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Clinical and Anatomopathological Findings in Patients with Oesophageal Cancer in Santiago de Cuba.

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Abstract

Oesophageal cancer is one of the most lethal neoplasms with the worst prognosis; its incidence and mortality have increased in recent decades, reaching seventh and sixth place worldwide, respectively. The magnitude of this disease is alarming; in 2020 alone, 604 000 new cases and 544 000 deaths will be reported. In Cuba, it has increased, and according to reports, it went from not being among the top 10 causes of cancer deaths in men to occupying ninth place. The aim of this study is to describe the clinical, diagnostic and anatomopathological characteristics of patients with oesophageal cancer in the province of Santiago de Cuba according to the main histological variants.

A cross-sectional descriptive observational study was conducted to determine these characteristics in the population of patients with oesophageal cancer admitted to the Provincial Hospital of Santiago de Cuba between January 2011 and December 2020, a sample of 195 patients was taken according to the inclusion and exclusion criteria established in the research. The results show that in a low percentage of patients (18, 5 %) predisposing diseases for oesophageal cancer were identified. Dysphagia and weight loss were the most prevalent symptoms, although they were accompanied by an important variety of symptoms and signs. Diagnosis was made at advanced stages, 71.3 % of cases were classified as stage IV, with no significant differences between one histological type and another. Liver metastases were the most frequent in squamous cell carcinoma (44.7 %) and in adenocarcinoma those in non-regional lymph nodes (28.0 %). The variables analysed in this study characterise a population in which the disease presents in advanced stages, regardless of histological variants, with the presence of locoregional lymph node involvement, metastases, mainly liver metastases, and a highly varied symptom profile with a predominance of dysphagia and weight loss.

Keywords: *oesophageal adenocarcinoma, oesophagus cancer, squamous cell cancer.*

Abbreviations:

American Joint Committee on Cancer (AJCC)

Computed tomography scan (CT)

Endoscopic ultrasound scanning (EUS)

Gastro-oesophageal junction (GOJ)

Gastro-oesophageal reflux (GOR)

Gastro-oesophageal reflux disease (GORD)

Magnetic Resonance Imaging (MRI)

Oesophageal cancer (OC)

Oesophageal adenocarcinoma (OAC)

Positron emission tomography (PET/CT)

Squamous cell carcinoma (OSCC)

Union for International Cancer Control (UICC)

Worldwide Oesophageal Cancer Collaboration (WECC)

Introduction

Cancer represents a true global pandemic, the incidence and prevalence of this disease are increasing rapidly in almost all countries and is considered by the World Health Organisation (WHO) to be the leading cause of death worldwide, accounting for almost 10 million deaths in 2020, i.e. almost 1 in 6 of the deaths recorded. The organisation itself declares it to be a major obstacle to increasing life expectancy in all countries of the world.[1,2] To give a brief but alarming overview of the problem it is worth noting that in 2018 alone 18.1 million new cases were reported worldwide and 9.5 million deaths while in 2020 the incidence increased to 19.3 million cases and mortality to 10.0 million and according to GLOBOCAN estimates the incidence will increase in the next 2 decades to 29.5 million per year until 2040.[3,4]

Oesophageal cancer (OC) is one of the most lethal neoplasms with the worst prognosis, second only to pancreatic cancer. The incidence of oesophageal cancer has increased over the last decades, reaching seventh place worldwide in incidence and sixth in mortality.

The magnitude of this disease is alarming, with 604 000 new cases and 544 000 deaths reported in 2020 alone, making it responsible for one in every 18 cancer deaths that year. Both mortality and incidence vary depending on geographical areas, with regions known as hotspots for oesophageal cancer, including northern China, Japan, the Caspian region of Iran, etc., where there are also marked differences with respect to the main histological variants of OC.[3–5] In Cuba, the incidence and mortality of this disease have increased, and according to the reports of the Statistical Yearbooks,[6] OC went from not being among the 10 leading causes of cancer death among men to occupying the ninth place. In 2020, there were 852 deaths from OC in the country (696 men and 156 women).

The aetiology of this entity is multifactorial, however, some diseases and habits have been described that increase the risk of OC, many of them more strongly associated with squamous cell carcinoma (OSCC) or oesophageal adenocarcinoma (OAC). The diagnosis of OC is often made at advanced stages, hence its high lethality and poor survival. Few studies have been carried out in Santiago that address the subject of oesophageal cancer, the most recent published study [3] corresponds to the authors of this research where an analysis is made of survival in patients with OC in the period 2016-2020.

For all of the above reasons, we decided to carry out this study in which our research objective is to describe the clinical, diagnostic and anatomopathological characteristics of patients with oesophageal cancer in the province of Santiago de Cuba according to the main histological variants.

Materials and Methods

1. General characteristics of the research

A cross-sectional descriptive observational study was carried out to determine the clinical and histopathological characteristics of the population of patients with oesophageal cancer admitted to the Saturnino Lora Provincial Hospital in Santiago de Cuba between January 2011 and December 2020.

2. Population and sample

The population consisted of all patients diagnosed with oesophageal cancer between 2011 and 2020, from which a sample of 195 patients was taken, taking into account the histological diagnosis. With the selected sample, an analysis of clinical variables of interest was performed: signs and symptoms, predisposing illnesses, tumour topography, tumour morphology, cell differentiation, metastasis, locoregional lymph node spread, and clinical TNM staging.

3. Inclusion criteria

- Subjects with histological diagnosis during necropsy.

4. Exclusion criteria

- Patients under 18 years of age
- Patients without a confirmatory histological diagnosis of the disease.
- Subjects with histological diagnoses other than squamous cell carcinoma and adenocarcinoma
- Subjects with neoplasms of the oesophagogastric junction Siewert-Stein II and III.

5. Methodology

The methodology used in this study was determined by the research aims. Consequently, methods were used to obtain scientific knowledge at the empirical level, such as observation to establish clinical characteristics of the subjects investigated; measurement: to demonstrate elements belonging to the entity under study and statistical-analytical to determine and evaluate the results obtained on the basis of the discussion with the postulates held by other authors.

6. Techniques and procedures

Primary and secondary sources were consulted to obtain the information; articles from national and international publications from the last 10 years indexed in Index Medicus were reviewed. The databases PubMed, Directory of Open Access Journals, Wiley, Scielo and ClinicalKey were used. The search strategy used included the keywords "oesophageal cancer", "oesophageal adenocarcinoma", "squamous cell carcinoma", and other keywords such as "staging", "metastasis", and their equivalents in Spanish and Portuguese, with no language limits. The data obtained were processed and analysed using summary measures for each variable and percentage. The analysis was carried out with the statistical programme SPSS for Windows version 20.0, where frequency distribution tables were created.

Analysis and Discussion of Results

Predisposing Illnesses

Table 1 shows the main predisposing diseases related to oesophageal cancer detected in our population according to each histological variant. Of the casuistry, only 18,5 % of the patients had any of these diseases. Of the patients with OAC, 62,2 % (23 subjects) reported some type of predisposing condition, while 8,4 % (13 subjects) of those diagnosed with OSCC reported some of these.

Predisposing Illnesses	Squamous cell carcinoma (n=13)		Adenocarcinoma (n=23)	
	No.	%	No.	%
Chronic gastritis	3	23,3	7	30,4
GORD	0	0.0	7	30,4
Caustic esophagitis	6	46,2	1	4,3
Hiatal hernia	1	7,6	5	21,7
Barrett's oesophagus	0	0,0	3	13,0
Achalasia	2	15,3	0	0,0
Oesophageal diverticula	1	7,6	0	0,0
Total	13	100	23	100

Table 1. Distribution according to Predisposing Illnesses and Histological Variants

These results, analysed as a whole, do not provide significant data to help compare both histological types, as there was incomplete recording in the clinical histories and a lack of knowledge on the part of the patients regarding previous conditions related to OC, as they had not undergone endoscopic or other studies to confirm these diagnoses, which generates under-reporting and does not allow us to assess the true magnitude of these diseases concerning OC. However, the results obtained are useful to indicate which specific conditions occurred more frequently in each of the histological types studied.

Among patients with OSCC who reported a predisposing disease, caustic oesophagitis was the most frequent, with 46,2 % reporting this condition as a pathological history, followed by chronic gastritis with 23,3 % and achalasia with 15,3 %. No history of GORD or Barrett's oesophagus was reported in these patients, and only one patient reported previous surgery for Zenker's diverticulum.

Caustic oesophagitis has been identified as an important factor in the development of OC. Mu et al[7] in a cohort study in Taiwan, found that the adjusted hazard ratio for OC was 2,33 (95 % CI = 1,41–3,86) in the¬ caustic poisoning cohort, higher than in the unexposed group, and concluded that ingestion of these substances is a risk factor for developing OC. Authors such as Mingol Navarro[8] outline that the development of OC in these patients occurs late, and malignant degeneration increases with the time of evolution.

Other authors [9,10] recognise chronic gastritis as a risk factor for OC. Hiripi et al,[10] in a German cohort, studied the causal association between H. pylori infection and chronic atrophic gastritis with gastric and oesophageal neoplasia; they found that gastritis can become a risk factor for OC, although the greatest risk is from gastric neoplasia.

Although there were only 2 patients with achalasia in our casuistry, it is important to pay attention to this disease, as it is well established as a risk factor for OC in general. [11–13] The relationship between achalasia and oesophageal carcinoma was first reported in 1872,[14] since then, several case reports and studies have been presented on the subject. Abnet et al,[15] in their research summarise the predisposing diseases for OSCC with the strongest evidence and achalasia appears with a high relative risk, but they state that the absolute risk may be low. However, the Mexicans Torres-Aguilera and Remes Troche,[14] state that the prevalence of OSCC, in subjects with achalasia, is 26 per 1000 cases, while the prevalence of OAC is 4 per 1000.

Patients with achalasia have a 50 times higher risk of developing OSCC than the general population, and the disease manifests 20 to 25 years after the onset of achalasia symptoms.[16] A median time interval of 5,7 years from diagnosis of achalasia to a diagnosis of OSCC has also been reported.[14] In our investigation, patients in whom achalasia was recorded as a personal pathological history had an interval of 4,7 and 5,2 years from confirmed disease to a diagnosis of oesophageal neoplasia, which was histopathologically confirmed as OSCC.

In terms of OAC, two antecedents coincided as the most frequent: GORD and chronic gastritis, with 30.4% (7 subjects; n=23), the former only occurring in patients with this type of histological variant as well as Barrett's oesophagus. GORD has a very high incidence and prevalence worldwide and accounts for approximately 75,0% of all oesophageal conditions.[17] Cases diagnosed with GORD correspond to 17,1% of all subjects with OAC, and is similar to the prevalence of the disease in Europe, where it ranges from 8.8% to 25,9 %.[18] Several studies from the 1990s[19–22] to the present day[23,24] have highlighted the association between GORD and OAC. Histopathological changes in the squamous epithelial cells of the distal oesophagus, due to the action of refluxed material and in interaction with other factors, lead to the development of BO that may progress to dysplasia, which can result in OAC. [25,26]

Barrett's oesophagus was present in 13,0 % of subjects with OAC who had predisposing diseases. Despite representing only 1,5 % of the caseload, it is clear that patients with this diagnosis developed OAC as well as patients with a diagnosis of GORD. OB is considered to be the only known pre-malignant lesion predisposing to this histological variety of oesophageal cancer.[27] So much so that endoscopic surveillance of OB is considered the mainstay of treatment of adenocarcinoma.[28] Chilean scientists [29] even use the term "Barrett's adenocarcinoma" to refer to OAC directly derived from OB.

Furthermore, 6 subjects (12,2 %) with OAC had a history of hiatal hernia, accounting for 83,3 % of hiatal hernia diagnoses, and in two of them, it was associated with GOR. According to Holmberg et al,[30] this disease has not been extensively studied as a predisposing factor for OAC and in their study, they determined that the presence or size of a hiatal hernia was not associated with any of the outcomes

when estimating the Odds Ratio (OR) on variables that could constitute absolute or relative risk factors for OAC specifically.

Symptoms and Signs

In this series, dysphagia was the prevalent symptom in most cases, with a total of 139 patients (71,3 %) presenting this symptom. During admission, 75,9 % were diagnosed with OSCC and 14,2 % with OAC. This result is in agreement with the reports of most national[31–33] and international series.[34,35] In addition to dysphagia, weight loss was the most frequently reported symptom among patients, mainly those who developed OSCC. This is related to the difficulty in feeding experienced by these patients due to the intraluminal growth of the tumour, which stenoses the lumen and eventually causes aphagia, which led 92,0 % of these patients to undergo surgery with palliative intent to ensure feeding and improve their quality of life, mainly gastrostomies.

Signs and symptoms	Squamous Cell Carcinoma		Adenocarcinoma	
	No.	%	No.	%
Dysphagia	117	76,0	22	53,7
Weight loss	72	46,8	4	9,8
Retrosternal pain	33	21,4	8	19,5
Sialorrhoea	21	13,6	2	4,9
Passive regurgitations	17	11,0	11	26,8
Odynophagia	14	9,1	0	0,0
Asthenia	12	7,8	0	0,0
Active regurgitations	11	7,1	7	17,1
Vomiting	6	3,9	1	2,4
Cough	5	3,2	1	2,4
Difficulty breathing	4	2,6	0	0,0
Anorexia	2	1,3	6	14,6
Epigastric pain	2	1,3	4	9,8
Haemoptysis	1	0,6	0	0.0
Heartburn	1	0,6	6	14,6
Fever	1	0,6	1	2,4

Note: *The percentage was not calculated based on the n for each histological variant, as the same patient presented with more than one symptom or sign.*

Table 2. Distribution according to Symptoms and Signs and Histological Variants

Passive regurgitations and retrosternal pain were the most common symptoms after dysphagia and weight loss. Odynophagia was present in 14 cases, 13 with tumours in the upper segment and 4 in the cervical oesophagus and middle third, and was associated in all cases with sialorrhoea. Simultaneous symptoms and signs were observed in several patients, with the frequent association of dysphagia with

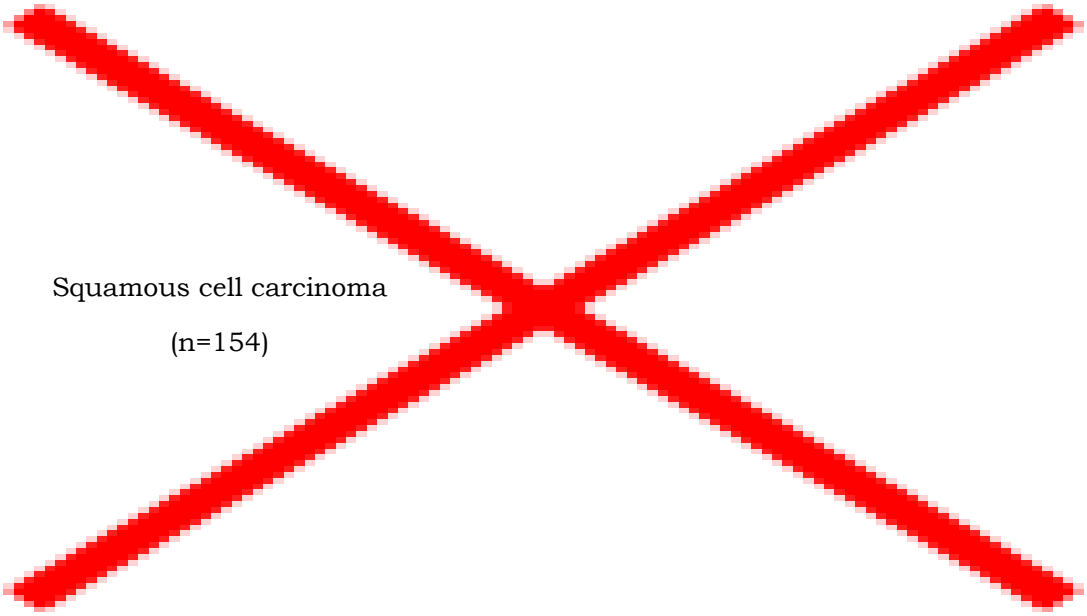
asthenia, weight loss and sialorrhoea in patients with upper and cervical OSCC. Dysphagia, retrosternal pain, asthenia, weight loss and regurgitations were also frequent symptomatic associations.

The symptom picture of patients with advanced-stage OC is very varied and is related not only to the intraluminal growth of the neoplasm but is also closely associated with locoregional spread, invasion of adjacent structures and distant metastases. It is common to see a general syndrome and the appearance of new clinical manifestations over time.

The clinical diagnosis of OC, in the series, was hindered and delayed by multiple factors, most of which, as we were able to ascertain while carrying out this research, depended on the patient, as more than 80,0 % of them did not go to the medical services in the presence of the first clinical signs, for various reasons. In other cases, however, it was found that the medical staff were slow in dealing with the diagnosis, especially when it came to carrying out paraclinical studies.

Tumour Topography

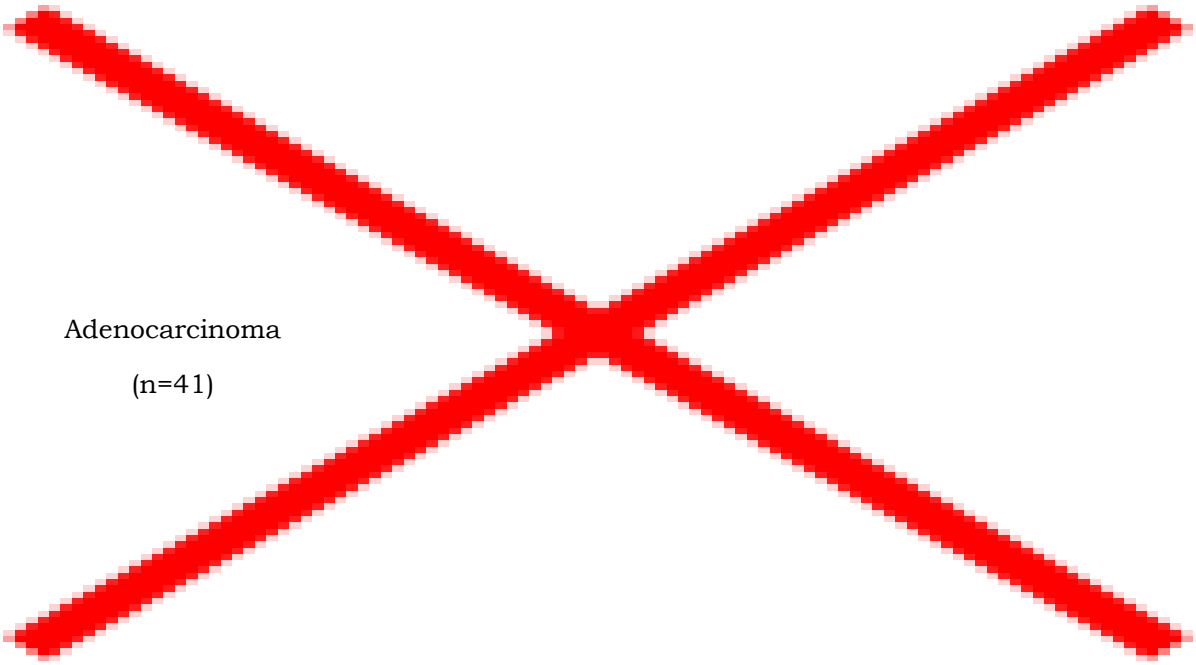
In our series, about the topography of the OC, the location in the middle third had a higher percentage weight with 51,8 % of all the subjects studied. OSCC was also more frequent in the middle thoracic portion with 63,0 % (n=154), as can be seen in Graph 1, while OAC was more frequent in the lower third with 90,2 % of the subjects with this histological variant (Graph 2). One of the cases of lower segment OAC corresponded to adenocarcinoma of the oesophagogastric junction classified as a Siewert-Stein I, and in addition, 4 patients were diagnosed with mid-portion OAC. These results are consistent, in terms of the predominance of the location of malignant tumours of the oesophagus in the middle third, with those reported by Cuban authors(28,29).



Graph 1. Distribution according to Tumour Topography and Squamous cell carcinoma

In Cuba, Cora Estopinán's series[31] reported an overall predominance of tumours located in the middle third, with 32 cases out of 59 studied. According to the histological variants, OSCC was predominantly located in the middle segment, while lower thoracic region OAC showed a slight superiority over those in the middle thoracic region, 7 versus 6. On the other hand, Ávalos García[32] reported 21 neoplasms in the middle thoracic portion and histologically all were classified as OSCC, while all the neoplasms in the lower third were OACs.

In the series from the Ricardo Palma University, Peru,[36] the preeminence was for OSCC located in the middle third, with 38,8 % (35; n=85) and 16,7 % for those in the lower segment; while OSCC had a unique location in the lower third, with 36,5 8 (31 cases). Overall, in this series, neoplasms in the lower region prevailed over those in the middle segment, which does not coincide with our research or with reports in other publications.



Graph 2. Distribución according to Tumour Topography and Adenocarcinoma

Similarly, Arias and Orellana, in Ecuador [37] reported that for OSCC the most common location was the middle segment with 45,3 % (n=83) and for OAC the distal portion in 80,6 % of individuals; but in more than half of the sample the neoplasms were located in the lower third. In our country, Hidalgo Herrera et al[38] also show hegemony of the lower third, largely due to the high incidence of OAC in this study. Vides de la Cruz,[39] who had a sample of 68 patients diagnosed with OC, reported that localisation in the upper intrathoracic region prevailed, followed by the middle segment in general. In particular, OAC was more frequent in the lower third with 45,4 % and OSCC in the upper oesophagus with 53,3 %.

It is important to note that none of these studies reflect in their discussion or methodology whether patients with tumours of the GOJ type II and III, according to the Siewert-Stein classification, were excluded from the diagnosis of OC, which may be the reason why the incidence of OAC and therefore the involvement of the lower segment is more frequent. In the present research, we found a case of a Siewert-Stein I adenocarcinoma that was included in the adenocarcinomas of the lower thoracic segment. As we collected data for this report, we found 6 reports of GOJ adenocarcinomas categorised as Siewert-Stein III and 1 as Siewert-Stein II and excluded from our case series.

Tumour Morphology

According to the results obtained —through endoscopy and anatomopathological studies of resected and necropsied deceased patients— the predominant morphological form in our series was the mixed type with 53 cases (27,9 %; n=195), followed by vegetating with 47 (24,2 %). For OSCC the main morphology was mixed at 27,7 % (43 patients; n=154) and in OSCC it was the infiltrative type with 29,3 % (12 cases; n=41), and the morphology could not be defined in 30 patients (26 OSCC and 4 OAC).

Gastroenterology texts [40] state that the most common form is polypoid or vegetating, although other literature [8] reports that mixed lesions are more common. In our research, we found a high number of polypoid lesions (26,5 %), but mixed lesions were predominant in 27,7 % of the subjects, although the difference between these two morphological types is minimal. Mixed OSCC was the most frequent within this histological type with 27,9 % (43; n=154) and infiltrating adenocarcinomas accounted for 29,3 % (12; n=41). These results are shown in Table 3.

Tumour morphology	Squamous cell carcinoma		Adenocarcinoma	
	No.	%	No.	%
Mixed type	43	27,9	10	24,4
Vegetative or polypoid	41	26,6	6	14,6
Infiltrating type	31	20.1	12	29,3
Without defined morphology	26	16,9	4	9,8
Localised ulcerated type	13	8,4	9	22,0
Total	154	100.0	41	100

Table 3. Distribution according to Tumour Morphology and Histological Variants

When comparing our findings with those obtained in other series, we found that Nazario et al,[33] despite not showing direct results in tables, in their publication report a marked predominance of infiltrative lesions and only 3 cases of polypoid lesions. Another investigation [31] reported a higher frequency of the vegetating type, reporting 88,1 % (52 cases) of the total in their series. Ávalos García et al,[32] reported that polypoid lesions predominated in their research.

Among international studies, Arias Orellana et al[37] report a higher incidence of the infiltrative type, with more than 50,0 % of the cases studied and with equal percentages for both histological types. A similar report was made by Vides de la Cruz,[39] with more than 60,0 % of his cases with infiltrating lesions; and Montiel Roa, in Paraguay, (167) reported a predominance of poorly differentiated infiltrating squamous cell carcinoma in his casuistry.

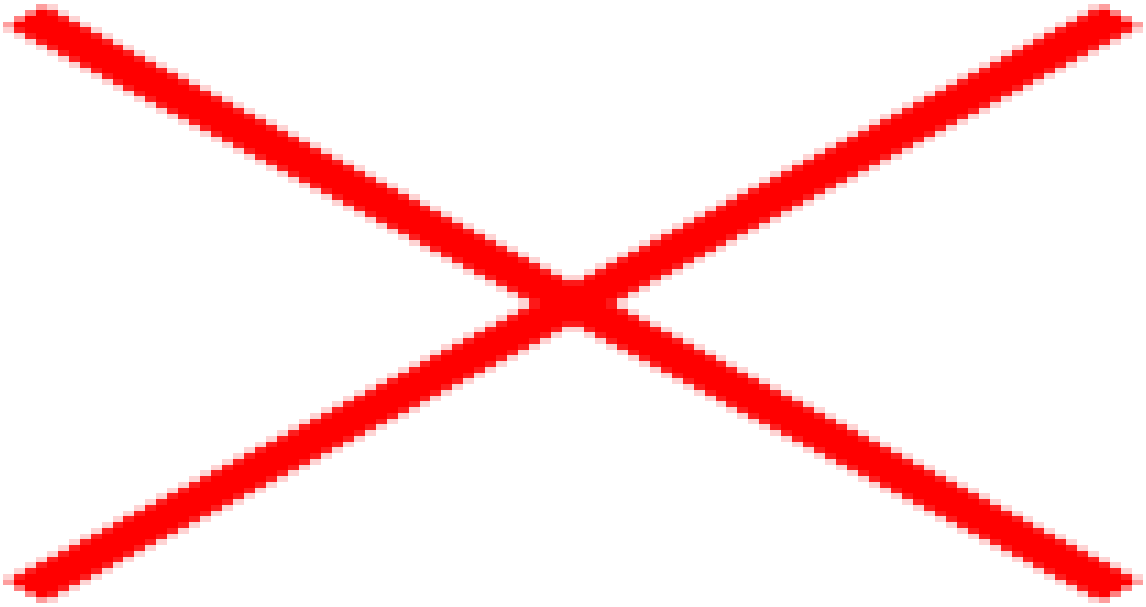
In Ecuador, Navas[35] reported a greater preeminence of localised ulcerative variants with 50,0 %, followed by vegetating with 15,9 %.

The presence of these mixed forms, as well as those of undefined morphology, in our study, coincides with the advanced stages of the disease, in which important changes in oesophageal morphology have occurred as a consequence of histopathological tissue alterations in the wall.

Grade of Cellular Differentiation

Differentiation is applied as a term in neoplasms to the cells that form their parenchyma, and indicates the degree to which parenchymal cells mimic comparable normal cells, both morphologically and functionally; thus well-differentiated tumours are made up of cells that resemble the mature cells of the tissue from which they originate.[41] This concept was introduced in the 7th AJCC/UIC TNM classification[42,43] for the staging of oesophageal neoplasms, hence its relevance to the analysis in this study.

Graph 3 shows the distribution of the degree of cellular differentiation of both histological types. It is clear that globally and particularly for OSCC and OAC, there is a predominance of moderately differentiated tumours, with 50,0 %, 50,6 % and 46,3 % respectively.



Graph 3. Distribution according to Grade of Cellular Differentiation and Histological Variants

In the series of Nazario et al[33] there was a clear predominance of well-differentiated squamous cell carcinoma, with 23 cases; they reported 5 cases in which it was not possible to establish the histological grading. Carballosa, in Guantánamo,[44] of the samples taken for histopathological studies, showed a higher frequency of well-differentiated OSCC, while the study of Faustino Pérez Hospital in Matanzas[31] reported 33 cases (55,9 %) of OSCC and 9 of OAC (15,9 %).

Metastasis

It is worth noting that in the research we decided, based on the findings obtained through paraclinical imaging studies and even through the histopathological results of necropsies, to analyse distant metastases and consider them according to their presence in one or more organs, designating them as simultaneous, when they occurred in several organs at the same time, or as metastases to a single organ when they affected a single organ. The involvement of non-regional oesophageal lymph node chains was taken into account.

Most of the metastases were diagnosed by CT and ultrasound, but it is worth mentioning that during necropsies performed on 26 of the patients with metastases, the diagnosis of metastases was confirmed and new ones were found. In summary, clinical metastases (cM) were defined in 121 cases, while in 8 patients they were established by necropsy (aM).

We found a total of 139 subjects (71,3 %; n=195) with distant dissemination, with liver metastases alone being the most frequent with 41,0 % (57; n=139), followed by simultaneous metastases with 20,1 % and non-regional lymph node metastases with 11,5 %. Metastatic lung, pancreatic, brain, bone and other metastatic lesions were also identified and are shown in Table 5.

Metastasis	Squamous cell carcinoma		Adenocarcinoma	
	No.	%	No.	%
To a single organ				
Liver	51	44.7	6	24.0
Lung	14	12.3	1	4.0
Non-regional lymph nodes	9	7.9	7	28.0
Pancreas	8	7.0	1	4.0
Spleen	2	1.8	4	16.0
Brain	3	2.6	0	0.0
Bones	2	1.8	0	0.0

Adrenal	1	0.9	1	4.0
Myocardium	1	0.9	0	0.0
Simultaneous	23	20.2	5	20.0
Total	114	100	25	100

Table 5. Distribution according to Metastasis and Histological Variants

According to each histological variant, we found that, for OSCC, liver metastases were the most frequent, at 44,7 %, followed by simultaneous metastases with 20,2 %. In OAC, the highest number of metastases occurred in non-regional lymph nodes, mainly hepatic and splenic, accounting for 28,0 %, with the expected involvement of the spleen and pancreas.

Invasion of lymph nodes 18 (hepatic) and 19 (splenic) was considered a metastatic lesion according to the criteria established by the AJCC/UICC in the Cancer Staging Manual, 7th edition 2009.[45] Confirmation of these lesions, as well as involvement in the rest of the organs, was confirmed by ultrasound and tomographic studies.

The literature on the study of OC reports that the most frequent site for metastases is the liver, which is consistent with our results. Horn et al[46] report that the 2,4 million cancer patients consulted in the Surveillance, Epidemiology and End Results (SEER) database showed that, with increasing age, liver metastases are more frequently associated with cancers of the oesophagus, stomach, small intestine and others, which was demonstrated in our study, where patients with OC and liver metastases were over 60 years of age, in contrast to lung metastases, which occurred more frequently in those under 50 years of age.

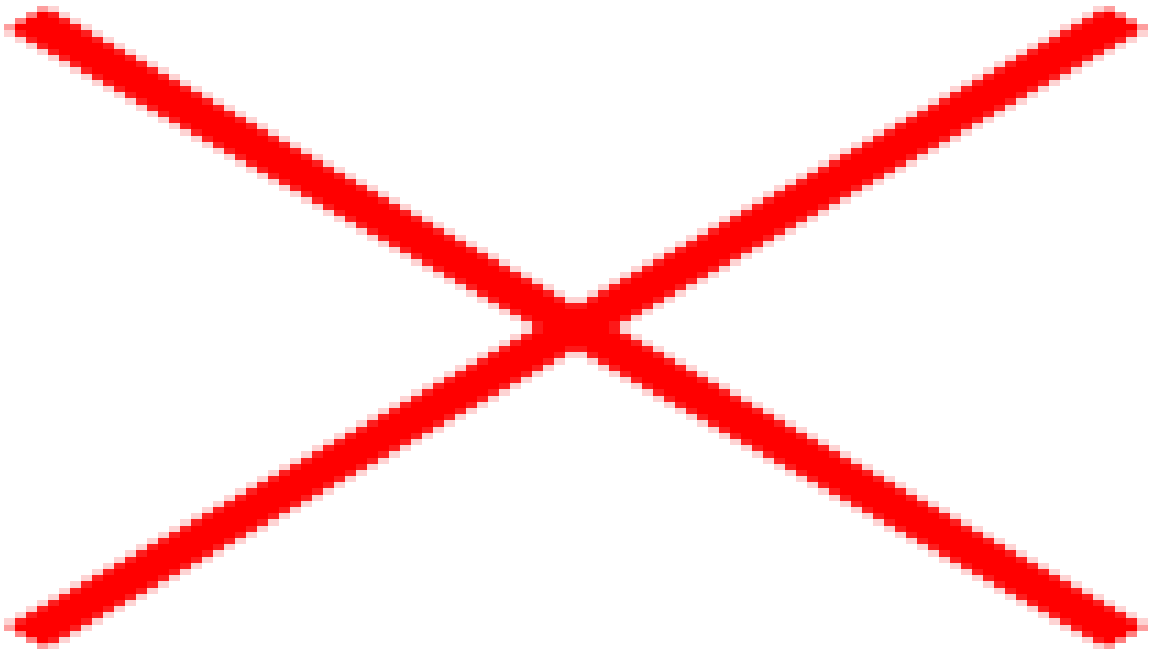
In Jin Zhang's research,[47] published in 2019, it was determined that out of a total of 25 955 oesophageal cancer patients registered between 2010 and 2015, obtained from SEER, 2 025 (8,0 %) had initial bone metastases. Among the patients with metastases in our caseload, bone metastases accounted for 1,4 %, all associated with OSCC.

Regarding simultaneous metastases, the liver-pancreas association was most common with 28,6 % (8; n=28), being predominant among OSCC patients, liver-lung association followed in frequency with 21,4 %, all in OSCC subjects. In addition, metastatic associations were identified between lung-brain, lung-pancreas, liver-brain, as well as between these organs and non-regional oesophageal nodes.

Locoregional Lymphatic Spread

Locoregional spread was confirmed in several lymph node chains, which were observed alone in the absence of metastases or infiltration of adjacent structures or vital organs in 21 patients who underwent resection surgery. Concurrent adenopathy, i.e. in more than one lymph node chain, was frequent and even occurred in patients with metastatic involvement and invasion of adjacent structures. The most frequent associations were those of the lymph nodes of the middle and lower mediastinum and those of the latter with the upper abdominal nodes.

Graph 4 shows the results of locoregional involvement in our series, which could be verified in 150 (76,9 %) subjects by using the paraclinical studies available in the institution; in the rest, the presence of this involvement was not evident.



Graph 4. Distribution according to Locoregional Lymphatic Spread and Histological Variants

It should be noted that the diagnostic tools available at our institution are not as sensitive for assessing the presence of regional lymphatic spread in oesophageal cancer, and we do not have more sensitive and specific paraclinical studies for this type of involvement. However, we will restrict ourselves to analysing the reports obtained by CT, ultrasonography and necropsy results to evaluate this variable.

It is necessary to quote Encinas de la Iglesias[48] who states, concerning CT, that it is less accurate for assessing regional lymph node extension (cN), with a specificity of 59,0 % and sensitivity of 81,0 %, but it should be taken into account when assessing the same if a more sensitive and specific diagnostic tool is not available for this purpose. The researcher himself points out that the added value of CT, unlike EUS, is that it can assess all the lymphatic drainage chains of the oesophagus.

Overall, the most affected lymph nodes were the upper abdominal lymph nodes with 34,0 % (51; n=150) and the middle mediastinal lymph nodes with 31,3 % (37; n=150). Involvement of lower mediastinal lymph nodes was 23,3 %, while those of the upper mediastinum and cervical lymph nodes were less frequently affected. The overall results of our series concerning lymph node involvement show upper abdominal lymph nodes predominance by a narrow margin with middle mediastinal lymph nodes, 51 subjects versus 47, which may be mainly due to the higher sensitivity of CT in the analysis of the former. Both the WECC[34,49] and Castillo Cabrera, in Peru,[36] report a higher incidence of lymph node involvement in the middle mediastinum.

Castillo Cabrera[36] in his series reported that 75,0 % (n=60) had lymph node involvement, with the middle mediastinum being the site of greatest involvement; although our results do not coincide with the preeminence of the middle mediastinal lymph node topography found by this author, we do present a similar percentage for the number of patients with locoregional dissemination, with 76,9 % (150; n=195) in this study. In the case of OSCC, the locoregional spread was more frequent to the middle mediastinal lymph nodes with a percentage of 35,0 % and in OAC it was the upper abdominal lymph nodes with 48,1 %, followed by the lower mediastinal lymph nodes with 37,0 %. These findings are consistent with those of the WECC, which reports a greater involvement of the middle mediastinal nodes in OSCC.[34,50]

As can be seen in Graph 4, the sites of lymph node involvement are not exclusive to a histological type or a specific location, this is because the dissemination of OC is quite anarchic in that it responds to the histological characteristics of the organ and does not follow a predictable sequence or pattern. Despite this, it is more common for OAC to affect the lymph nodes of the lower mediastinum and upper abdominals, while OSCC usually affects those of the upper and middle mediastinum, and cervical lymph node infiltration is generally specific to these.

Gallegos Plaza[51] states that the lymphatic drainage routes involve lymph nodes in the abdomen, thorax and neck and that the submucosa is rich in lymphatic vessels, with an extensive intramural network that extends longitudinally from the hypopharynx to the stomach; and the muscular propria has a less developed network, but drains segmentally in the periesophageal lymph nodes, all of which favours anarchy in terms of lymphatic dissemination of cancers in this organ.

The lymphatic spread of OCs is increased with the depth of the tumour in the oesophageal wall for both histological types, which explains why in patients with more advanced local extension, the possibility of distant metastasis and therefore a worse prognosis is to be expected.

About the infiltration of structures adjacent to the oesophagus, this was observed in 23 patients, 6 of whom showed pleural infiltration, 2 showed infiltration of the pericardium and 1 of the diaphragm; the rest showed involvement of large vessels, trachea or spinal column.

TNM Stage

The staging of oesophageal cancer has gone through different stages since the AJCC/UIC produced the first edition of the Cancer Staging Manual in 1977. The various editions of this TNM classification have gradually introduced changes in the staging of OC with each revision.

TNM Stages	Squamous cell carcinoma		Adenocarcinoma	
	No.	%	No.	%
IIA	1	0.6	1	2.4
IIB	2	1.3	1	2.4
IIIA	11	7.1	2	4.9
IIIB	4	2.6	5	12.2
IIIC	22	14.3	7	17.1
IV	114	74.0	25	61.0
Total	154	100	41	100

Table 6. Distribution according to TNM Stage and Histological Variants

Of the 195 medical records reviewed for our study, we found none that categorically established a systematic approach to TNM staging; none of the patients was explicitly categorised into a specific stage, which made analysis of the medical records difficult. Staging is necessary to provide adequate therapy for patients with EC or any other type of neoplasm. Certainly, there is a lack of techniques that are necessary for stagings, such as EUS and PET/CT, but this does not preclude staging.

The AJCC/UIC recommends, in its different editions of the Cancer Staging Manual,[42,45,52] the need to always perform staging regardless of the diagnostic means available. This element is also highlighted by Dueñas García et al,[53] for whom it is imperative to always perform staging and who point out that, if the accuracy of the TNM classification is affected by the diagnostic methods used, the C factor can optionally be used to express this variety:

C1: evidence by conventional diagnostic means (physical examination, laboratory tests and plain radiology).

C2: evidence obtained by special diagnostic means (ultrasound, CT, MRI, scintigraphy, endoscopy, etc.).

C3: evidence provided by surgical exploration, including biopsies and cytology.

C4: evidence after definitive surgery and pathological examination of the resected surgical specimen.

C5: evidence from the necropsy.

Although the use of EUS improves the staging of oesophageal neoplasms and according to literature reports[54–56] it is highly accurate in assessing oesophageal wall penetration and invasion of adjacent structures, CT images have an important value in analysing distant metastases, locoregional invasion, especially if lesions are larger than 1cm,[57] as well as involvement of neighbouring organs and penetration of the oesophageal wall. Gollub[58] states that CT has a sensitivity of 93,0 % in nodal disease. Some authors[9] report that the combination of EUS-CT is more accurate for the evaluation of locoregional lymph node lesions.

Perona Garcelán[59] reports that, in his series, CT was highly accurate, especially in the assessment of tumour diameter and length. For this author, CT has proved effective in assessing the aorto-tumour ratio with an accuracy of 92,0 %; the estimation of the relationship with the tracheobronchial tree in 88,0 %; pleural invasion in 92,0 %; and pulmonary and hepatic metastases in 96,0 % and 98,0 % respectively. This author reports that tumour staging by CT was 88,0 % consistent with that obtained after surgery.

CT is a test considered by the Latin American Society of Gastroenterology and Oncology,[60] since 2017, as the test with the best performance as a single procedure in Chile, with 69,0 % accuracy, and has been proposed as the initial study to rule out metastases and T4, and depending on this, other studies, such as EUS and PET/CT, will be continued.

Encinas de la Iglesias[48] reports that CT in local tumour evaluation (cT) is fundamentally aimed at ruling out infiltration of adjacent organs and its sensitivity for aortic and tracheobronchial involvement ranges from 100 % and 52,0 - 97,0 % respectively, and its value for cT1 and cT2 stage disease is limited, but not for cT3 and cT4.

Of the many diagnostic tools available worldwide for the staging of oesophageal neoplasms, PET/CT, SPECT/CT, EUS and imaging biomarkers, in our centre we only have an endoscopy, oesophagogram and CT mainly, so we have adjusted our study to the results obtained with these tests. Minimally invasive surgery, although available, was not used to stage patients. Considering that it is not essential, but necessary, to use EUS for OC staging and applying the elements recommended by Dueñas García et al, we undertook the task of staging the patients according to the 7th edition, taking as a reference

the results of Seung Yeon,[61] who, in his casuistry, established the staging using the results obtained from CT, ultrasound, endoscopy and histopathological findings. In the present research, we evaluated the patients' medical records, the results of paraclinical and histopathological studies obtained by biopsy, and clinical staging (cTNM) was designed for those whose data allowed it. In the case of 6 subjects, the staging was performed with the results of necropsies (aTNM), categorising patients as shown in Table 7.

In our series, the highest percentage of subjects showed metastatic disease, is located in stage IV, where, globally, we found 71,3 %, while 26,1 % were located in stages IIIA-IIIC, and only 2. Of the patients studied as IIIC, 14 had infiltration of vital organs (T4b) and 9 had infiltration of the pleura, pericardium or diaphragm (T4a). According to histological type, both were dominated by subjects categorised as stage IV with 74,0 % and 61,0 % for OSCC and OAC respectively.

The results found are consistent with the national and international literature, which states that oesophageal neoplasms are diagnosed late. Montiel Roa,(62)in his study, concludes that most of the patients were found to be in an advanced stage, essentially metastatic. Gómez-Urrutia et al[63] also reported similar results to ours; in their casuistry, 66,6 % and 61,5 % of the cases presented OSCC and OAC stage IV respectively. For Moreno and Nieto,[64] stage IIIB accounted for 57,9 %, and 47,4 % were stage IVA.

Conclusion

The variables analysed in this study characterise a population in which the disease presents in advanced stages, regardless of histological variants, with the presence of locoregional lymph node involvement, metastases, mainly liver metastases, and a highly varied symptom profile with a predominance of dysphagia and weight loss. We also found an under-reporting of predisposing diseases in our case series, despite which we found a higher incidence of OSCC among patients with caustic oesophagitis and of OAC in those with chronic gastritis and GORD.

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