

## Outcome of superficial squamous cell carcinoma of the esophagus. A clinicopathological study<sup>1</sup>

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### ABSTRACT

**PURPOSE:** To analyze the clinicopathological features and outcome of patients with pathologically proven superficial squamous cell carcinoma of the esophagus.

**METHODS:** A total of 234 consecutive cases of esophageal carcinoma in a 15-year period were reviewed.

**RESULTS:** Superficial esophageal cancer was found in five patients (2.1%). They were four men and one woman and the mean age was 52.5 years. Smoking and alcohol were the main risk factors. Achalasia due to Chagas disease occurred in one patient and a second primary tumor developed in the larynx in another patient. Four patients underwent esophagectomy and one patient received chemoradiotherapy. The histopathologic diagnosis was of squamous cell carcinoma in all cases. Intramucosal tumor (Tis) was identified in three cases and superficially invasive carcinoma in two cases. Four patients are free of disease with survival times of two, four, six and nine years. The patient who developed laryngeal cancer died six years after esophagectomy.

**CONCLUSION:** Long-term survival in patients with esophageal cancer is related to early diagnosis. Therefore, a less aggressive surgical approach, such as endoscopic resection, may be a good option for these patients, if depth of tumor invasion can be accurately predicted by the new imaging tools.

**Key words:** Carcinoma, Squamous Cell. Esophageal Neoplasms. Early Detection of Cancer.

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## Introduction

The outcome of patients with esophageal cancer remains dismal with 5-year survival about 10% despite advances in diagnosis, staging and therapeutic procedures<sup>1-3</sup>. This high mortality rate has been mainly related to late diagnosis<sup>1,2,4</sup>. In developing countries more than 90% of esophageal cancers are at late stage when the diagnosis is established, with only a minority of patients elected for curative surgery<sup>4</sup>.

Therefore, the best strategy to improve the chances of long-term survival is the identification of lesions at early stage<sup>5,6</sup>. However, detection of early esophageal cancer is very unusual even in European countries and North America, where expensive techniques are available<sup>7-9</sup>.

Endoscopically, it is often difficult to identify early superficial neoplastic lesions in the esophageal mucosa by conventional endoscopy, but application of iodine has been useful to enhance the detection of discrete neoplastic lesions<sup>10-13</sup>. In addition, new types of endoscopic techniques, including magnifying endoscopy, narrow-band imaging (NBI) and endocytoscopy are promising tools for detection of neoplastic lesions at early stage<sup>6,14-16</sup>.

There are few reports on the prevalence and pathobiologic characteristics of early esophageal cancer in developing countries like Brazil, where this tumor is the fourth leading cause of cancer-related mortality in men<sup>17</sup> and squamous cell carcinoma is the most common histological type, accounting for more than 90% of cases<sup>17</sup>.

The aim of this retrospective study was to analyze the clinicopathological features and outcome of superficial esophageal squamous cell carcinoma in a cohort of patients from southern Brazil.

## Methods

A total of 234 consecutive patients with esophageal carcinoma were referred to Botucatu University Hospital-UNESP, a Medical Center at the Midwestern São Paulo State, Brazil, in a 15-year period between January 1996 and January 2010. Among them, five patients (2.1%) were retrospectively enrolled in the study due to the pathological diagnosis of superficial esophageal cancer, which was defined as a carcinoma limited within the mucosa or submucosa irrespective of lymph node metastasis<sup>3</sup>. Patients' medical records were reviewed for age, gender, endoscopic tumor appearance (flat or nodular), pathologic tumor characteristics (pT), lymph node metastasis (pN) and

clinical outcome. In all resected surgical specimens the pathologic features such as tumor size, presence or absence of lymph node metastasis and lymphovascular invasion were assessed according to previously published criteria<sup>18</sup>. Tumor *in situ* was characterized by an intramucosal tumor (Tis). Superficially invasive carcinoma was defined as a tumor infiltrating the mucosa or submucosa without invasion of the muscularis propria (T1). Depth of tumor invasion was considered as T1a: Tumor invading lamina propria or muscularis mucosae. T1b: Tumor invasion of the submucosa. On the histopathological analysis tumor differentiation was graded on Hematoxylin and Eosin stained slides, based on the predominant tumor differentiation present in more than 75% of the tumor component. The study was approved by the local Hospital Ethical Committee

## Results

The clinicopathological features of the patients with superficial esophageal cancer are summarized on Table 1.

**TABLE 1** - Clinicopathological features of superficial esophageal cancer.

Variable	n
<b>Gender</b>	
Male	4
Female	1
<b>Age</b>	
The youngest	45 years
The oldest	58 years
Mean	52.5 ± 5.4 years
<b>Risk Factors</b>	
Alcoholism + Smoking	2
Alcoholism + Smoking + Achalasia	1
Alcoholism + Smoking + Hot beverages	1
Family history of cancer	1
<b>Tumor Location</b>	
Upper third	0
Middle third	2
Lower third	3

Four patients were male and one was female, aged from 45 to 58 years (mean: 52.5 ± 5.4 years). They were all leukodermic patients. They reported slight dysphagia, ranging from 3 to 5 months (mean: 4.2 ± 0.9 months). Weight loss was also reported and ranged from 4% to 16% (mean: 7.5 ± 5.9).

Concerning risk factors, the four male patients had

a history of alcoholism and smoking for 30 years. One of them had achalasia due to Chagas disease with esophageal and colonic involvement. The female patient denied having the previously cited history, but her father had died from brain cancer. All patients were in good clinical and nutritional conditions, with body mass index within normal range (mean: 23.7±0.2 kg/m<sup>2</sup>).

Endoscopy showed flat or ulcerated lesions in the middle third of the esophagus in two patients and in the distal region in another three patients. Biopsies of the lesions revealed squamous cell carcinoma in all patients. Endoscopy failed to identify the neoplastic lesion in the patient with advanced megaesophagus.

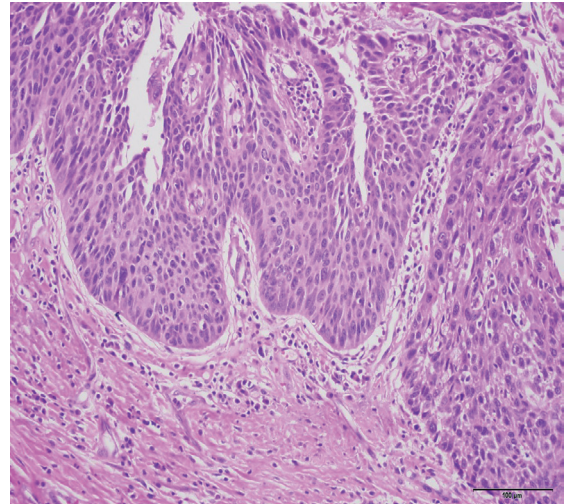
After verifying normal results for abdominal and thoracic CT scans as well as for cardiac and pulmonary assessment, three patients underwent subtotal transhiatal esophagectomy followed by cervical gastroesophageal anastomosis, jejunostomy and pyroplasty. One patient was submitted to video-assisted surgery and another patient denied surgical treatment and was referred to chemoradiotherapy. The patient with advanced megaesophagus was submitted to transhiatal esophagectomy aiming at treating the esophagopathy. The neoplastic lesion was incidentally found during pathological examination of the surgical specimen.

Surgical resection of the tumor was complete in the four patients submitted to esophagectomy. The pathological findings of surgical specimens are shown on Table 2.

On macroscopic examination, a slightly elevated lesion was found in one case, a flat mucosal appearance was observed in two cases, being one case with irregular and confluent erosions. An ulcerated lesion was observed in one case and an incidental mass was found on macroscopic examination in the megaesophagus

from the patient with Chagas disease.

Tumor size ranged from 1.0cm to 2.5cm. Histologically, all tumors showed features of conventional squamous cell carcinoma well-differentiated in four cases and moderately-differentiated in one case (Figure 1).



**FIGURE 1** - Histologic features of intramucosal squamous cell carcinoma of the esophagus (H&E stain, 200x).

The depth of tumor invasion was intramucosal in three cases (Tis) and submucosal in the other two cases, T1a in one case and T1b in another case. Lymphovascular tumor invasion and nodal metastasis were not identified in any case. There were no post-operative deaths. One patient developed cervical fistula, followed by stenosis, which evolved favorably after endoscopic dilatation. Pulmonary complications such as pleural effusion and pneumonia occurred in two patients and went into total remission

**TABLE 2** - Histopathological findings and outcome of superficial esophageal cancer.

Case	Age/ Gender	Procedure/ Tumor Location	Tumor Size & Type	Depth Invasion	Histologic Grade	Tumor Stage	Outcome
1	53/ F	Surgery Middle	15mm Flat	Im	Well dif	Tis	Alive 9 Yr
2	45/M	Surgery Middle	17mm Flat	Im	Well dif	Tis	Dead Laryns Ca
3	58/M	Surgery Distal	15mm Ulcer	Sm	Mod dif	T1a	Alive 6Yr
4	54/M	Surgery Distal	25mm Elev	Sm	Well dif	T1b	Alive 2yr Chagas
5	52/M	Chemoradio Distal	10 mm Elev	Im	Well dif	Tis	Alive 4yr

SCC = Squamous Cell Carcinoma Im = Intramucosal tumor (*in situ*) Sm = Submucosal tumor  
Tis = Carcinoma *in situ* T1a = Tumor invades muscularis mucosa T1b = Tumor invades submucosa

following antibiotic therapy and pleural drainage.

Among all patients, four of them are alive with survival times of two, four, six and nine years, in good clinical conditions and free of the disease. One patient developed a second primary tumor in the larynx and died six years after surgery.

## Discussion

In this study, we analyzed the clinicopathological features and outcome of five patients from southern Brazil with pathologically proven superficial esophageal squamous cell carcinoma surgically treated to add more information on the pathobiologic characteristics of early esophageal cancer and to contribute to therapeutic decision-making.

We have found that only 2.1% of all patients surgically treated for esophageal carcinoma (n=234) presented the lesion at early stage. The reported incidence of superficial esophageal carcinoma varies from 10-20% of all resected carcinomas in Japan<sup>19</sup> whereas it is much less frequent in European countries and North America<sup>1,3,7</sup>. This wide range in incidence can be attributed in part to the pathological criteria used for the diagnosis of esophageal carcinoma and to the high number of endoscopies performed in asymptomatic individuals associated to the routine use of iodine staining (Lugol) which enhances the presence and extent of small malignant lesions in the esophageal mucosa, even those not visible radiologically and endoscopically<sup>10-13</sup>.

Regarding the pathological criteria of squamous dysplasia and squamous cell carcinoma, the views of Western and Japanese pathologists have significant differences. Japanese pathologists report the diagnosis of squamous cell carcinoma in lesions, in which, Western pathologists would consider as dysplasia<sup>20-22</sup>.

Concerning risk factors, our data showed that tobacco smoke and alcohol were the main risk factors for esophageal cancer. A second primary tumor developed in the larynx in one patient and achalasia due to Chagas disease occurred in another patient. In this patient the neoplastic lesion was found only after esophageal resection performed for treatment the advanced megaesophagus. It was not detected preoperatively, probably due to lack of adequate preparation for endoscopy. Although our series of cases is very limited, it reproduces the well known risk factors for esophageal squamous cell carcinoma<sup>1,3,6</sup>.

In our study, three patients had intramucosal tumor (Tis), invasion of the muscularis mucosae (T1a) was found in one case and of the upper third of the submucosa (T1b) in another case. Lymphovascular tumor invasion and nodal metastasis were not identified in any case. These pathological findings associated with

the small tumor size, which was less than 3 cm in all cases, may explain the long-term survival achieved after curative surgical resection in our patients. Only one patient died six years after esophagectomy due to a second primary tumor in the larynx.

Treatment of early esophageal cancer may be performed using several procedures<sup>19,23-25</sup>. Esophagectomy has been considered the most radical and associated with significant morbidity and mortality, particularly in elderly patients and/or those with concurrent illness. Less invasive surgical procedures, such as endoscopic mucosal resection has been advised for these patients<sup>19,23</sup>. In our study the patients with superficial esophageal cancer were referred to subtotal esophagectomy, as preoperative staging with endoscopic ultrasonography was not available, and without it, tumor extension to superficial esophageal wall could not be assessed.

Endoscopic procedures, such as endoscopic mucosal resection and endoscopic submucosal dissection have become possible choices for the treatment of esophageal cancer at early stage<sup>19,23</sup>. A judicious use of these procedures must be considered and patients should only be referred to them when the lesions are small and shorter than 2cm, with circumferential involvement less than 50%, limited to the mucosa and without lymphatic or vascular invasion<sup>24</sup>.

Other endoscopic treatment option for superficial esophageal cancer refers to ablation using radiofrequency. This technique was used by Bergman *et al.*<sup>25</sup> in patients with intraepithelial neoplasia with 97% complete response. According to Galey *et al.*<sup>24</sup>, endoscopic resection of the mucosa has advantages over ablation using radiofrequency, as it allows the preservation of the specimens for histopathological studies.

In our study, three out of the four operated patients are free of the disease four, six and nine years, in good clinical conditions and receiving annual follow-up care. One of the operated patients relapsed to distilled spirits drinking, as he used to do in the preoperative period. As a consequence, laryngeal cancer developed, possibly because of the increase in the speed of alcohol absorption, as a result of the anatomical change induced by esophagectomy. The patient died six years after surgery. The patient who underwent chemoradiotherapy has been in good clinical conditions for four years after treatment.

## Conclusions

Surgical resection provides long-term survival for patients with esophageal cancer at early stage. Less invasive surgical procedures, such as limited resections with endoscopic

resection may be the best option for these patients, if depth of tumor invasion can be accurately predicted by the new imaging tools. Therefore, early small tumors require surgeons to identify superficial lesions exclusively, before the decision between surgical and endoscopic procedures.

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