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ESOPHAGEAL CARCINOMA: IS SQUAMOUS CELL CARCINOMA DIFFERENT DISEASE COMPARED TO ADENOCARCINOMA? A transversal study in a quaternary high volume hospital in Brazil

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ABSTRACT - ***Background -*** Esophageal cancer is one of the leading causes of mortality among the neoplasms that affect the gastrointestinal tract. There are several factors that contribute for development of an epidemiological esophageal cancer profile in a population. ***Objective -*** This study aims to describe both clinically and epidemiologically the population of patients with diagnosis of esophageal cancer treated in a quaternary attention institute for cancer from January, 2009 to December, 2011, in Sao Paulo, Brazil. ***Methods -*** The charts of all patients diagnosed with esophageal cancer from January, 2009, to December, 2011, in a Sao Paulo (Brazil) quaternary oncology institute were retrospectively reviewed. ***Results -*** Squamous cell cancer made up to 80% of the cases of esophageal cancer. Average age at diagnosis was 60.66 years old for esophageal adenocarcinoma and 62 for squamous cell cancer, average time from the beginning of symptoms to the diagnosis was 3.52 months for esophageal adenocarcinoma and 4.2 months for squamous cell cancer. Average time for initiating treatment when esophageal cancer is diagnosed was 4 months for esophageal adenocarcinoma and 4.42 months for squamous cell cancer. There was a clear association between squamous cell cancer and head and neck cancers, as well as certain habits, such as smoking and alcoholism, while adenocarcinoma cancer showed more association with gastric cancer and gastroesophageal reflux disease. Tumoral bleeding and pneumonia were the main causes of death. No difference in survival rate was noted between the two groups. ***Conclusion -*** Adenocarcinoma and squamous cell carcinoma are different diseases, but both are diagnosed in advanced stages in Brazil, compromising the patients' possibilities of cure.

HEADINGS - Adenocarcinoma. Squamous cell carcinoma. Epidemiologic factors. Period analysis.

INTRODUCTION

Esophageal cancer (EC) is among the ten most common cancer worldwide and it is one of the leading causes of mortality among the neoplasms that affect the gastrointestinal tract. During the last four decades, the incidence of EC increased significantly[8]. In Brazil, for instance, it is the 6th most frequent cancer in men and 15th in women. In the year of 2014, 10,780 new cases of EC were diagnosed in Brazil and, in 2011, it was responsible for 7,636 deaths. Even though the survival rate for patients with EC has improved over the decades, it is still very poor, for curative treatment is only destined to patients with early or, at most, locally advanced disease[6].

The mortality and incidence trends for EC have varied in many countries over the last decades, especially regarding histological subtypes – adenocarcinoma and squamous cell carcinoma. There are marked differences between these subtypes in terms of incidence, natural history and treatment outcomes. Over the world, but most importantly in Western Europe and North America, it has been observed a higher incidence of esophageal adenocarcinoma (EA), in comparison with squamous cell carcinoma (SCC), which is possibly due to the increase of obesity and gastroesophageal reflux (GERD) incidence in those regions. Even so, SCC still accounts for about 90% of cases of EC worldwide. In Brazil, where SCC is also predominant, corresponding to 96% of all EC cases, it has also been noticed an increasing incidence of esophageal adenocarcinoma[7,12,14].

An important characteristic of esophageal cancer is its strong association with known risk factors, for example alcoholism, tabagism, Barrett esophagus (BE) and human papiloma virus infection. Also, a marked characteristic of EC is its heterogenic incidence, higher in Asian countries and a milder incidence in European and American countries. A great diversity is also observed in Brazil, with four cases in every 100 thousand inhabitants in the North of the country and 15 cases for the same size population in the South.

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Given the important participation of esophageal cancer in incidence and mortality rates and the observed changes regarding the prevalence of EA, this study aims to describe both clinically and epidemiologically the population of patients with diagnosis of EC treated in a quaternary attention institute for cancer from January, 2009 to December, 2011, in Sao Paulo, Brazil, in order to establish a profile of these patients and compare it with data of other services.

METHODS

The charts of all patients diagnosed with esophageal cancer from January, 2009, to December, 2011, in a Sao Paulo (Brazil) quaternary oncology institute (ICESP - Instituto do Cancer do Estado de Sao Paulo) were retrospectively reviewed.

Patients were analyzed according to demographic aspects (gender, age, age of diagnosis, body mass index, ethnicity and performance status), known risk factors (alcoholism, smoking, Barrett esophagus, achalasia), associated diseases and neoplasms, localization of the tumor, histologic type, staging, treatment, complications and survival.

The population studied was composed of 565 individuals (n=565), of which 20.7% were female and 79.3% male. The age at diagnosis ranged from 32 to 94 years old.

Regarding statistical analysis, for contingency tables, a Fisher exact test was used; to compare independent means, Student-t test was empolyed.

RESULTS

Among all patients (n=565), 105 (19.13%) had the diagnosis of adenocarcinoma, 444 (80.87%) had squamous cell carcinoma, and 16 (2.83%) had other esophageal neoplasms, such as neuroendocrine or gastrointestinal stromal tumors.

The mean time between first symptoms and diagnostic was 4.31±2.85 months and the mean time to initiate treatment was 4.01±3.12 months.

Comparing gender prevalence between EA and SCC, there were no significant differences – both affect predominantly males, who represented 78.4% of patients with EA and 82.9% of patients with SCC (*P*=0.351).

Racial distribution of incidence is illustrated in Figures 1 and 2, both showing a prevalence of Caucasian patients in both subtypes of EC. Statistical analysis of this distribution showed that EA affects Caucasians in a significantly higher proportion than black, Asian or grayish brown patients (*P*=0.01).

Average age at the diagnosis was 60.66 years old (StDev 9.73 years old) for SCC and 62.46 years old (StDev 13.03 years old) for EA, with no statistic difference (*P*=0.213). Average time from the beginning of symptoms to the diagnosis was 3.52 (StDev 2.39) months for EA and 4.2 (StDev 3.04) months for SCC (*P*-value for the difference=0.036). Average time for initiating treatment when esophageal cancer is diagnosed is 4 (StDev 2.42) months for EA and 4.42 (StDev 2.96) months for SCC (*P*-value for the difference=0.22).

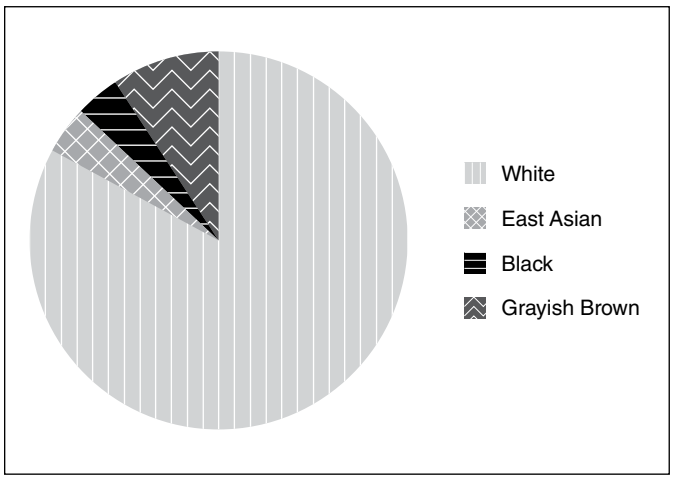

FIGURE 1. Racial distribution of Esophageal Adenocarcinoma

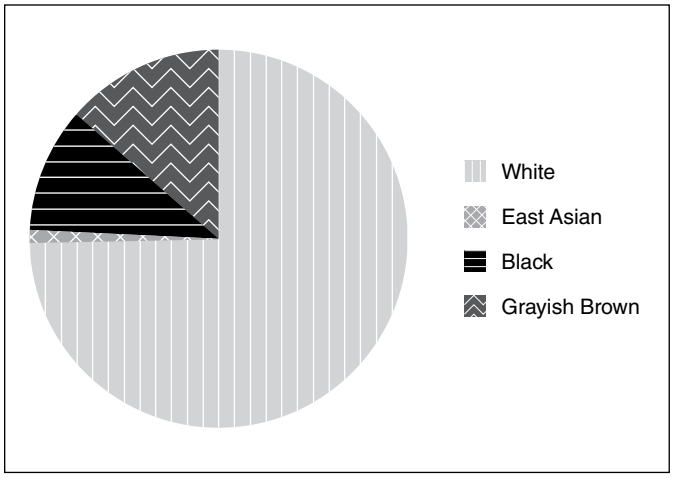

FIGURE 2. Racial distribution of Esophageal Squamous Cell Carcinoma

Initial clinical stage is seen in Figures 3 and 4, showing a predominance of advanced stages at diagnosis (IIIC and IV) in more than half of the cases, in both EA and SCC.

Body mass index (BMI) at the time of diagnosis and weight loss after beginning of symptoms are described in Table 1. Adenocarcinoma patients had a higher BMI at diagnosis, but SCC patients had a higher weight loss.

Status performance at the diagnosis was evaluated by ECOG and Karnofsky (KPS) functional evaluation, with no significant difference of performance status among patients with EA and SCC.

Regarding associated neoplasms, 18.4% of patients diagnosed with EA had an associated neoplasm - previous, posterior or synchronic to the EC, 42.1% of which were synchronic. For SCC, however, only 12.4% had associated neoplasm, 42.6% of which were synchronic. As seen in Table 2, the neoplasms associated with SCC were predominantly head and neck tumors.

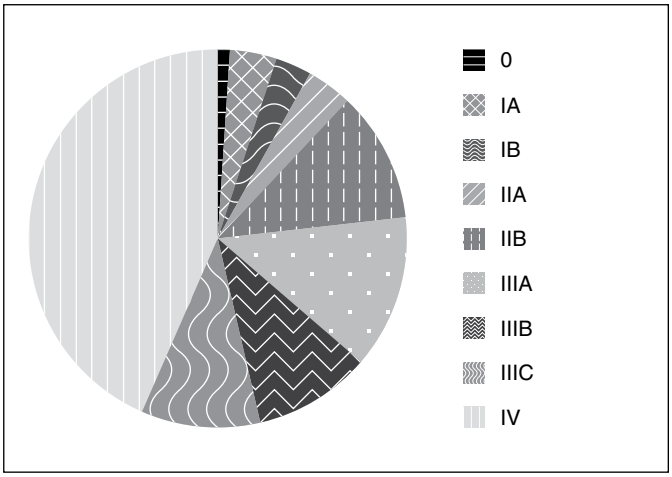

FIGURE 3. Initial clinical stage in esophageal adenocarcinoma

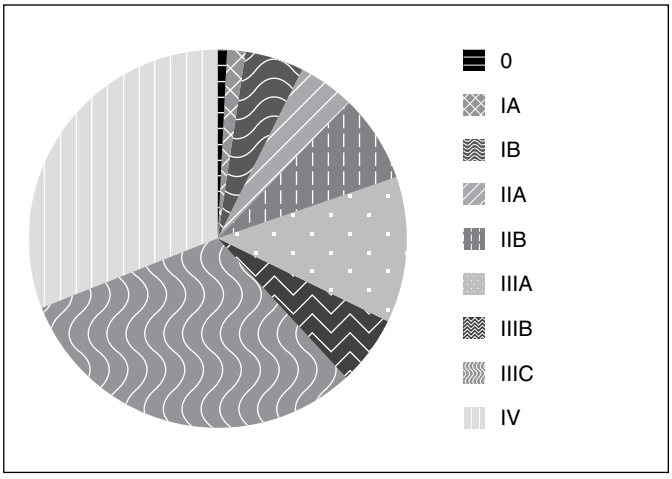

FIGURE 4. Initial clinical stage in esophageal squamous cell carcinoma

TABLE 1. Body mass index (BMI) and weight loss after begin of symptoms. Adenocarcinoma patients had a higher BMI at diagnosis, but squamous cell carcinoma patients had a higher weight loss

BMI and weight loss	Adenocarcinoma	Squamous cell carcinoma	95% CI for difference
BMI at the diagnosis (kg/m²)	23.31	20.43	1.603; 4.151
BMI variation since initial symptoms to the diagnosis (kg/m²)	3.97	3.87	-0.847; 1.038
BMI variation per month (kg/m² per month)	1.14	3.87	-3.282; -2.174
Weight loss (%)	14.6	16.6	-5.25; 1.39

TABLE 2. Main associated neoplasms. Head and neck tumors are much more often found in association to squamous cell carcinoma patients, meanwhile gastric adenocarcinoma is more often associated with gastric adenocarcinoma

Main associated neoplasms	Neoplasms associated with SCC (%)	Neoplasms associated with EA (%)	*P*-value for the difference
Colorrectal neoplasm	0	3	0.101
Head and neck SCC	7	1	0.005
Gastric adenocarcinoma	0	5	0.020
Prostatic cancer	0	1	0.476

SCC: squamous cell carcinoma; EA: esophageal adenocarcinoma.

Familiar oncologic past was also investigated (see Table 3), but only family history of colorrectal cancer was statistically associated with higher incidence in EA.

Habits and addictions were also evaluated. Alcoholism and smoking were more prevalent among SCC patients in comparison with EA patients ($P<0.05$). The mean smoking load (packs per day multiplied by years smoking) was 20.89 (SE mean 3.4) for EA patients and 45.27 (SE mean 3.96) for SCC patients.

Presence of known association with non-oncologic diseases is described in Table 4, showing that Barrett esophagus and Gastroesophageal Reflux Disease (GERD) are more frequent in EA patients. On the other hand, chronic obstructive pulmonary disease (COPD) is more common in SCC patients.

The survival rate of patients with EA was of 13.2 months (±StDev 10.2 months) and of 14 months (±StDev 11.2 months) for patients with SCC, with no significant difference between them.

TABLE 3. Familial oncological past. History of colorrectal tumors in the family is more common in esophageal adenocarcinoma patients

Familial oncological past	EA- At least one first degree family member with neoplasm (%)	SCC- At least one first degree family member with neoplasm (%)	*P*-value for the difference
Colorrectal cancer	8	2	0.031
Gasric adenocarcinoma	6	3	0.203
Esophageal cancer	3	2	0.100
Prostate cancer	5	2	0.353
Breast cancer	7	4	0.227
Head and neck cancer	3	5	0.386
Cervical cancer	3	1	0.246
Lung cancer	6	3	0.172

TABLE 4. Comorbidities. Barrett esophagus and GERD are more frequent in esophageal adenocarcinoma patients. On the other hand, chronic obstructive pulmonary disease (*COPD) is more common in SCC patients

Non-oncologic associated diseases	EA (%)	SCC (%)	*P*-value for the difference
Diabetes mellitus	15	9	0.062
Systemic hypertension	34	28	0.167
Obesity	8.4	3.58	0.058
Barrett esophagus	12	0	0.000
GERD	17	0	0.000
Hiatal hernia	9	0	0.001
Pulmonary tuberculosis	3	5	0.076
Chagas disease	1	2	0.289
COPD*	4	9	0.021

EA: esophageal adenocarcinoma; SCC: squamous cell carcinoma.

The main causes of death and main complications associated with EC were also studied and are described in Tables 5 and 6, respectively. Tumoral bleeding and pneumonia were the leading causes of death for both EA and SCC patients, even though tumoral bleeding, tracheoesophageal fistula and pulmonary abscess/pleura empyema are far more often in SCC.

TABLE 5. Causes of death. There was no statistical significance in causes of death for esophageal adenocarcinoma or squamous cell carcinoma

Causes of death	EA (%)	SCC (%)
Pneumonia	42	64
Tumoral bleeding	14	11
Massive hemoptysis	2	1
Pulmonary thromboembolism	2	1
Acute abdominal obstruction	6	0
Vascular acute abdomen	2	0
Cerebrovascular accident	2	0
Cholangitis	2	0
Acute pulmonary edema	2	0
Infectious endocarditis	4	0
Surgical complications	2	1
Intracranial hypertension	2	1
Urinary tract infection	4	2
Acute renal injury	4	3
Febrile neutropenia	4	0
Hepatorenal syndrome	2	0
Other causes of sepsis (excluded pneumonia and urosepsis)	14	11

EA: esophageal adenocarcinoma; SCC: squamous cell carcinoma.

TABLE 6. Complications in esophageal carcinoma. Tumoral bleeding, tracheoesophageal fistula and pulmonary abscess/pleura empyema are far more often in squamous cell carcinoma, meanwhile venous or pulmonary thromboembolism is more common in esophageal adenocarcinoma

Complications	EA (%)	SCC (%)	*P*-value for the difference
Tumoral bleeding	6	13	0.044
Tracheoesophageal fistula	0	10	0.000
Venous or pulmonary thromboembolism	9.52	3	0.022
Pulmonary abscess or pleural empyema	0	4.95	0.003

EA: esophageal adenocarcinoma; SCC: squamous cell carcinoma.

DISCUSSION

Incidence rates of esophageal cancer are very heterogeneous worldwide and even in the same country. Southern Brazil, for instance, has the highest rate of esophageal cancer in South America, meanwhile Northern Brazil has a very low incidence of the disease (4:100 000 inhabitants)[2,12].

Even though many studies show a changing pattern in the incidence of esophageal adenocarcinoma when compared to squamous cell carcinoma worldwide and in São Paulo[2,9], in our service, there is still an absolute predominance of the latter. A recent research performed in Rio Grande do Sul State (Southern Brazil), showed that not only the prevalence rate of esophageal cancer, along a 20 year-period, remained stable, but also, the proportions of SCC and ADC did not change– 92% of the cases are SCC and 7.9% are EA[5].

Some studies also show a higher prevalence of esophageal carcinoma in black males, with a trend of increasing incidence of adenocarcinoma among white males. In our service, however, most of the patients with EC, either EA or SCC, were white males, and the predominance of white patients in the population with EA was statistically significant (P=0.001)[2].

The association between SCC and smoking and alcoholism found in this study is consistent with literature[11]. Also, the association of SCC with head and neck tumors, found in the present study, is well reported in other researches and is probably related to the fact that exposition to tobacco and alcohol is present in most patients with those diseases.

An interesting finding of this study, which does not correlate with current worldwide data is the higher incidence of EC among white males. Most of the information available today shows a higher incidence among afro-descendants. However, in this study, the vast majority of patients were male Caucasians, with statistically relevance in patients with EA, in special. This may be due to the higher number of white people in Sao Paulo than other Brazilian places[3,13].

Regarding associated neoplasms, meanwhile SCC is known to be frequently associated with oropharingeal tumors (probably because of field cancerization), it seems that EA is associated with gastric adenocarcinoma – the incidence of gastric adenocarcinoma in patients with EA was 500:10 000 and in the general Brazilian population it is about 1:10 000. This finding is also in accordance with literature[4,10].

In this study, familial history of esophageal cancer did not correlate to increased risk of EC. However, familial history of colorrectal cancer was associated with higher risk of esophageal adenocarcinoma. No conclusive studies about familial past and esophageal cancer have been performed so far. There are some researches, though, that suggest possible association between Barrett esophagus with colorrectal cancer, but the mechanism by which this occurs is not well established yet[1,15].

Another important finding of this study is the long time for diagnosing the cancer. It was noted that the time between first symptoms and diagnosis is even longer for SCC. That leads to more advanced stages at diagnosis, and, added to another long period until starting treatment in Brazil, hinders the patients' chances of curative treatment.

CONCLUSION

Each population has its demographic features in esophageal cancer, due to each particularity in population habits and genetics. Adenocarcinoma and squamous cell carcinoma are indeed different diseases, from epidemiological features to biological behavior. Nevertheless, Brazilian late diagnosis and delay in starting treatment are factors that contribute to the high incidence of advanced stages for both diseases. More effort should be made in order to earlier diagnose and initiate treatment of these patients so that their prognosis can be improved.

Authors' contributions

Kimura CMS: data collection and text composing. Tustumi F: data collection and satistical analysis. Takeda FR: research design and execution. Sallum RAA: research design. Ribeiro Junior U: research design. Cecconello I: research design.

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RESUMO - ***Contexto*** **-** Câncer esofágico é uma das principais causas de morte por câncer dentre as neoplasias do trato gastrointestinal. Há diversos fatores que contribuem para o desenvolvimento de um perfil epidemiológico de câncer de esôfago em uma população. ***Objetivo*** **-** Este estudo visa descrever tanto clínica quanto epidemiologicamente a população de pacientes com diagnóstico de câncer esofágico tratados em um instituto quaternário de atendimento ao câncer desde janeiro de 2009 a dezembro de 2011, em São Paulo, Brasil. ***Métodos*** **-** Os prontuários de todos os pacientes diagnosticados com câncer de esôfago de janeiro de 2009 a dezembro de 2011 em um Instituto quaternário de tratamento oncológico foram revisados retrospectivamente. ***Resultados*** **-** Carcinoma epidermóide foi responsável por 80% dos diagnósticos de câncer esofágico. Idade média ao diagnóstico foi de 60 anos para adenocarcinoma (EA) e 62 para carcinoma epidermóide e o tempo médio entre início dos sintomas até o diagnóstico foi de 3,52 meses para adenocarcinoma e 4,2 para carcinoma epidermóide. O tempo médio para iniciar tratamento foi de 4 meses para adenocarcinoma e 4,42 meses para carcinoma epidermóide. Houve uma clara associação entre carcinoma epidermóide e neoplasias de cabeça e pescoço, bem como com alguns hábitos, tais como tabagismo e etilismo. Adenocarcinoma, por sua vez, mostrou-se associado a câncer gástrico e doença do refluxo gastroesofágico. Sangramento tumoral e pneumonia foram as principais causas de morte para ambos os tipos de câncer. Não foi observada diferença na sobrevida entre os dois grupos. ***Conclusão*** **-** Adenocarcinoma e carcinoma epidermóide são doenças diferentes, mas ambas ainda são diagnosticadas em estados avançados no Brasil, comprometendo a possibilidade de cura dos pacientes.

DESCRITORES - Adenocarcinoma. Carcinoma de células escamosas. Fatores epidemiológicos. Análise transversal.

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