,45]. Overall, PEG placement has been reported to have a mortality rate of 0.3–1% and morbidity rate of 3–5.9% [46].

Several concerns have arisen over the use PEG in patients with esophageal cancer. Placement itself can be hindered by inability to get the scope beyond the obstructing lesion. There have been a few case reports of metastasis to the feeding tube exit site [47,48], but this is probably a rare complication. PEGs have also been avoided in operable patients because of the potential for injury to the gastroepiploic artery rendering the stomach unusable as a replacement conduit for the esophagus [49]. The incidence of this complication is not known. Margolis and coworkers reported on a series of 119 patients with esophageal cancer and planned PEG placement. Placement was successful in 87% (n = 103) of patients with 46% (n = 47) requiring either laser ablation or dilation in order to place the PEG. There were no placement related deaths, and 4% of the patients had major complications including suppurative wound infections, persistent leakage at the exit site, and protracted ileus. None of the patients developed metastasis to the port site. Sixty-one patients went on to resection and the stomach was able to be used as a conduit in every case. However, it should be noted that 38% of the patients studied had PEG placement at the time of laparoscopic staging; thus laparoscopy may have been used to help guide tube placement and avoid the gastroepiploic artery. When they compared the surgical outcomes of those that had PEG placement to those that did not, they found similar rates of leak, stricture, and delayed gastric emptying. Although the PEG group revealed significantly better tolerance of chemotherapy and better survival rate at 12 months [50]. A retrospective review by Stockeld and coworkers of PEG placement in 229 esophageal cancer patients found similar results. The successful placement rate was high (97%), and the procedure associated mortality was 1%. One case of injury to the gastroepiploic artery was noted among the 67 patients that went on to esophagectomy, but the stomach in this case still had adequate blood supply to be used as a conduit. They attributed the low rate of injury to the gastroepiploic artery to careful avoidance of the greater curve of the stomach during placement [51].

Placement of a jejunostomy tubes avoids potential injury to the stomach. Jejunostomy tubes can be placed using either an open or laparoscopic technique [43]. A method of direct percutaneous endoscopic jejunostomy placement has also been described. Little data has

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**TABLE III. Nutritional Assessment Parameters**

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<th>Adequate nutrition</th>
<th>Moderate malnutrition</th>
<th>Severe malnutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>Weight loss &lt;5%</td>
<td>Weight loss 5–9%</td>
<td>Weight loss ≥10%</td>
</tr>
<tr>
<td>PNI &lt; 40</td>
<td>PNI 40–50</td>
<td>PNI ≥50</td>
<td>BMI &lt; 20 kg/m²</td>
</tr>
<tr>
<td>SGA class A</td>
<td>SGA class B</td>
<td>SGA class C</td>
<td></td>
</tr>
<tr>
<td>No dysphagia</td>
<td>Mild dysphagia</td>
<td>Severe dysphagia</td>
<td></td>
</tr>
<tr>
<td>Albumin &gt; 3.5 g/dl</td>
<td>Albumin &lt; 3.5 g/dl</td>
<td>Albumin &lt; 3.5 g/dl</td>
<td></td>
</tr>
<tr>
<td>Prealbumin &gt; 15 mg/dl</td>
<td>Prealbumin 10–15 mg/dl</td>
<td>Prealbumin &lt;10 mg/dl</td>
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PNI, prognostic nutritional index; SGA, subjective global assessment; BMI, body mass index.

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been published on the use of percutaneous endoscopic jejunostomy tubes in esophageal cancer patients. The primary disadvantages of DPEJ tube placement as compared to PEGs are higher rates of moderate to severe complications (2–10%) and lower reported success rates for placement (approx. 70%) [52–54].

All feeding tube placement techniques have the disadvantage of subjecting the malnourished patient to an invasive procedure. Placement also causes a delay in initiation of chemotherapy. Oncologists routinely wait 7–14 days after placement before initiating chemotherapy to allow resolution of local inflammation and contamination that develops at the insertion site. In some cases, the patient’s chance at treatment could be completely eliminated if a tube placement complication occurs.

**STENTING**

Preoperative esophageal stenting represents an additional alternative to either feeding tube placement or TPN. Stents do not provide additional nutritional support outside of what the patient can consume orally, but they can provide relief of dysphagia. Correction of dysphagia during neoadjuvant chemoradiation can potentially allow enough improvement in nutritional status to avoid artificial nutrition. Stenting also eliminates the delay in initiation of chemoradiation associated with feeding tube placement.

Self-expanding metal stents (SEMS) were developed in the 1990s. They are now widely used for palliation of inoperable esophageal cancer. However, several types of complications have been associated with SEMS including bleeding, perforation, tumor ingrowth, reflux, pain, and stent migration [55,56]. Also, the inability to safely remove metal stents has limited their use in the neoadjuvant setting. More recently removable self-expanding silicone stents have been utilized. The efficacy of self-expanding silicone stents in relieving dysphagia has been demonstrated in patients with unresectable esophageal cancer [57–59], but they are also an attractive option for patients in the neoadjuvant setting because they can be removed at the time of resection or once chemoradiation has resolved the tumor mass.

We previously reported our experience with five patients undergoing silicone stent placement prior to neoadjuvant therapy. All patients had improvement in dysphagia scores and all patients were able to tolerate chemoradiation without additional supplementation [60]. Our current experience with a total of 25 neoadjuvant patients found a significantly better rate of tolerance of chemoradiotherapy with silicone stenting compared to 21 patients who were treated with feeding tubes, and 12 patients that were maintained on oral diets alone (8% vs. 38% vs. 42%, P = 0.022). Prior to surgery, the stent group also had a decreased percentage weight loss (1.5% vs. 5.4% vs. 5.7%, P < 0.001) and a greater improvement in albumin levels (0.14 vs. 0.39 vs. −0.45, P < 0.001). All patients again had improvement of their dysphagia scores, but two of the esophageal stenting patients required nasogastric tube placement a week prior to surgery for additional nutritional support. No major complications resulted from stent placement, and there was no statistically significant difference in the rate of major operative complication (20% vs. 71% vs. 42%, P = 0.070) (unpublished data).

Siddiqui et al. have also reported a pilot study of using silicone stents in the neoadjuvant setting. Placement was successful in five of six patients. In one patient, the endoscopist was unable to traverse the tumor. All patients had consistent improvement in the dysphagia scores, and none of the patients required supplemental nutrition. The patients showed an impressive mean weight gain of 6 kg. In contrast, many studies of neoadjuvant TPN or enteral supplementation report a weight loss despite supplementation.

Silicone stents have higher rates of migration compared to SEMS [57,59]. The patients who show better response to neoadjuvant therapy are actually more likely to have stent migration. Fortunately, this complication can be easily addressed by endoscopic removal or by removal at the time of resection through the stomach by way of the pyloromyotomy.

The utility of stents rests solely on their ability to relieve dysphagia. They do not eliminate anorexia or the metabolic derangements that lead to tumor associated malnourishment. Our data seems to indicate, however, that relief of dysphagia can provide enough nutritional support to allow the patient to complete neoadjuvant therapy. There is evidence to support that dysphagia is the primary contributor to malnutrition in esophagectomy patients rather than metabolic effects from the tumor [61–63]. Saito et al. [63] found that the degree of dysphagia was an independent predictor of protein-calorie malnutrition in patients with esophageal cancer. Patients with stents that do develop anorexia can be treated with a short course of nasogastric tube feedings prior to surgery.

Esophageal stents have the distinct advantage over feeding tubes of improving patient quality of life by restoring the ability to swallow. Approximately 10% of patients who initiate multimodal therapy do not proceed to surgery because of the development of disseminated disease, complications of chemoradiotherapy, or patient preference [64,65]. These patients likely gain little benefit from routinely placed feeding tubes because they fail to have subsequent resections. Esophageal stenting provides palliation in this subset of patients as well nutritional benefit to those that go on to surgery.

**IMMUNO-ENHANCED NUTRITION**

Another area of research in improving the nutrition of patients with esophageal cancer has been the use of enteral formulas supplemented with arginine, n-3 fatty acids, or nucleotides in hopes of improving immune system function. There is a lack of high quality data supporting the use of these immunonutrients, but a few studies have indicated that their use may improve outcomes of hospitalized patients as compared to standard formulas [34,66]. The effect of immunonutrients on inflammatory mediators requires several days to develop; therefore, it has been theorized that immunonutrients must be supplemented prior to surgery to yield any benefit [67]. Prospective randomized trials on patients undergoing surgery for gastrointestinal cancer indicate that preoperative supplementation with immunonutrient-enhanced enteral formulations may lead to a decrease in overall complications [68–70]. Improvements in complication rates have also been reported in well-nourished patients using diets supplemented with immunonutrients [71]. However, various flaws in the design of these studies have been noted [72]. Studies finding no benefit to immuno-enhanced nutrition have also been reported [73–75]. Further research will be required to determine if immuno-enhanced formulas improve esophagectomy outcomes.

**HORMONAL APPETITE STIMULATION**

Limited investigational work has been done on using appetite stimulating medications in esophagectomy patients. Nandrolone decanoate and oxandrolone are anabolic-androgenic steroids that have been shown to cause appetite stimulation and improvement of malnutrition. Oxandrolone has been found to help improve the rate of weight gain in recovering burn patients [76], patients with AIDS related cachexia [77], and in patients with cancer [37]. Nandrolone decanoate and oxandrolone have the potential to cause adverse effects associated with androgenic anabolic steroids, but the most common adverse effects in clinical trials have been transient elevations of transaminase levels which is reversible after discontinuation of treatment [78].

Specifically in the setting of resection for esophageal cancer, Darnton and coworkers performed a prospective, randomized, double blinded study on the effectiveness of treatment with nandrolone decanoate.
decanote post-operatively. The study enrolled 19 patients in the treatment arm and 21 patients in the placebo arm. Treatment was started at 1 month post-operatively. No significant differences in weight gain, appetite score, and percent mid arm muscle circumference were noted over 3 months. There was a slight improvement in mid arm muscle circumference at 6 months in the treated group. The authors noted that the treatment had minimal side effects and recommend further trials with larger numbers of patients and higher doses of steroid [79].

To date no large randomized studies have been conducted looking at the potential benefits of preoperative anabolic-androgenic steroids therapy in patients with esophageal cancer. Nor have studies examined the pre-esophagectomy use of megestrol, a progestrone derivative and commonly used appetite stimulant in surgical patients. The use of appetite stimulating drugs in esophageal cancer represents a potential area for further research.

CONCLUSIONS

Preoperative nutritional support is crucial to the management of the esophageal cancer patient undergoing multimodal therapy. Careful nutritional assessment and multidisciplinary approaches should be used to identify of patients with nutritional risk. The use of nutritional supplementation in the appropriate patient can improve esophagectomy outcomes. Preliminary results indicate that removable self-expanding plastic stents hold promise as technique to improve nutritional outcomes, and they should be studied in future randomized trials.

REFERENCES