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Original Article

COMPLICATIONS OF THE RESCUE ESOPHAGECTOMY IN ADVANCED ESOPHAGEAL CANCER

Avaliação das complicações da esofagectomia de resgate na terapêutica cirúrgica do câncer de esôfago avançado

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ABSTRACT – ***Background*:** Even though the esophageal cancer has innumerous treatment options its prognosis is still unsettled. Because esophagectomy is rarely curative, new and emerging therapies come to light such as isolated chemotherapy and radiotherapy or combined chemoradiation, followed or not by surgery. The rescue esophagectomy is an alternative for those patients with recurrent or advanced disease. ***Aim*:** To evaluate the results of the rescue esophagectomy in patients with esophageal cancer who had previously undergone chemoradiation and describe local and systemic complications of the procedure. ***Methods***: Eighteen patients with unresectable esophageal squamous cell carcinoma were treated with chemoradiation followed by rescue esophagectomy. All of them presented the preoperative clinical conditions required to indicate the surgical procedure. Transthoracic esophagectomy with right side thoracotomy plus midline laparotomy was performed. Patients were evaluated with regard to any postoperative complications. ***Results*:** There were five patients with evidence of fistula at the level of the anastomosis, and four of them progressed satisfactorily. Postoperative dilation was needed in five out of eighteen patients due to stenosis of the esophagogastric suture line. Seven patients did develop pulmonary infection with a fatal outcome for two of them. Among the patients who were available for a five-year follow-up, there was a rate of 53.8% of disease-free survival. ***Conclusions –*** These patients presented an elevated morbidity of the procedure related to many factors such as the long period between chemoradiation and surgery, which leads to tissue injury resulting in anastomotic fistulas. Nevertheless, esophagectomy seems to be valuable in cases without any other therapeutic option.

HEADINGS - Thoracic surgery. Esophagectomy. Neoplasms.

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RESUMO - *Racional*: Apesar das inúmeras opções terapêuticas, o prognóstico da neoplasia maligna de esôfago continua sombrio. Devido à baixa taxa de cura da esofagectomia, foram desenvolvidas novas propostas de tratamento como a quimioterapia e radioterapia isoladas ou associadas, concomitante ou não à cirurgia, além da quimiorradiação exclusiva. A esofagectomia de regaste surge como opção terapêutica para aqueles pacientes com recorrência ou persistência da doença após tratamento clínico. ***Objetivo*:** Avaliar os resultados da esofagectomia de resgate em pacientes com câncer de esôfago submetidos previamente à quimiorradiação exclusiva, assim como descrever as complicações locais e sistêmicas. ***Método*:** Foram analisados retrospectivamente 18 pacientes com diagnóstico inicial de carcinoma epidermóide de esôfago irressecável, submetidos previamente à quimiorradioterapia. Após o tratamento oncológico eles foram examinados quanto às suas condições clínicas pré-operatórias. Foi realizada a esofagectomia por toracotomia direita e reconstrução do trânsito digestivo por cervicolaparotomia. Os mesmos foram avaliados no período pós-operatório tanto em relação às complicações locais e sistêmicas como em relação à qualidade de vida. ***Resultados*:** As complicações foram frequentes, sendo que cinco pacientes desenvolveram fístula por deiscência da anastomose. Quatro desses evoluíram de maneira satisfatória. Cinco também apresentaram estenose esofagogástrica cervical, mas responderam bem à dilatação endoscópica. Infecção pulmonar foi outra complicação observada e presente em sete pacientes, sendo inclusive causa de óbito em dois deles. Dentre os em que se conseguiu realizar seguimento com tempo médio de 5,6 anos, 53,8% estão vivos sem doença. ***Conclusões*:** Existe elevada morbidade da esofagectomia de regaste principalmente após longo espaço de tempo entre quimiorradiação e a cirurgia, propiciando maior dano tecidual e predisposição à formação de fistulas anastomóticas. No entanto, os resultados se mostram favoráveis àqueles que não possuem mais opções terapêuticas.

DESCRITORES - Cirurgia torácica. Esofagectomia. Neoplasias.

INTRODUCTION

The esophageal carcinoma is still a devastating disease, ranking tenth in the list of most common cancers in the world and third between all tumors of the gastrointestinal tract[1,5,19].

The United States recorded an annual esophageal cancer growth tendency of 10% as well as 13,700 deaths per year[10,22]. In Brazil, esophageal carcinoma is the eighth most common cancer with 10,550 new cases in 2009. It is also the sixth most deadly[18]. The south and the southeast regions of Brazil have higher incidence rates. The state of São Paulo and Rio Grande do Sul bring together the majority of cases[9].

The delayed diagnosis, the excessive weight loss due to dysphagia and the association of cardiopulmonary diseases as a result of tobacco abuse, contribute to a challenging clinical control of the patients diagnosed with advanced esophageal carcinoma, leaving the physician in charge with very few therapeutic possibilities [4,23]. Data from various specialized treatment centers indicate that only 30-40% of patients are actually submitted to a radical esophagectomy, what leads to a very unfavorable prognosis[10,18,23].

Due to the low effectiveness of the esophagectomy in terms of cure, new therapeutic approaches have been encouraged recently, such as radiotherapy, chemotherapy or a combination of both pre or postoperatively, or even exclusive radical chemoradiation [15,33].

The exclusive radical chemoradiation is best indicated for patients with locally advanced esophageal carcinoma or for those without nutritional and clinical conditions to undergo surgery. The five-year survival rate for these patients vary from 10-30% with unsatisfactory locorregional control and 40-60% estimated recurrence rates[14,24].

Thus, the only chance of potential cure for patients with recurrent or persistent disease regardless previous chemoradiation would be the rescue esophagectomy. This surgery has recently provided a five-year survival rate of 25% and it is exclusively indicated upon chemoradiation failure, unlike planned esophagectomy, which is part of a multimodal therapy[19,20,24,31]. The planned esophagectomy follows neoadjuvant chemotherapy and it is always performed unless there is a formal contraindication such as disease progression or a declining overall health status[15,24,33].

The rescue surgery is endowed with greater technical difficulty and operative morbidity due to the severe fibrosis in between the periesophageal anatomic structures. Such finding develops after high doses of radiation applied to the tumor bed and the longer time interval from the end of treatment until surgery[5,18,19,24,31].

These facts, coupled with skepticism regarding the cure of esophageal carcinoma explain the reluctance of many surgeons to perform this procedure as well as the minimal national spread of this therapeutic modality.

This study aims to evaluate the results of rescue esophagectomy in patients with advanced esophageal cancer who underwent prior exclusive radical chemoradiation, regarding its local and systemic complications.

METHOD

During the period of January 1996 to December 2011 the Department of Thoracic Surgery of the Celso Pierro Maternity and Hospital– PUC-Campinas, SP, Brazil, admitted eighteen patients with advanced and unresectable esophageal cancer eligible for rescue esophagectomy after failure of exclusive radical chemoradiation. The surgery was indicated within six to nine months after the oncological treatment. Sixteen patients (88.8%) were male aged 59 to 76 years old. All were smokers of 20-40 cigarettes/day varying the period of smoking from 35 to 58 years. They also referred to be alcohol consumers of about two to three shots of distilled spirits a day through a period varying from 30 to 45 years.

Preoperative evaluation

Was performed after the oncological treatment in order to not only confirm the diagnosis but also the resectability of the tumor through a more adequate restaging of the malignant lesion. This review was accomplished through:

a) Upper digestive endoscopy: this exam demonstrated a tumoral lesion in the proximal esophagus in three patients, in the middle third in nine patients and in the distal third in the remaining six patients. Microscopy revealed squamous cell carcinoma in all patients.

b) Chest and abdominal computed tomography: no signs of metastatic disease were detected, indicating tumoral resectability.

c) Tracheobronchoscopy: no evidence of infiltration.

Clinical and nutritional evaluations were satisfactory.

Surgical technique

Transthoracic esophagectomy with right side thoracotomy plus midline laparotomy was performed followed by retrosternal gastric transposition and esophagoplasty with circular mechanical suture.

Postoperative evaluation

The main focus was to detect systemic (cardiovascular, respiratory or infectious) and local complications (stenosis and dehiscence of the cervical esophagogastric anastomosis) through daily clinical examination as well as image and laboratory findings.

Regarding suture dehiscence of cervical esophagogastric anastomosis with subsequent fistula, the clinical diagnosis was made by observing the output of salivary secretion through the neck until the seventh postoperative day. In the absence of clinical signs of fistula, a cervical contrasted radiography was performed to assess whether there was contrast leakage at the suture level.

In relation to the stenosis, the suspicion was guided by symptoms of dysphagia, mainly from the 30th postoperative day. The upper digestive endoscopy and the contrasted radiographic study of the esophagus strengthened the diagnosis.

The quality of life and overall survival rate were evaluated from the day the patient started a physiologic deglutition, according to the dysphagia intensity and signs of tumoral recurrence.

RESULTS

In the analysis of the first 30 days of the postoperative period, five patients (27.7%) had dehiscence of the cervical esophagogastric anastomosis between the fourth and seventh days. Four of them had a good outcome with conservative treatment by cervical drainage plus enteral nutrition, leading to fistula closure by the 15th to 21th day after surgery. From then on patients did start progressive oral nutrition according to their acceptance. The remaining patient had the fistula diagnosed during the second postoperative day, and even being held surgical exploration, the patient progressed to sepsis and death. Seven patients (38.8%) presented with pulmonary infection. Five of them had a good response to specific antibiotics and two patients died from sepsis.

In the mid-term assessment between the 30th and 90th days, five patients (38.8%) developed stenosis of the cervical esophagogastric anastomosis, and four of them had already presented with dehiscence. All of them went through four to ten endoscopic dilation sessions with satisfactory results.

In the long term evaluation of thirteen patients within a period of time varying from one to thirteen years (mean of 5.6 years), four patients (30.7%) died, being one of the due to metastatic lung and liver disease and the other three due to locorregional recurrence.

Currently two patients (15.3%) are alive with locorregional and pulmonary metastasis undergoing chemotherapy. The other seven living patients (53.8%) show no signs of disease and refer to be very satisfied with the treatment.

DISCUSSION

Esophagectomy has always been the treatment of choice for esophageal cancer, although its cure rates generally do not exceed 40% considering the fact that patients usually have occult metastasis at the time of diagnosis[12,24,33]. Another reason is the intrinsic anatomic relation of the esophagus with vital structures of the mediastinum, which makes it difficult to obtain an adequate oncological resection[21,22,24].

Due to the low success of the isolated surgical resection, other therapeutic modalities have been developed in association with the surgery, including radiotherapy, chemotherapy or even chemoradiation, as adjuvant or neoadjuvant therapies. Occasionally there is indication of exclusive chemoradiation, without surgery[12,13,14,15,30,33].

The combination of radiotherapy and chemotherapy is currently accepted as the first-line treatment for locally advanced esophageal lesions and for those patients who have clinical limitation to undergo the surgery [4,12,13,14,18,22,23,24]. This was demonstrated in this study, since all patients were previously submitted to exclusive chemoradiation due to their locally advanced cancer with mediastinal impairment.

The rescue esophagectomy has currently been disclosed once the exclusive chemoradiation presents an inherent failure of up to 60% with median survival of 12 to 18 months and a five-year survival rate of 10 to 30% [5,13,15,23,24,30,33]. However it is well known that the morbidity of the rescue esophagectomy is higher when compared to the conventional esophagectomy after neoadjuvant therapy[20,24,30].

Some series have demonstrated greater tissue injury in patients undergoing the rescue esophagectomy, since the total dose used in the initial curative chemoradiation is higher (50 to 60 Gray), compared to 30 to 40 Gray used in the group of patients who try neoadjuvant therapy[24,28,30].

It is also relevant the fact that the conventional planned esophagectomy has lesser time interval between completion of chemoradiation and surgery, usually 20 to 30 days. The indication of the rescue esophagectomy is often late, usually months, allowing enough time to develop intense fibrosis, making it difficult to dissect the esophagus

and mediastinal structures and contributing to its greater morbidity[13,20,24,30,31]. In this series all patients underwent the surgery within about six months after chemoradiation.

Regarding the type of esophageal resection it is important to remember that although the main goal of surgery is to carry out a complete resection, such thing is extremely difficult to accomplish after chemoradiation. Thus, most series that perform the rescue esophagectomy advocate an entire thoracic esophagus resection through direct visualization by right thoracotomy in order to make it easier for the dissection and thus minimize complications [17,20,24,27,31]. Some authors have also suggested a more conservative exploration, without the need for a complete mediastinal dissection to avoid airway devascularization. Tachimori et al[28] have recently shown in a comparison trial that 31% of 59 patients undergoing the rescue esophagectomy were able to have three mediastinal lymph node chains dissected, against 91% of 553 patients who were submitted to esophagectomy without preoperative therapy.

This was the reason why was here performed esophagectomy by thoracotomy in 18 patients, since it gives a broader view of the mediastinum and eases the esophagus dissection even with intense fibrosis after radiotherapy. None of the patients had wide mediastinal lymph node chains dissected.

Digestive tract reconstruction following esophageal resection is responsible for most septic and pulmonary complications in the postoperative period. Some authors recommend that this should be done in a second surgical procedure, especially in patients with poor nutritional status[26,31]. Although the organ to be transposed during the reconstruction presents a good perfusion in the abdomen, this may be compromised by the immediate anatomical distension when reconstructions in performed all in one act[5,26,31]. Therefore, the best technique to reconstruct the digestive tract is via anterior mediastinal pathway, which minimizes the chances of an anastomotic fistula at the cervical level and facilitates its diagnosis allowing a conservative therapy[20,26,28,31,32]. Was thus decided in this study to perform the gastric transposition via retrosternal in all patients. Four out of five who developed anastomotic fistula had a good outcome with conservative treatment.

The etiology of esophagogastric anastomotic dehiscence is multifactorial, but technical errors and inadequate tissue perfusion are the most important causes[5,16]. The vascularization of the transposed stomach is made by the right gastroepiploic vessels, since the left gastric artery, the left gastroepiploic artery and short gastric vessels have been sectioned. The gastric conduit still receives blood supply from the submucosal vascular plexus. Many times the previous irradiation obliterates some of the submucosal vessels, contributing to the development of ischemia and anastomotic dehiscence. Despite being better perfused than the stomach, the esophageal stump may also be compromised by radiotherapy depending on the extent of the radiation[5,18,24,31].

The morbidity of the esophagogastric anastomotic dehiscence depends on the location of the anastomosis, the viability of the gastric conduit and the condition of the tissue surrounding the anastomosis, which may block a subsequent fistula. The most favorable situation happened in this study in which the dehiscence occurs at the level of the neck with a viable gastric conduit protected by soft tissue around the anastomosis.

Despite small sample, five out of 18 patients developed anastomotic dehiscence even with the aid of mechanical suture, known to be safer and to decrease the incidence of fistulas[2,3,6,7]. Four of them had a good outcome after local drainage and daily bandages. Recently some authors have shown that conservative management may not succeed, especially in patients developing early fistulas and in those who received high doses of radiation [5,21,27,28,31]. This may explain the fatal outcome of the remaining patient, despite having been held surgical exploration in the second postoperative day.

Pulmonary infections contributed with two deaths, affecting a total of seven of these patients. Many series point out smoking as an important related factor, which probably led to a chronic obstructive pulmonary disease, aggravating the outcome of such pulmonary infections[13,20,24,31]. Besides, the poor typical nutritional status of the majority of patients with esophageal cancer combined with the suppression of the immune system by chemoradiation may also have favored infection. Tachimori et al[28] had the same conclusion, noticing a higher incidence of pulmonary complications in the group of patients submitted to rescue esophagectomy (54% of 59 patients) versus 33% of 553 patients who underwent esophagectomy without any previous treatment.

Another relevant point is the cervical edema after the esophageal dissection, which compromises deglutition and facilitates tracheobronchial tree aspiration of secretion[5]. Moreover, the use of a nasogastric tube to aid decompression of the transposed stomach in the immediate postoperative period favors the permanent opening of the upper and lower esophageal sphincters[5,31].

Along with the pulmonary infections, many of these patients previously irradiated, present with actinic pneumonitis. This condition is probably the first aggression to the lungs, intensified

by the production of inflammatory cytokines after surgery[25]. Mechanical ventilation during or immediately post surgery may also contribute to an inflammatory cascade in the lungs, especially when longer periods of ventilation are needed, with a higher fraction of inspired oxygen[29]. Lymphatic obstruction caused by both irradiation and surgical excision (mediastinum emptying), may also be an important factor for acute pulmonary injury[11].

Complications such as necrosis, airway fistula, lesion of the recurrent laryngeal nerve, pleural effusion and chylothorax have also been described, but none of them were present among these patients[5,8,24]. All complications have a direct relation to the amount of mediastinum radiation received by each patient.

Lately, some authors have been studying factors that could enhance the longevity of patients after rescue esophagectomy. Tumors staged as T1 until T3 and tumor-free surgical margins were related to the best results in terms of life spam[13,24,28]. Swisher et al[27] in a study of 13 patients who had undergone rescue esophagectomy demonstrated a five-year survival rate of 25% longer when compared to 99 patients submitted to bimodal neoadjuvant therapy.

Despite small sample, 53.8% of these patients were disease-free after a follow-up period varying from three and a half years to seven years.

CONCLUSION

The rescue esophagectomy is technically feasible but has a non-negligible morbidity. It is the only possibility of cure in patients with recurrent or persistent disease after exclusive chemoradiation. This procedure represents the best second-line treatment option, although it needs a larger number of patients and new longer studies in order to evaluate the results with greater accuracy.

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