



Trabajo Original

Nutrición artificial

Feasibility, safety and outcome of endoscopic gastrostomy in patients with esophageal cancer

Viabilidad, seguridad y resultado de la gastrostomía endoscópica en pacientes con cáncer de esófago

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Abstract

Background and aims: esophageal cancer (EC) is an important health problem worldwide with high morbidity and mortality. EC patients are likely to develop malnutrition. The aim of this study was to assess the feasibility and safety of endoscopic gastrostomy (PEG) feeding in EC cancer, and to identify risk factors associated with poor prognosis.

Methods: a retrospective observational study was performed using records from EC patients referred for PEG. Age, gender, cancer histologic subtype, indication for gastrostomy, and mortality data were recorded. NRS 2002, body mass index (BMI), hemoglobin, serum albumin, transferrin and total cholesterol were collected at the day of PEG. An association between anthropometric, clinical and laboratorial data with patient survival was assessed.

Results: data were obtained for forty-one EC patients (36 men and 5 women) aged 39-88 years (mean, 62 years). Gastrostomy was possible in all patients referred to PEG (27 patients selected for curative treatment and 14 patients for palliative nutrition). No major complications occurred. Mean survival after PEG was 18.1 months, and mortality rate at 3 months was 31.7 %. Most patients (34; 82.9 %) died under PEG feeding. Mean BMI was 21.3 kg/m² and 14 patients (34.1 %) patients had low BMI. Serum albumin, transferrin and total cholesterol were low in 10 (24.4 %), 20 (48.8 %) and 18 (43.9 %) patients, respectively. Higher BMI (R = 0.30), serum albumin (R = 0.41) and transferrin (R = 0.47) tended to be positively correlated with survival (p < 0.005).

Conclusions: PEG is a feasible and safe technique for enteral feeding in EC patients. Higher BMI, serum albumin and transferrin levels at admission predict a better outcome. Enteral feeding through PEG should be considered early in EC patients due to their higher risk of malnutrition, which is associated with shorter survival.

Keywords:

Esophageal cancer.
Percutaneous endoscopic gastrostomy.
Nutritional support.

Resumen

Introducción y objetivos: el cáncer de esófago (EC) es un importante problema de salud en todo el mundo, con elevada morbilidad y mortalidad. Los pacientes con EC presentan una elevada probabilidad de desarrollar desnutrición. El objetivo de este estudio fue evaluar la viabilidad y seguridad de la alimentación por gastrostomía endoscópica (PEG) en los EC e identificar los factores de riesgo asociados con un peor pronóstico.

Métodos: se realizó un estudio observacional retrospectivo utilizando registros de pacientes con EC remitidos para PEG. Se registraron la edad, el género, el subtipo histológico del cáncer, la indicación de gastrostomía y los datos de mortalidad. El NRS 2002, el índice de masa corporal (IMC), la hemoglobina, la albúmina sérica, la transferrina y el colesterol total se recogieron el día de la PEG. Se evaluó la asociación de los datos antropométricos, clínicos y de laboratorio con la supervivencia del paciente.

Resultados: se obtuvieron datos de cuarenta y un pacientes con EC (36 hombres y 5 mujeres), con edades entre 39 y 88 años (media 62 años). La gastrostomía fue posible en todos los pacientes remitidos a PEG (27 pacientes seleccionados para tratamiento curativo y 14 pacientes para nutrición paliativa). No ocurrieron complicaciones mayores. La supervivencia media después de la PEG fue de 18,1 meses y la tasa de mortalidad a los 3 meses fue del 31,7 %. La mayoría de los pacientes (34; 82,9 %) murieron bajo alimentación con PEG. El IMC medio fue de 21.3 kg/m² y 14 pacientes (34,1 %) pacientes presentaron un IMC bajo. La albúmina sérica, la transferrina y el colesterol total fueron bajos en 10 (24,4 %), 20 (48,8 %) y 18 (43,9 %) pacientes, respectivamente. El IMC alto (R = 0,30), la albúmina sérica (R = 0,41) y la transferrina (R = 0,47) tienden a correlacionarse positivamente con la supervivencia (p < 0,005).

Conclusiones: la PEG es una técnica factible y segura para la alimentación enteral de los pacientes con EC. Los niveles más altos de IMC, albúmina sérica y transferrina al ingreso predicen un mejor resultado. La alimentación enteral a través de PEG debe considerarse temprano en los pacientes con EC debido al mayor riesgo de desnutrición, que se asocia a una supervivencia más corta.

Palabras clave:

Cáncer de esófago.
Gastrostomía endoscópica percutánea.
Apoyo nutricional.

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INTRODUCTION

Esophageal cancer (EC) is one of the most frequently reported malignancies and the sixth leading cause of death from cancer in the world (1). Unfortunately, EC has a poor prognosis with a total 5-year overall survival rate of 18 %, and therefore there is worldwide concern regarding its increasing incidence (2,3).

The primary therapy for EC is dependent upon tumor stage, location, histological type, and patient medical condition. Curative therapeutic options include surgical resection of the primary tumor, chemotherapy and radiotherapy. Frequently, it is useful to combine therapies (4).

Efforts have been made to identify the main risk factors for EC in order to perform the diagnosis in an early stage and decrease mortality. However, a majority of patients are asymptomatic until advanced stages of the disease, when EC is most frequently diagnosed. This precludes curative treatment and makes palliation the only suitable option for most EC patients (5). For advanced tumors, palliative treatment includes brachytherapy, chemotherapy, and endoscopic palliation techniques such as esophageal dilatation, intraluminal stents, laser therapy, photodynamic therapy, and gastrostomy (4).

Dysphagia is the main symptom, either caused by obstruction or by compromised oral intake during treatment (6). During therapy most patients experience a worsening of dysphagia due to side effects such as esophagitis and oral mucositis (4). Hence, patients with EC are more likely to develop weight loss and malnutrition (7). Besides the insufficient nutritional intake due to dysphagia, anorexia and increased metabolic demands related to tumor burden also play an important role in the deterioration of nutritional status (8).

Malnutrition has been recognized as an important prognostic factor in cancer patients as it reduces quality of life, increases treatment-related adverse events, and decreases overall survival (7,9). Therefore, nutrition support is essential for EC management, and enteral nutrition via percutaneous endoscopic gastrostomy (PEG) may be important (8).

According to some recommendations (4,10,11), enteral tube feeding of EC patients should be indicated in the following situations:

1. Patients undergoing chemotherapy or chemoradiation therapy who are suffering from dysphagia.
2. Patients with upper esophageal stenosis (even if not severe) who are candidate to curative treatment, because difficult long-term oral intake is expected due to mucositis and esophagitis during the treatment.
3. In palliative treatment, in patients with EC involving the upper esophageal sphincter, or in proximal esophageal tumors where stents are poorly tolerated.
4. Patients with refractory stenosis after a stent or palliative radiation therapy, where endoscopic dilation has failed.

However, there is limited data regarding indications for PEG feeding in EC patients. Most of the studies have examined the usefulness of PEG for aerodigestive cancer (4,12,13), and there are more reports of head and neck cancer patients than of esophageal cancer patients (14-17). This is clinically relevant because the therapeutic alternatives are different.

Therefore, the present study aims to evaluate PEG feeding for nutritional support in EC patients through a retrospective review of the experience of our Artificial Feeding Team.

We intended to:

1. Demonstrate the feasibility and safety of PEG and its low complication rate in EC patients.
2. Characterize the nutritional status of EC patients when they are referred and undergo a gastrostomy procedure.
3. Assess the survival of PEG-fed, EC patients.
4. Evaluate the association of EC patient status when referred for PEG with clinical outcome, in order to identify risk factors associated with poor prognosis.

MATERIALS AND METHODS

A single center, observational, longitudinal and retrospective study was performed in a large hospital setting. This study was approved by the ethics committee of our institution.

PATIENTS

A retrospective analysis of a prospectively collected database was performed in consecutive patients with EC cancer that were referred to the Artificial Feeding Team (GENE) of the Gastroenterology Department at Hospital Garcia de Orta for 11 years (from 2008 until 2018), who underwent endoscopic gastrostomy to improve nutritional support and were followed in the Artificial Nutrition Outpatient Clinic. All gastrostomies were performed using a Pentax slim gastroscope with a 9.0-mm diameter.

All patients or their representatives were informed about the PEG procedure and the feeding protocol evaluation, and gave their informed consent. Patients underwent PEG after fasting for 12 hours. Antithrombotic therapy was managed according to guidelines (18). Defects in coagulation were corrected prior to the procedure. All patients had to be stable before PEG. Unstable patients were refused or postponed.

Two gastroenterologists performed all procedures with patients under deep sedation with propofol, midazolam, fentanyl, and/or droperidol. During the procedure, oxygen saturation, heart rate, and electrocardiographic signs were monitored. The "pull" method was used in palliative patients. The "push" method with gastropexy was applied routinely in patients undergoing curative treatment in order to avoid ostomy metastasis. This approach avoids the passage of the tube through the mouth, pharynx and esophagus, allowing a safe procedure without risk of seeding cancer cells in the gastrostomy tract (19,20).

The eligibility criterion for the study was a histologically confirmed carcinoma of the esophagus, regardless of histological type.

The indications for gastrostomy were one of the following situations:

1. Dysphagia or malnutrition in patients selected for chemotherapy or chemoradiation therapy with curative intent.

2. Stenosis of upper esophagus before chemotherapy or chemoradiation therapy.
3. EC located in upper esophagus when stents are poorly tolerated, PEG being the definitive nutritional palliation.
4. Refractory stenosis after palliative radiation therapy or stent.

The study's exclusion criteria included patients with surgical gastrostomy, where PEG was not feasible because of diaphanoscopy of the stomach was not achieved or, most commonly, due to complete obstruction that precluded gastroscopy.

NUTRITIONAL RISK SCREENING 2002

A NRS 2002 was performed in every patient as part of a systematic hospital routine.

ANTHROPOMETRIC EVALUATION

The anthropometric evaluation was performed using BMI and MUAC on the day of the gastrostomy procedure or the day before. Three consecutive MUAC measurements were obtained; the value recorded in the clinical file represents the mean of those three measurements.

- Body mass index (BMI): BMI was obtained in most patients using the equation $\text{weight} / \text{height}^2$. If patients were unable to stand up for weight and height evaluation, BMI was estimated using the mid-upper arm circumference (MUAC) and regression equations described by Powell-Tuck and Hennessy (21). This method has been previously used and proven to provide a reliable BMI estimation in PEG patients (22).
- MUAC was measured in centimeters using a flexible measuring tape wrapped around the mid-upper arm, halfway between the olecranon process and the acromion process.

Patients were classified according to their age as having low weight if BMI was $< 18.5 \text{ kg/m}^2$ for patients < 65 years, or BMI $< 22 \text{ kg/m}^2$ for patients 65 years or older. Patients above those limits were considered to have a normal BMI.

The diagnosis of malnutrition (23) was based on:

- Low BMI ($< 18.5 \text{ kg/m}^2$)
- OR
- Unintentional weight loss ($> 10\%$ over an indefinite amount of time or $> 5\%$ over the last 3 months) and BMI $< 20 \text{ kg/m}^2$ if over 70 years of age, or $< 22 \text{ kg/m}^2$ for patients 70 years or older.

LABORATORY EVALUATION

A blood sample was obtained just before the PEG procedure. Serum albumin, transferrin, total cholesterol and hemoglobin were measured as part of patient global nutritional evaluation. Hemoglobin levels $< 12 \text{ g/dL}$ allowed the diagnosis of anemia.

Albumin $< 3.5 \text{ g/dL}$ and transferrin $< 200 \text{ mg/dL}$ were considered low values, suggestive of malnutrition and/or poor prognosis.

STATISTICAL ANALYSIS

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS® Inc., Chicago, IL, USA), version 21, and Microsoft Office Excel Professional 2017®. Normality was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean \pm standard deviation or median \pm interquartile range, and categorical variables as percentage. The demographic variables analyzed in every patient were age, gender, time span from diagnosis to PEG, survival after diagnosis until death (or until December 31st, 2018), and survival after PEG until death (or until December 31st 2018).

The anthropometric and laboratory variables considered were BMI, hemoglobin, serum albumin, transferrin, and total cholesterol levels.

After a descriptive analysis of all variables, we used Spearman's test to assess the correlation between those markers and patient survival. Inferential tests were performed at the 5 % level of statistical significance.

RESULTS

PATIENTS

We evaluated 41 EC patients, 36 men (87.8 %) and 5 women (12.2 %) with ages ranging from 39 to 88 years (mean: 62 years; median 61 years) who underwent PEG for nutritional support. Twenty-four patients were younger than 65 years. The demographic data of our sample are listed in table I.

Regarding histology, 37 patients (90.2 %) were diagnosed with squamous cell carcinoma, (6 of them (14.6 %) with hypopharynx invasion), and 4 patients (9.8 %) with adenocarcinoma.

PEG PROCEDURE AND COMPLICATIONS

It was possible to perform PEG in all referred patients. A PEG tube was placed for palliative nutritional support in 11 patients (26.8 %) with EC located in the upper esophagus, 2 (4.9 %) with stenosis after radiotherapy, and 1 (2.4 %) after stent failure because of persistent dysphagia and low nutritional intake. Gastrostomy was performed in 20 (48.8 %) patients with dysphagia or malnutrition undergoing chemoradiation therapy or chemotherapy, and in 7 (17.1 %) with upper esophageal stenosis selected for curative treatment.

The time span from EC diagnosis to gastrostomy ranged from less than one month to 97 months (median, 1 month). A total of 27 patients (65.9 %) underwent PEG during the first month after diagnosis. The patient who underwent gastrostomy after 97 months from diagnosis presented without dysphagia and with adequate oral intake at the time of diagnosis. He refused surgery

Table I. Baseline patient characteristics according to age

		< 65 years	≥ 65 years	Total
Male		22 (54 %)	14 (34 %)	36 (88 %)
Female		2 (5 %)	3 (7 %)	5 (12 %)
NRS 2002 ≥ 3		24 (59 %)	17 (41 %)	41 (100 %)
BMI n = 40	Low BMI	7 (17.5 %)	7 (17.5 %)	14 (35 %)
	Normal BMI	17 (42.5 %)	9 (22.5 %)	26 (65 %)
Hemoglobin n = 34	Low hemoglobin	7 (20.5 %)	7 (20.5 %)	14 (41 %)
	Normal hemoglobin	14 (41 %)	6 (18 %)	20 (59 %)
Albumin n = 39	Low albumin	4 (10 %)	6 (15 %)	10 (25 %)
	Normal albumin	20 (51 %)	9 (23 %)	29 (74 %)
Transferrin n = 38	Low transferrin	12 (32 %)	8 (21 %)	20 (53 %)
	Normal transferrin	12 (32 %)	6 (16 %)	18 (47 %)
Total cholesterol n = 38	Low total cholesterol	9 (23.5 %)	9 (23.5 %)	18 (47 %)
	High/Normal cholesterol	14 (37 %)	6 (16 %)	20 (53 %)

but underwent chemoradiotherapy without weight loss. After 10 years of follow-up with an adequate nutritional status, the patient has an EC recurrence or a *de novo* cancer in the same location, with dysphagia and stenosis, and was then subjected to gastrostomy.

During follow-up, minor complications occurred in 2 patients with local infection around the PEG tube, that was treated with dressings and antibiotics. There were no major complications, namely buried bumper syndrome or complications needing surgery. There was no procedure-related mortality.

NUTRITIONAL RISK SCREENING 2002

All patients presented with NRS 2002 ≥ 3, signaling their nutritional risk.

ANTHROPOMETRY

Regarding the 41 patients included in this study, we recorded BMIs from 40 patients at admission. In 33 patients BMI was assessed using the equation $\text{weight} / \text{height}^2$, and in the remaining 7 patients it was estimated using the Powell-Tuck and Hennessy regression equations. At admission, BMI ranged from 15 to 33 (mean: 21.3; median: 22). Adjusting to age, 14 patients (35 %) displayed a low BMI. Overall, 14 patients (66 %) were considered malnourished.

Patients with low and normal BMI had a mean survival of 11.2 and 22.5 months, respectively. There was a positive correlation between BMI and survival ($R = 0.304$), with statistical significance ($p = 0.02$).

Table II. Distribution of patients according to indication for PEG tube placement

Curative treatment	Dysphagia or malnutrition undergoing chemoradiation therapy or chemotherapy	20 (48.8 %)
	Upper esophageal stenosis	7 (17.1 %)
Palliative treatment	EC located in the upper esophagus	11 (26.8 %)
	Stenosis after radiotherapy	2 (4.9 %)
	Stenosis after stent failure	1 (2.4 %)

CLINICAL OUTCOME

No patient was lost to follow-up. By the end of 2018, of the 41 included patients, 36 (87.8 %) had died and 5 (12.2 %) survived. Survival after PEG ranged from less than one month (3 patients) to a maximum of 105 months. Mean survival after PEG was 18.1 months (median: 6 months). Mortality rate at three months was 31.7 %. Mean survival after EC diagnosis was 24.1 months. A survival analysis after endoscopic gastrostomy using the Kaplan-Meier method is shown in figure 1.

Amongst all the 27 patients selected for curative treatment, the PEG tube was removed in 7 patients (25.9 %) (2 patients died after removing the PEG tube from unrelated causes, and 5 patients were alive by the end of the study). The time span from gastrostomy to removal ranged from 3 months to 38 months (mean: 15.6 months).

Mean survival in patients selected for curative and palliative treatment was 25.1 and 4.8 months, respectively.

Patient age presented a poor correlation with survival after EC diagnosis ($R = -0.4$, $p = 0.02$) and survival after PEG ($R = -0.4$; $p = 0.01$).

LABORATORY ASSESSMENT

At admission, Hb was recorded in 34 patients, 30 men and 4 women. Overall, the mean value of Hb was 12.8 g/dL (minimum: 7.6 g/dL; maximum: 18 g/dL). Regarding gender, 14 male patients and 3 female patients presented with anemia. Male patients presented the highest Hb levels when compared with female patients ($p = 0.01$), with a mean level of 13.2 g/dL and 10.1 g/dL in men and women, respectively.

Serum albumin, transferrin, and total cholesterol levels were also recorded at admission in 39, 38, and 38 patients, respectively. Serum albumin, transferrin, and total cholesterol were low in 10, 20, and 18 patients, respectively.

Data from Spearman's correlation test showed that higher serum albumin ($R = 0.41$, $p = 0.02$) and transferrin concentrations were positively correlated with longer survival ($R = 0.47$, $p = 0.006$). Cholesterol also showed a positive correlation with survival ($R = 0.02$) without reaching statistical significance ($p = 0.89$).

DISCUSSION

EC is an important health problem worldwide with a high mortality rate (2). Patients with EC have a poor prognosis and often suffer from dysphagia, weight loss and malnutrition (5). Nutritional support is essential in the management of these patients and enteral nutrition by PEG is an option, either when patients are selected for curative or palliative treatment (24).

Regarding histology, there are two major types of EC: squamous cell carcinoma and adenocarcinoma. In the 1960s, squamous cell carcinoma was the more prevalent subtype, but in the past 50 years in Western countries there has been a markedly increasing incidence of adenocarcinoma, and adenocarcinoma has overtaken squamous cell carcinoma as the most common histologic subtype (24,25). Interestingly, in this study squamous cell carcinoma was the prevalent histologic subtype. This fact can be related to the main risk factors for squamous cell carcinoma—alcohol and tobacco smoking. In this study, risk factors were not evaluated, but male gender was prevalent and, in our population, men more often smoke and drink when compared to women.

Gastrostomy should be performed as early as possible: in advanced stages because the stenosis of the esophagus is less pronounced than in later stages; in patients with dysphagia selected for curative treatment because it is mandatory to improve

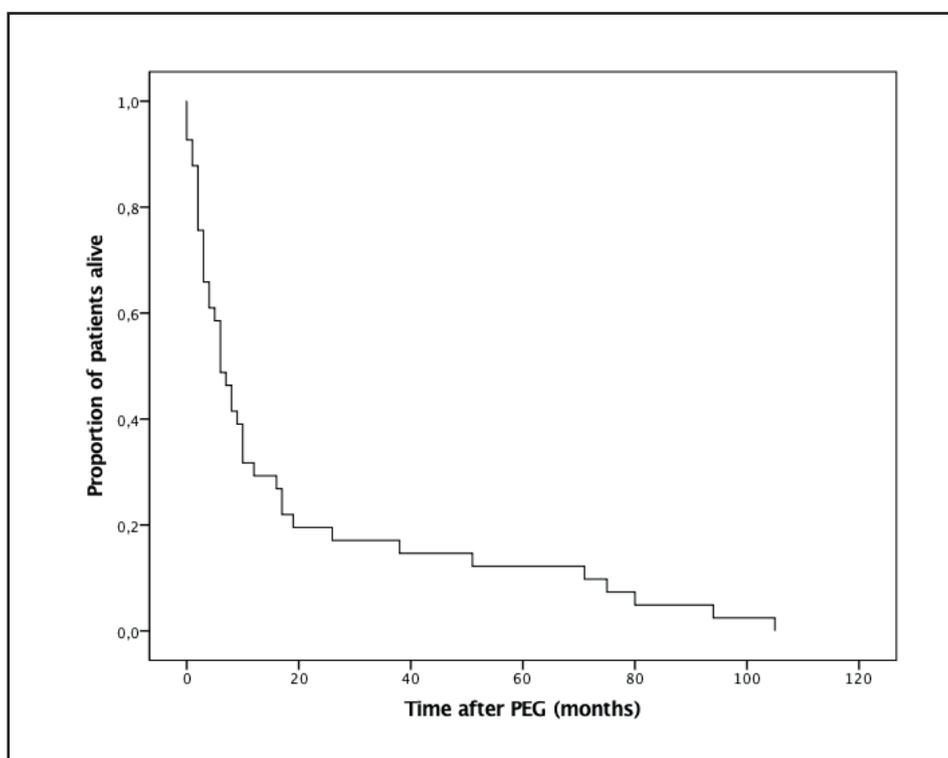


Figure 1.

Kaplan-Meier curve of patient survival after percutaneous endoscopic gastrostomy (survival analysis). The graphic shows that more than 50 % of patients are alive within the first 6 months after PEG tube placement.

nutritional support for therapy (24,26). In this study, most gastrostomies (65.9 %) were performed within one month. However, one patient only underwent PEG tube placement after 97 months from diagnosis. This patient had no weight loss or dysphagia during 10 years of follow-up. Only after this time had he a clear indication for gastrostomy due to EC recurrence. Probably, this was a *de novo* lesion (a new EC), but this was not demonstrated.

No procedure complications were observed in this study, confirming that, despite its minimally invasive nature, PEG is a safe procedure in these patients. In fact, only 2 patients had minor complications that were easily treated, such as local infections.

A clinical and nutritional evaluation was performed at the time of gastrostomy in order to characterize the nutritional status of the EC patients referred to receive the PEG procedure.

EC patients are more likely to experience weight loss and have a higher risk of malnutrition than patients with other cancer locations (27). Interestingly, in this study the majority of the patients had a normal BMI and only 34.1 % presented with a low BMI. One possible reason is that only 14 patients presented with advanced tumor and were referred for palliative treatment, and these patients are often at higher risk of malnutrition. In addition, PEG was performed very soon after the diagnosis. However, according to the newer criteria for malnutrition diagnosis (23), most of these patients could be considered malnourished.

EC has a poor prognosis and 5-year survival rates range from 15 % to 25 % (28). In the present study, the mean survival time after PEG was 18.1 months, and the mortality rate at three months was 31.7 %. In patients selected for curative treatment dysphagia may worsen due to side effects, and this may exacerbate a poor nutritional status (6). Hence, PEG tube placement is indicated in these patients (4). In this study, all patients underwent gastrostomy before aggressive treatment. It was possible to remove the PEG tube in 7 patients, and 5 of them were still alive after PEG tube removal at the end of the study. Considering the poor prognosis of malnourished patients and their potential failure to tolerate treatment, these numbers demonstrate the importance of nutritional support for survival. In fact, these patients showed a mean survival after PEG of 25.1 months.

In palliative treatment, there are many studies showing advantages for enteral nutrition by PEG as compared to nasogastric tubes. Besides, a nasogastric tube interferes more with a patient's life than a well-functioning PEG (8,29). In all 14 patients with advanced EC proposed for gastrostomy the procedure was performed. Guidelines do not recommend PEG in palliative patients with an unfavorable prognosis if expected survival is in the range of few to several weeks (10). However, in our study mean survival time was 4.8 months.

In the present study, clinical and laboratory evaluations were performed at the time of gastrostomy in order to identify factors related with longer survival. Our data demonstrate that patients with a low BMI had shorter mean survival when compared to patients with normal BMI, with a positive correlation between BMI and longer survival.

Regarding laboratory values, serum albumin, transferrin, and total cholesterol are known as biomarkers of prognosis, and of

nutritional and inflammatory status. Data showed that higher levels of albumin and transferrin were correlated with longer survival.

This study has some limitations. This is a retrospective study and therefore collected data are dependent on the accuracy of clinical files. In addition, individuals were not randomized and there was no control group to compare survival between patients who underwent gastrostomy and those who did not. Lastly, serum albumin, transferrin, and total cholesterol levels may also be influenced by multiple factors besides nutrition, as they are negative acute phase reactants.

Our results show that established malnutrition prior to gastrostomy is associated with poor survival in patients with EC. In spite of the limited data regarding EC patients and that a majority of studies have examined the usefulness of PEG for aerodigestive cancer (4,10,11), including head and neck cancer (14-17), our experience demonstrates that whether EC patients are selected for curative or palliative treatment, PEG should always be considered to improve nutritional status since these patients have a significant survival expectancy.

CONCLUSION

Patients with EC have a poor prognosis and high mortality rates. In our experience, survival after endoscopic gastrostomy is substantial, and PEG is a feasible and safe procedure in this clinical setting. A better nutritional status at admission with a higher BMI, and higher serum albumin and transferrin levels, predicts a better outcome. Based on our results we recommend early enteral feeding through PEG for EC patients undergoing curative treatment and also in the palliative setting when esophageal stents cannot be placed or are insufficient to maintain nutritional status.

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