Chagasic Megaesophagus—Associated Carcinoma: Clinical Pattern and Outcomes

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ABSTRACT

PURPOSE Approximately 4% to 10% of patients diagnosed with Chagas-induced megaesophagus disease develop esophageal carcinoma. However, the natural history and clinical pattern of this entity are not well described.

METHODS Herein, we retrospectively analyzed 593 patients with esophageal carcinoma treated at a single Brazilian institution. We identified 32 patients with Chagas disease, of whom 11 had megaesophagus. The epidemiologic profile and oncological treatment outcomes were evaluated.

RESULTS Although baseline characteristics were similar among the three groups, patients with Chagas megaesophagus–associated carcinoma (CMAC) presented with a lower rate of smoking. This factor reinforced the concept that achalasia is the predominant risk factor for cancer development. The CMAC group had a higher rate of tumor in situ (two of 11 patients) compared with the other groups. These patients were treated with endoscopic resection, and no recurrence was detected. Eight of 11 patients with CMAC were diagnosed with locally advanced disease. Patients with locally advanced CMAC presented with a median progression-free survival of 7.8 months and a median overall survival of 9.1 months.

CONCLUSION If CMAC is not promptly detected, it has a dismal prognosis, indicating that a high index of suspicion of esophageal carcinoma is required for patients with Chagasic megaesophagus. Additional studies are needed to improve the surveillance and treatment approaches for this neglected disease.

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INTRODUCTION

Esophageal carcinoma is the seventh most incidental malignancy in the world (572,000 new cases per year) and was responsible for one in every 20 cancer deaths in 2018.1 Chagasic megaesophagus, an endemic disease in Latin America, increases the risk of esophageal carcinoma by greater than 33 times in relation to the normal population.2 Chagasic megaesophagus is a late manifestation of Chagas disease (caused by the protozoan Trypanosoma cruzi).3,4 Achalasia may be the result of diffuse destruction of the myenteric plexus in Chagas disease. This neuronal insult results in uncoordinated contractions and the reduction of organ peristalsis, leading to progressive dilation of the esophagus (megaesophagus) and causing odynophagia, dysphagia, epigastralgia, sialorrhea, and malnutrition.3,5 In Brazil, approximately 2 million people are infected with the parasite, and GI dysfunction (mainly megaesophagus, megacolon, or both) can occur in 10% to 15% of patients with chronic infection.6 The prevalence of Chagasic megaesophagus–associated carcinoma (CMAC) ranges from 3.9% to 10%.6–8 However, survival outcomes of CMAC, as well as the epidemiologic profile, are poorly described. Herein, we sought to evaluate the clinical, epidemiologic, and survival aspects of patients with megaesophagus and esophageal carcinoma.

PATIENTS AND METHODS

In this retrospective case-control study, patients treated between 2000 and 2016 at the State University of Campinas (UNICAMP) with a diagnosis of esophageal carcinoma were included for analysis. Data were collected from medical records of patients with esophageal carcinoma diagnosed at UNICAMP Hospital, under the approval of the institution’s ethics committee (#2.874.590). Two control groups were selected: (1) patients without Chagas disease, and (2) patients with Chagas disease without megaesophagus. The study group was composed of patients with CMAC. Chagas disease was confirmed by serum or parasitology tests. Demographic data, tumor characteristics, treatment, and survival data were collected through a case report form created through the
Research Electronic Data Capture software hosted at UNICAMP. For the outcomes evaluation, the last date of follow-up or the date of death was considered. Overall survival (OS) was characterized by the time between disease diagnosis and death from any cause. For progression-free survival (PFS), we considered the period from disease diagnosis until the date of the first event (ie, disease progression or death). Post-treatment clinical response assessment was performed with endoscopy and tomography (Response Evaluation Criteria in Solid Tumors [RECIST]) and anatomopathological examination after esophagectomy.

Characterization of the study population was performed through frequency tables for qualitative variables, and measures of central trend and dispersion for the quantitative variables were used to compare different groups. To verify statistically significant differences between CMAC and control groups, χ² or Fisher’s exact test were applied accordingly. Survival analysis was performed using Kaplan-Meier curves with log-rank tests for significance. Alpha level was set at 5%. All statistical analyses were performed with Stata 12.

RESULTS

Comparison of Demographic Characteristics of Patients With Chagas Disease

We identified a total of 593 patients who were diagnosed with esophageal carcinoma between 2000 and 2016. Among the 593 individuals, 32 had Chagas disease and 11 had CMAC. The demographic and clinical-pathologic characteristics are listed in Table 1 and were well balanced among the three esophageal cancer groups. The mean age of patients ranged from 58 to 61 years. The majority of patients were male, with active alcohol consumption and Eastern Cooperative Oncology Group performance statuses ranging from 0 to 1. The most prevalent nutritional diagnosis was eutrophics, with a median body mass index ranging from 20 to 22 kg/m². Approximately half of patients underwent gastrostomy. Other chronic manifestations of Chagas disease, such as cardiopathy and megacolon, were observed in four and three of the 11 patients with CMAC, respectively.

Smoking status differed among patients with Chagas disease, especially in the CMAC group. Of 561 patients without Chagas disease, 91.8% were former or active smokers, with a median cumulative smoking rate of 35 pack-years (interquartile range [IQR] = 34 pack-years). In contrast, in the group of patients with Chagas disease without megasophagus, 76.2% were smokers, with 30 pack-years (IQR = 44 pack-years), whereas in the CMAC group, this proportion corresponded to 63.6% (P < .0001), with 10 pack-years (IQR = 15 pack-years, P = .0021).

Tumor Characteristics and Treatment

Tumor characteristics are listed in Table 2. Squamous cell carcinoma was the most predominant histologic type, and the median tumor length ranged from 4 to 5 cm. Interestingly, although not statistically significant, for patients with CMAC, the most common tumor site was the lower-third segment (Fig 1), whereas in control patients, lesions were located predominantly in the middle third. Patients with CMAC presented with a higher rate of in situ tumors (P = .04). Because of the greater number of early tumors in the megasophagus group, a lower proportion of patients presented with an indication for neoadjuvant treatment. In our cohort, the tracheobronchial fistula was found in 64 patients without Chagas disease and in one patient in the Chagasic disease group without megasophagus. In the CMAC group, this complication was not found.

Approximately 50% of patients were candidates for esophagectomy in all groups. The reasons for surgical contraindication included locally advanced or metastatic disease, performance status, surgical risk (eg, comorbidities, age), family decision, or patient refusal. A total of 88.9% of patients without Chagas disease who were candidates for surgery underwent concomitant neoadjuvant treatment. This proportion was similar among patients with Chagas disease without megasophagus (90.9%) and was different in the CMAC group (40%).

Survival Outcomes

The analysis of patients with locally advanced disease demonstrated a poor prognosis for the three groups. Median PFS was 10.2 months for patients without Chagas disease, especially in the CMAC group. Of 561 patients without Chagas disease, 91.8% were former or active smokers, with a median cumulative smoking rate of 35 pack-years (interquartile range [IQR] = 34 pack-years). In contrast, in the group of patients with Chagas disease without megasophagus, 76.2% were smokers, with 30 pack-years (IQR = 44 pack-years), whereas in the CMAC group, this proportion corresponded to 63.6% (P < .0001), with 10 pack-years (IQR = 15 pack-years, P = .0021).

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among other risk factors for the development of esophageal cancer, Chagasic megaesophagus is a poorly explored etiological factor.\textsuperscript{5} Nevertheless, Chagas disease is still a public health problem, particularly in Latin America, where 17.4 million people are infected.\textsuperscript{3} To our knowledge, among other risk factors for the development of esophageal cancer, Chagasic megaesophagus is a poorly explored etiological factor.\textsuperscript{5} Nevertheless, Chagas disease is still a public health problem, particularly in Latin America, where 17.4 million people are infected.\textsuperscript{3} To our knowledge,
this cohort represents one of the largest reports on clinical outcomes of patients with esophageal cancer and Chagas disease with or without Chagasic megaesophagus.

The established association between esophageal neoplasia and Chagasic megaesophagus is probably a consequence of chronic esophagitis caused by food stasis and prolonged mucosal contact with dietary carcinogens. According to our analysis, the highest proportion of nonsmokers were in the CMAC group. In addition, the frequency and duration of smoking, calculated in pack-years, were also lower in the megaesophagus group. These factors reinforced the hypothesis that Chagasic megaesophagus is an independent risk factor for the development of esophageal carcinoma.

Congruent with previous reports, the most common histology observed in patients with CMAC was squamous cell carcinoma. Although not statistically different, tumors that were not associated with megaesophagus had a predilection for the middle-third segment, whereas for patients with CMAC, the most frequent tumor location was the distal-third segment. These results are similar to those in another Brazilian cohort and are aligned with the hypothesis that esophageal stasis is associated with constant mucosal irritation, a process that predominates in the lower third of the esophagus.

Our study was limited by its retrospective nature, non-homogeneous TNM group stage, and nonstandardized guideline for determination of progression date. Despite these limitations, a greater number of in situ tumors was observed in the megaesophagus group. Importantly, a meta-analysis of 11,978 patients and a recent large national population-based control study of 7,487 patients with achalasia identified an esophageal cancer prevalence of 2.8% and 1.3%, respectively. Although the 2018 International Society for Diseases of the Esophagus achalasia guidelines do not make any recommendations about surveillance, the authors of the meta-analysis proposed endoscopic screening 10 years after achalasia onset. Furthermore, a recent comprehensive review concluded that the diagnosis of achalasia by clinical features is not enough to distinguish this entity from other esophageal diseases and emphasized the need for endoscopy to exclude the presence of cancer. Our results are in accordance with this recommendation because patients with in situ tumors did not experience recurrence after endoscopic resection, and survival outcomes of patients with CMAC that was not promptly diagnosed were associated with shorter PFS and OS, as previously reported. In addition, the prevalence of cancer in Chagasic megaesophagus reported in previous studies is higher (3.9% to 10%) than that reported for achalasia, suggesting the involvement of other factors. Along this line and in accordance with a previous report, we observed a high prevalence of active alcohol consumption and smoking in patients with CMAC, indicating that these factors may potentiate the carcinogenic effect of achalasia.

In conclusion, patients with CMAC presented with a dismal prognosis if the tumor was not recognized in advance. In addition, our results indicate that Chagas disease predisposes the development of esophageal cancer; as such, a high index of suspicion is required in patients with Chagasic megaesophagus. Additional studies are needed to evaluate the best surveillance strategy to be implemented for patients with Chagasic megaesophagus.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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