ORIGINAL PAPER

Clinical–morphological profiles of esophageal carcinoma's main types

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Abstract

Aim: The purpose of the study was to define and then to compare particularly the morphological profiles of the main morphological types of esophageal carcinoma (EC). *Patients, Materials and Methods*: The studied group included 46 operated EC patients. Few parameters were clinical (gender and age). The rest of them described both gross and histological features of the entire group and of the two main histological types of carcinoma (lesion' site, lateral extension, lesion dimensions, gross aspect, and histological type, and tumor grade, and stage). Stratification scales of cases were defined according to each parameter in order to compare the data and a statistical apparatus [Student's *t*-test and χ^2 (*chi*-squared) test] was used. *Results*: The studied tumors were encountered mostly in mature adult and elderly men, usually in the lower segments of the esophagus. Many of them had between five and ten cm in the long diameter and produced stenosis. Most of them had infiltrating appearance combined often with protruding or/and ulcerated aspects. Usually, the tumors were poorly differentiated and in stage III. The two main histological types of EC showed different morphological profiles. Data from the literature revealed sometimes wide ranges of variation for the studied morphological parameters. Our results were within these ranges of variation. *Conclusions*: ECs proved to be aggressive and late diagnosed tumors in general, with distinct morphological and behavioral profiles for the two main histological types. Comparisons with literature data confirmed many of our observations regarding the clinical and morphological aspects of both ECs as a whole and its histological types.

Keywords: esophageal carcinoma, squamous cell carcinoma, adenocarcinoma.

⊟ Introduction

Esophageal cancer (EC) became in 2018 the seventh most common form of cancer in incidence and remained the sixth common cause of death from cancer worldwide, according to the GLOBOCAN [1], with approximately more than a half of the total cases occurring in China, especially northern part of the country, which is part of the so called "esophageal cancer belt" that includes in addition portions of northern Iran, southern Russia, and central Asian countries [2, 3]. However, both its overall incidence and mortality have been decreasing in the last decade, due to the progresses of diagnostic and treatment technologies [4, 5].

The two main morphological types of EC, *i.e.*, squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) became more and more two distinct conditions from point of view etiology, incidence trends, prognosis, and treatment strategies [6–8].

Thus, ESCC continues to be the most common histological type, accounting for 90% of all ECs worldwide, each year [3, 6, 9, 10]. It has the most uneven geographic distribution of all cancers, with a higher incidence in developing countries, from the above mentioned "EC belt" to which eastern to southern Africa, and parts of southern South America are added and lower incidence in developed countries like USA [3, 9]. It is also far more common in black and Asian male individuals, with a male/female (M/F) moderate ratio of 2.7 [9, 11, 12]. The main risk factors are low socioeconomic status, tobacco smoking, alcohol consumption and diet, with synergic effect on increasing risk when combined [13].

EAC, in turn, once an exceedingly rare histological type of EC, is about to become the most prevalent form of EC in the developed countries, such as those from Northwest Europe and North America but with low incidence rates in developing countries, such as those from Eastern and Southeastern Asia, and sub-Saharan Africa, being considered nowadays the most lethal condition gastroenterologists face [9, 14–16]. It has also one of the highest male-to-female ratios reported for cancers of non-reproductive organs, namely 7–10/1, being largely a disease of white individuals [15, 17]. The major risk factors for EAC are gastroesophageal reflux disease and obesity, both leading to the only described precursor lesion for this cancer, namely Barrett's esophagus [11, 14, 18–20].

However, the staging for both histological types is similar [3].

In Romania, EC is not so frequent, being in the 22nd position (0.88%) of all new cases of cancer and in the 19th position (1.3%) of all deaths by cancer in 2018 [1].

Aim

Based on these considerations, we proposed to identify all cases operated for EC in the Surgical Clinics of our Hospital during a period of five years and to define and compare the morphological profiles mainly of the first two important histological forms of EC, namely ESCC and EAC.

⊡ Patients, Materials and Methods

The basis for this study was composed of a group of 46 patients admitted and operated in the Surgical Clinics of the Emergency County Hospital of Craiova, Romania, during a period of five years (from June 2005 to June 2010) for whom the post-operative histopathological (HP) examination established the diagnosis of EC.

The inclusion criteria for patients in groups were existence of surgical intervention with the removal of the tumor proliferation and the HP diagnosis of EC.

The study was of retrospective type, therefore the studied material consisted of two categories of data sources:

(*i*) The medical records of the selected patients from archives of Surgery Departments, represented by: clinical records, surgery protocols, imagistic diagnosis registers and HP diagnosis registers;

(*ii*) Imagistic records and HP slides from each case archived in the Departments of Pathology and Imagistics.

Two categories of parameters were assessed, being grouped as following:

(*i*) Clinical profile that included: gender and age;

(*ii*) Morphological profile that included: lesion's site, lateral extension, lesion dimensions, lesion gross aspect, histological type, tumor grade, and tumor stage.

The samples removed by surgery were processed using the classical HP technique (formalin fixation and paraffin embedding), and then stained with Hematoxylin–Eosin (HE). HP aspects were selected with a CX31 Olympus microscope using the ×4 magnification eyepiece. For image acquisition, optical plan-apochromatic corrected objectives with magnification of ×4, ×10, ×20 and ×40 were used.

The most significant features were acquired using a LiveViewPro II digital camera, saved directly on the computer, and processed using specialized image analysis software: analySIS Pro, ACDSee 4.0 and Aperio Image Scope (v12.3.2.8013).

We tried to find in the literature studies to compare the assessments of our parameters with. Not all the papers consulted assessed the entire set of parameters we used. Also, not all papers referred to EC as a whole and to its main histological types separately at the same time. Thus, one group of papers referred only to some parameters of EC as a whole, another more consistent group referred to some parameters of both EC and its histological types and, finally, the third group included papers referring only to ESCC (Table 1).

Table 1 – *References from the literature used for comparison with our data*

References	Authors, year	Data origin	Period	No. of cases	Observations
[21]	Feller *et al.*, 2015	Switzerland	1982–2011	7280	EC
[22]	Mukhula *et al.*, 2017	Malawi	2010–2015	272	EC
[5]	Qiu *et al.*, 2020	SEER Database	2004–2014	4305	EC Without chemotherapy With and without surgery
[23]	Castoro *et al.*, 2011	Italy	1992–2007	248	EC, ESCC, EAC
[24]	Gabel *et al.*, 2016	Tanzania	2006–2013	626	EC, ESCC, EAC
[25]	Kauppila *et al.*, 2018	Sweden	1990–2013	1116	EC, ESCC, EAC
[26]	Shin *et al.*, 2018	Korea	1993–2013	30 977	EC, ESCC, EAC
[27]	Salem *et al.*, 2018	USA	2009–2017	1391	EC, ESCC, EAC
[28]	Jacobsen *et al.*, 2020	Germany	1992–2014	631	EC, ESCC, EAC
[29]	Then *et al.*, 2020	USA	2004–2015	37 723	EC, ESCC, EAC
[30]	Chen *et al.*, 2009	China	1993–2006	1850	ESCC
[31]	Cheng *et al.*, 2013	China	2003–2011	1893	ESCC
[32]	Dong *et al.*, 2015	China	2000–2014	3587	ESCC
[33]	Chen *et al.*, 2016	China	2008–2013	648	ESCC
[34]	Chang *et al.*, 2017	Taiwan	2006–2014	2061	ESCC
[35]	Meng *et al.*, 2018	China	2007–2012	**235**	ESCC

EC: Esophageal cancer; EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; SEER: Surveillance, Epidemiology, and End Results.

The assessment of some parameters required the development of classification systems of cases that generated further stratification scales of cases according to each parameter. For age evaluation, the scales are presented in Table 2.

Table 2 – *Stratification scale for age*

Age group	Period [years]	Age period
P1	0–14	Child (Ch)
P2	15–24	Adolescent (Ad)
P3	25–44	Young adult (YA)
P4	45–64	Mature adult (MA)
P5	>65	Elderly (Eld)

For tumor site, we used the division by regions of the esophagus defined in the last edition of *American Joint Committee on Cancer* (*AJCC*) *Cancer Staging Manual* [19]: SI – cervical segment, SII – upper thorax, SIII – middle thorax, SIV – lower thorax, and SV – abdominal segment/esophagogastric junction (EGJ).

For lateral extension of tumors, we used the scale: C – circumferential, Not C – not circumferential to which we added the presence/absence of stenosis (ST).

For tumor dimensions, the longitudinal diameter was measured and the results were divided in three groups: D1 – <5 cm, D2 – >5 cm <10 cm, D3 – >10 cm.

The gross aspect presented three main appearances: protrusive/bulging (P/B), infiltrative (I) and ulcerated (U), with some subgroups resulted from the combination of these three main aspects.

For the HP appearance, the lesions were grouped in: carcinomas and non-neoplastic lesions.

Grading and staging of the studied tumors followed the guidelines of the 8th edition *AJCC/International Union Against Cancer* (*UICC*) staging of esophageal and EGJ cancers [20].

The obtained data were introduced and processed using Microsoft Excel module of the Microsoft Office 2016 Professional software along with the XLSTAT 2014 add-in program for MS Excel.

For "Age" parameter, minimum (VMIN), maximum (VMAX), mean (AV) values and the standard deviation (STDEV) were determined.

Diagrams (graphs) illustrating evolution tendencies of different assessed parameters statistical comparisons between them as well as comparisons with other studies have been done with the help of the "Graph" instrument from "Word" and "Excel" modules of the Microsoft Office 2016 Professional software suite and the XLSTAT 2014 add-on for the Excel module.

Statistical instruments used were: Student's *t*-test for two independent samples/two-tailed test for "Age" parameter and χ^2 (*chi*-squared) test for all the other parameters.

⊟ Results

General description

The first step in our study was the general assessment of the entire list of settled clinical and morphological parameters.

The only two clinical parameters we selected were the gender and the age. Almost all our patients (≈90%) were males, two thirds of them having the age between 45 and 64 years and the rest over 65 years (Table 3, a and b).

Table 3 – *General assessment of clinical and morphological parameters*

Parameter	Subtype	No. of cases	
(a) Gender			
Males		**41**	
Females		5	
(b) Age			
P3 – Young adult		1	
P4 – Mature adult		**30**	
P5 – Elderly		15	
(c) Site			
SI – Cervical thorax		1	
SII – Upper thorax		1	
SIII – Middle thorax		12	
SIV – Lower thorax		8	
SV – Esophagogastric junction (EGJ)		**22**	
Extended		3	
(d) Lateral extension/stenosis			
Circumferential (C)	*Simple*	3	7
	+ stenosis (ST)	4	
Not C	*Simple*	**20**	**39**
	+ ST	19	
(e) Dimension			
D1 – <5 cm		13	
D2 – >5 cm <10 cm		**28**	
D3 – >10 cm		5	
(f) Gross aspect			
Protrusive/bulging (P/B)	*Simple*	6	10
	P/B + U	4	
Infiltrative (I)	*Simple*	**14**	**32**
	I + P/B	4	
	I + U	9	
	I + P/B + U	5	
Ulcerated (U)		4	
(g) Histopathology			
Non-neoplastic	*Dysplasia*	1	2
	Barrett esophagus	1	
Carcinomas	*Squamous*	**23**	
	Adenocarcinoma	17	
	Other types	4	
(h) Grading			
G1		6	
G2		12	
G3		**26**	
(i) Staging			
I	*IC*	1	1
II	*IIA*	3	5
	IIB	2	
III	*IIIA*	1	**25**
	IIIB	**24**	
IV	*IVA*	12	13
	IVB	1	

Many tumors were confined to a single esophageal segment, the most frequently affected being the fifth segment (Figure 1c) – EGJ/abdominal part (almost half

of cases), followed by the third segment – middle thorax (Figure 1a) with another quarter of the cases (Table 3c). However, in three cases, the longitudinal axis of the tumors spanned two neighboring esophageal segments: the upper and middle thoracic segments in a 48-year-old man, the middle, and the lower thoracic segments in a 54-year-old man and lower thoracic and abdominal segments in a 54-year-old man.

Although most of the tumors (≈85%) did not extend fully circumferentially, half of them produced stenosis of the esophageal lumen (Figure 1, a and e; Table 3d).

The studied tumors were usually large, almost two thirds of them measuring between 5 cm and 10 cm in the greatest diameter. However, nearly one third of the tumors had less than 5 cm in the greatest diameter (Table 3e).
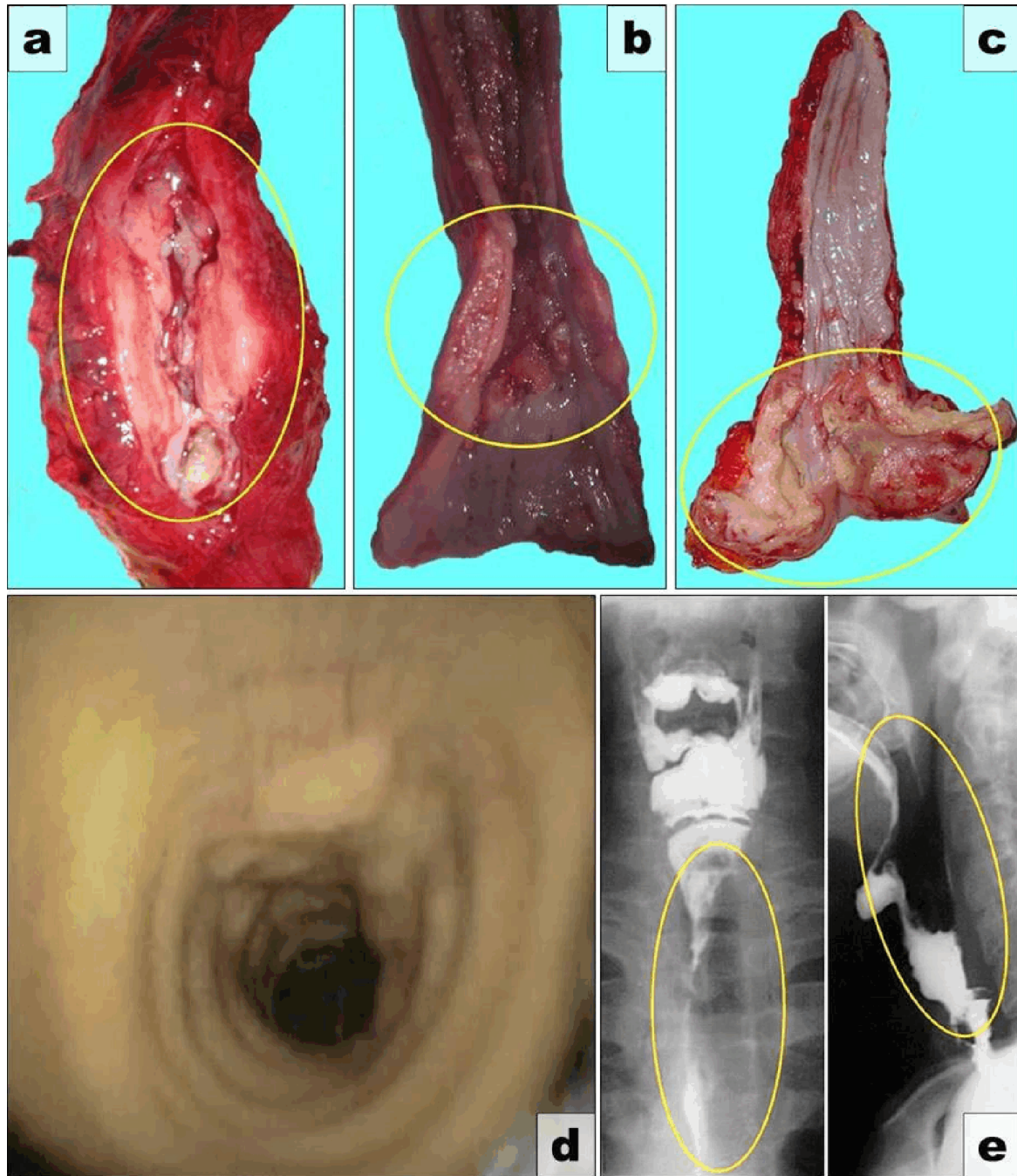
Figure 1 – *Gross aspects of studied tumors: (a) Tumor placed in the middle esophageal segment, with protruding, infiltrating and ulcerated appearance, and producing stenosis; (b) Tumor placed in the lower esophageal segment, with infiltrating appearance;(c) Tumor placed in the EGJ/abdominal part, with infiltrating and ulcerated appearance; (d) Tumor with protruding appearance – endoscopic image; (e) Highlighting of stenosing behavior on barium contrast radiographies. EGJ: Esophagogastric junction.*

As gross aspect, more than two thirds of the proliferations had an infiltrating appearance and in almost half of these cases the infiltration was not combined with other gross aspect (Figure 1b). The next main aspect was

the protrusion (Figure 1d), which was usually associated with either infiltration or ulceration or with both (Figure 1a). Simple ulcerations were rare (less than 10%) but ulcerated appearance was combined with other gross aspects in

almost 40% of the cases. As a final remark, in almost half of the tumors the gross appearance was a combination between the three main aspects (protrusion, infiltration and ulceration) (Figure 1a; Table 3f). At the hospital admission, clinical examination and ancillary investigations raised the suspicion of esophageal malignant proliferation in 46 patients who further underwent surgical intervention.

HP assessment of surgical samples revealed non-neoplastic conditions in two cases (Table 3g). In one case, a 39-year-old man, the lesion, placed in the lower thoracic segment, had an ulcerated appearance of around 3 cm,

without infiltration. The histological examination revealed only ulceration of the esophageal mucosa, surrounded by areas of leukoplakia (Figure 2a). The other case, 75-year-old man, the lesion, placed in the middle thoracic segment and measuring 4 cm in the longitudinal diameter, had a combined protruding and infiltrating appearance, with a complete circumferential extension and causing stenosis. Then surprise was that histological examination revealed only normal mucosa with an area of Barrett esophagus, a well-known precancerous lesion, established as precursor of EAC, but without any malignant transformation (Figure 2b).
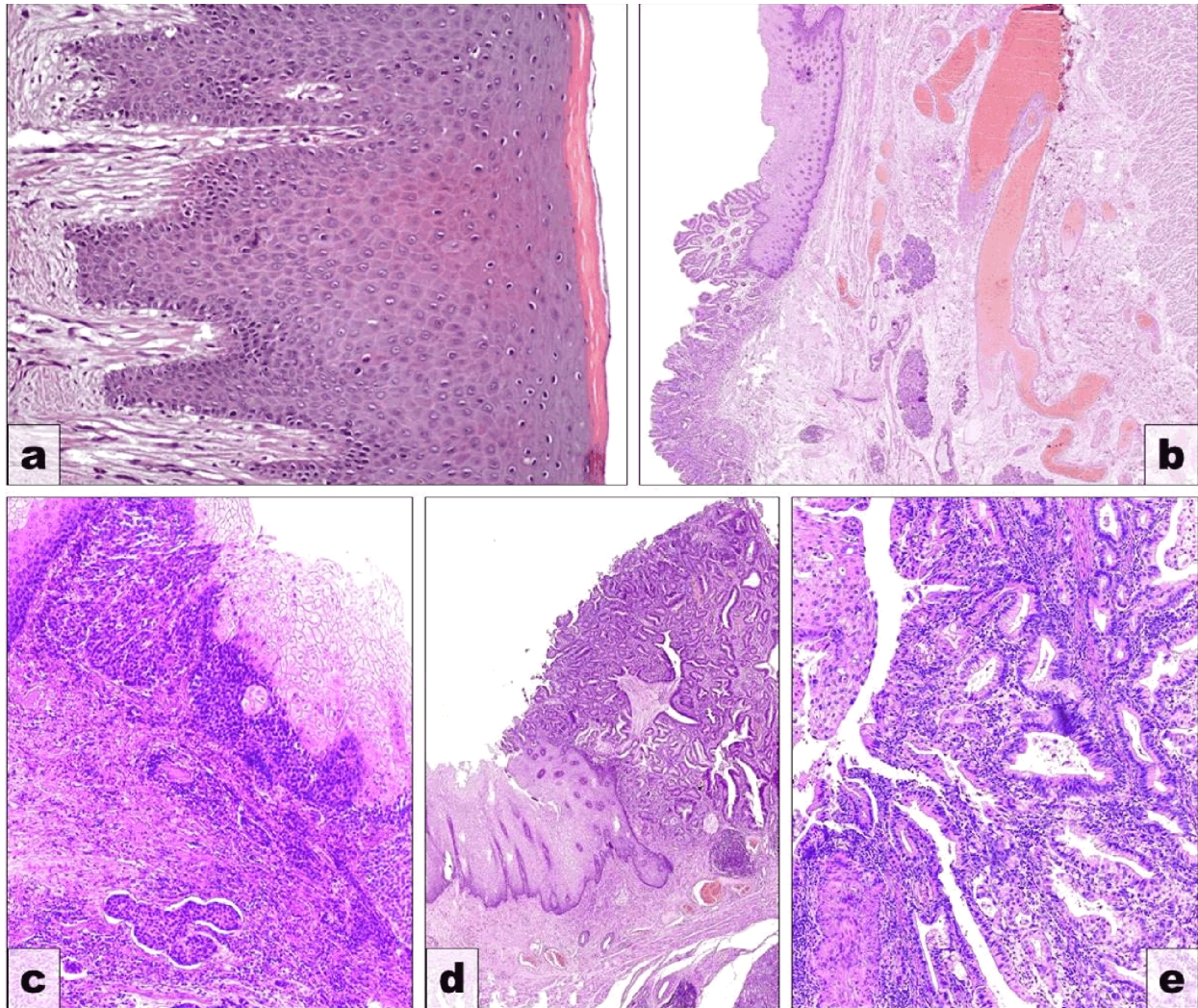

Figure 2 – *Histopathological features of studied cases: (a) Leukoplakia; (b) Barrett esophagus; (c) Poorly differentiated squamous cell carcinoma with vascular invasion; (d) Well differentiated adenocarcinoma; (e) Adenosquamous carcinoma. HE staining: (a, c and e) ×100; (b and d) ×40.*

All the other tumors proved to be epithelial malignant proliferations raised from esophageal mucosa. More than half of them were of squamous type (Figure 2c) and more than one third were of glandular type – adenocarcinomas (Figure 2d; Table 3g).

However, there were four patients with other types of carcinomas than the classical ones harbored by the esophageal mucosa but related with proliferations with secretory pattern (Table 3g). One patient, a 66-year-old woman, had a protruding and stenosing proliferation situated in the EGJ segment whose histological appearance was of adenosquamous carcinoma (Figure 2e). Another

patient, a 67-year-old man, had a 6 cm long tumor placed also in the EGJ segment with combined infiltrating and protruding appearance, with ulceration, realizing also the stenosis of the esophageal lumen that revealed the histological pattern of a "signet ring cell" carcinoma. The same aspect was present to a 58-year-old woman, with a large tumor of 9 cm long but who seemed to infiltrate the EGJ segment from the cardia. Finally, the fourth patient, a 62-year-old man, had a 5 cm long tumor protruding from but also infiltrating the esophageal wall, placed in the EGJ segment had a histological appearance of mucinous carcinoma.

Another important morphological parameter was the degree of differentiation. More than half of studied tumors (59%) were poorly differentiated (Figure 2a), and more than one quarter (27%) were moderately differentiated (Figure 2b; Table 3h) so, generally speaking, aggressive proliferations.

Finally, the staging assessment revealed that more than half of our cases (56.8%) were in stage III (practically, with one exception, in stage IIIB) and, in addition, almost one third (29.5%) were in stage IV (with one exception, in stage IVA), in other words, tumors advanced in their real morphological evolution.

Comparison of the main histological types

The second phase of our study was to assess the possible differences between the two main histological types of EC.

Clinical parameters

Gender

A first difference between the two types of tumors was that there was no woman in the ESCC group whereas almost 20% of patients with EAC were women (Figure 3; Table 4). The *chi*-squared test validated this difference.
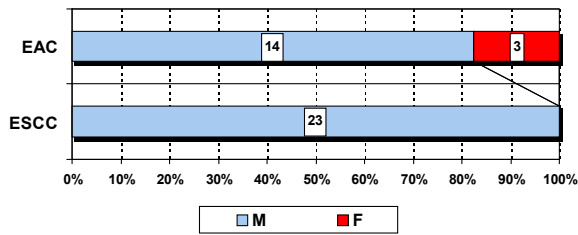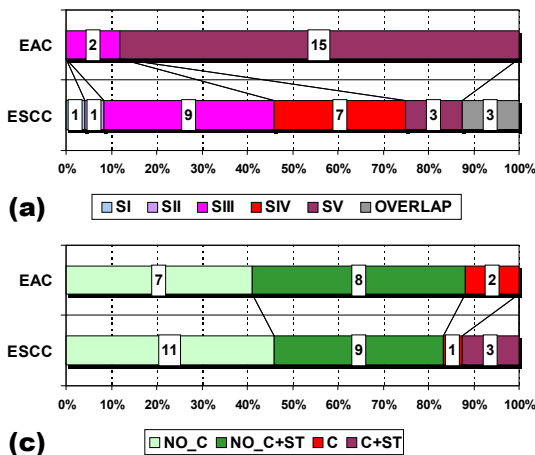

Figure 3 – *Gender distribution in the two main groups. EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; M: Male; F: Female.*

Table 4 – *Statistical assessment of gender distribution*

Statistical parameter	Value
Chi-squared (observed value)	4.3879
Degrees of freedom (DF)	1
p-value	0.0362
Alpha	0.05

Age

The second difference between the two types of tumors was that patients with EAC were significantly older than those with ESCC, difference that was also statistically validated (Figure 4).
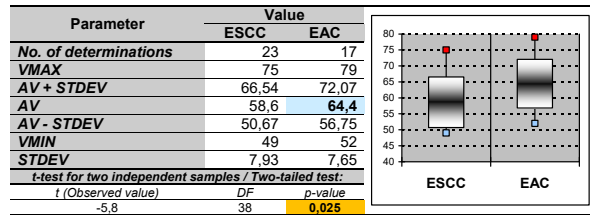
Parameter	Value	
	ESCC	EAC
No. of determinations	23	17
VMAX	75	79
AV + STDEV	66,54	72,07
AV	58,6	64,4
AV - STDEV	50,67	56,75
VMIN	49	52
STDEV	7,93	7,65
t-test for two independent samples / Two-tailed test:		
t (Observed value)	*DF*	*p-value*
-5,8	38	0,025

Figure 4 – *Age distribution in the two main groups. EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; AV: Average value; DF: Degrees of freedom; STDEV: Standard deviation; VMAX: Maximum value; VMIN: Minimum value.*

Morphological gross parameters

Site

Another striking difference was the tumor site. Thus, whereas EACs were almost all placed in the fifth esophageal segment (EGJ), almost all ESSCs were harbored by the middle thoracic followed by the lower thoracic segment of the esophagus, in other words, un upper position of ESCCs as compared with EACs (Figure 5a). This difference was also statistically validated (Table 5a).

Dimensions

Tumor dimensions followed the same trend of distribution, with many of the tumors measuring between 5 cm and 10 cm in their long diameter in both groups and a higher percentage of large tumors in the ESCC group (Figure 5b). These almost similar distributions were also signaled statistically (Table 5b).

Lateral extension

The same similarity of behavior was present in the case of lateral extension and presence of stenosis. Both types of tumors had no circumferential extension in most of the cases, but they produced stenosis in half of the cases, similarity also signaled in statistical terms (Figure 5c; Table 5c).

Figure 5 – *(a–d) Comparative distribution of the morphological gross parameters in the two main groups. EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; SI: Cervical segment; SII: Upper thorax; SIII: Middle thorax; SIV: Lower thorax; SV: Abdominal segment/esophagogastric junction (EGJ); D1 to D3: Longitudinal diameter; C: Circumferential; NO_C: Not circumferential; ST: Stenosis; I: Infiltrative; P/B: Protrusive/bulging; U: Ulcerated.*

Table 5 – *Statistical assessment of morphological gross parameters*

Statistical assessment	(a) Tumor site	(b) Tumor dimensions	(c) Lateral extension	(d) Gross aspect
Chi-squared (observed value)	4.3879	1.1381	3.1786	0.9075
Degrees of freedom (DF)	1	2	3	2
p-value	**0.0362**	0.5661	0.3649	0.6352
Alpha	0.05	0.05	0.05	0.05

Gross aspect

The distribution of main gross aspects was also almost similar in the two groups, with EACs more infiltrating than the others and ESCCs with a higher percentage of protruding tumors (Figure 5d). But these small differences in how tumors looked like were not validated statistically (Table 5d).

Histological parameters

Grading

The degree of differentiation had different patterns of distribution in the two groups of tumors. Thus, the great majority of ESCCs (75%) were poorly differentiated tumors (Figures 2c and 6a). In contrast, EACs were in the same percentage moderately (Figures 2d and 6b) and well differentiated. This divergent behavior was validated in statistical terms (Figure 7a; Table 6a).

Local invasion (T staging)

A first observation was that all tumors, regardless the histological type, were invasive at least in the muscular layer (pT2).

The way the tumors behaved locally, in the esophageal wall, was however different. Thus, ESCCs had a significant percentage of tumors that invaded only the muscular layer (Figure 6a) but usually they extended in the adjacent structures (pT4) (Figure 6d). Conversely, EACs invaded in most cases the entire esophageal wall, including the adventitia (pT3) (Figures 6b, 6c and 7b). However, this different behavior was not validated in statistical terms (Table 6b).
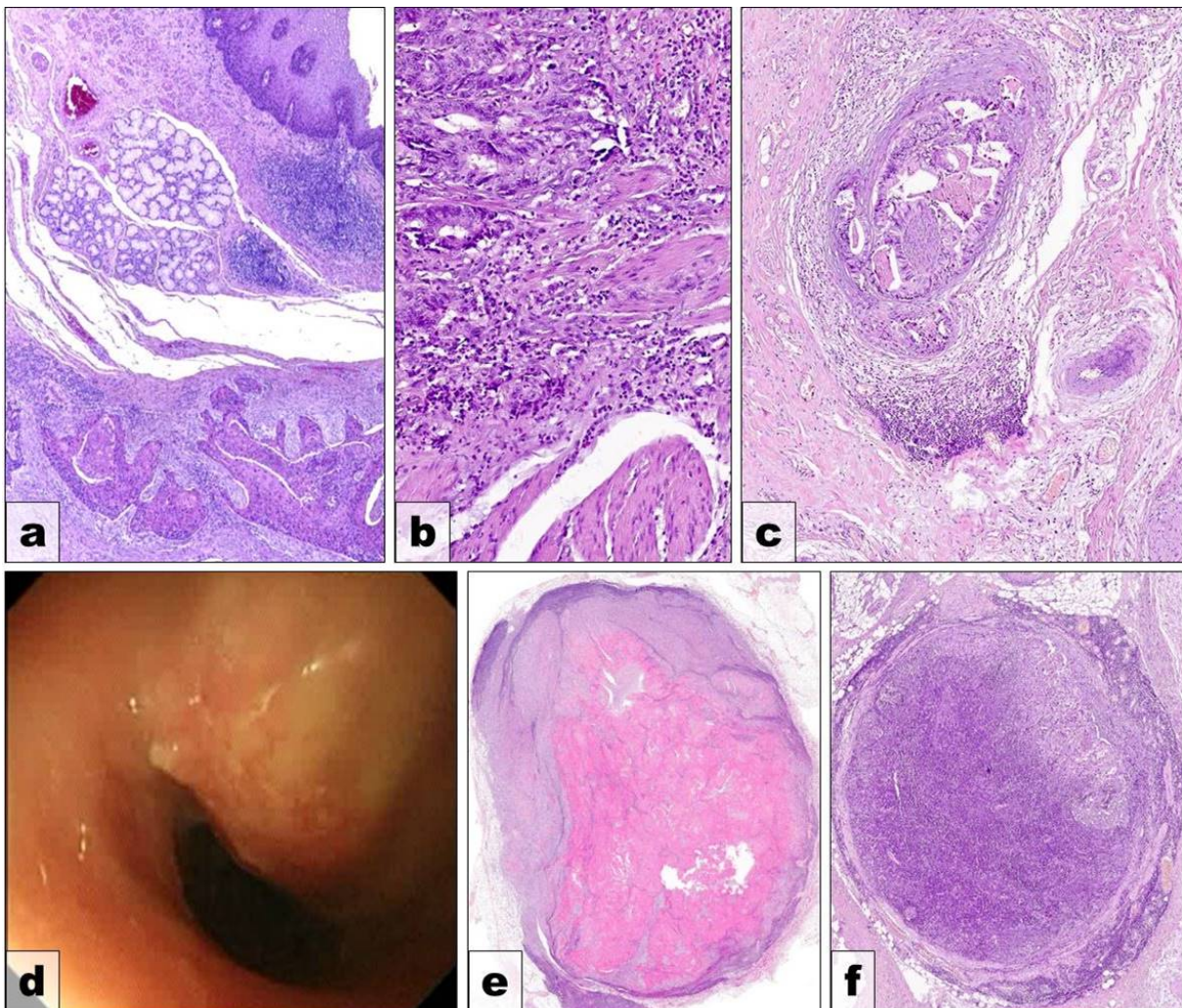

Figure 6 – *Different aspects of EC behavior: (a) Poorly differentiated ESCC with invasion in the muscular layer; (b) Moderately differentiated EAC with invasion in the muscular layer; (c) Moderately differentiated EAC with perineural invasion; (d) Invasion of an EC in the bronchial wall – bronchial endoscopy; (e) Massive lymph node invasion of an ESCC; (f) Incipient lymph node invasion of an EAC. HE staining: (a, e and f) ×40; (b and c) ×100. EAC: Esophageal adenocarcinoma; EC: Esophageal cancer; ESCC: Esophageal squamous cell carcinoma.*

Regarding particular aspects of the local invasion, vascular invasion with the presence of tumor emboli (Figure 2c) was almost three times more common in EACs than in ESCCs (13% *vs.* 35%) and absent in the group of other types of EC. Perineural invasion (Figure 6c) was rare – two cases from the ESCC group and one case from the EAC group. However, two of the four cases with other types of EC presented this feature.

Lymph node involvement (N staging)

Both types of carcinomas proved a propensity to rapidly invade the regional lymph nodes (Figure 6, e and f), more enhanced in EACs than in ESCCs but also this difference, visible on the graph (Figure 7c) was not valid from statistical point of view (Table 6c).

Distant invasion (M staging)

The existence of distant metastases could be checked histologically in only around half of the cases of both groups

and it was proved in only two cases (Figure 7d; Table 6d).

The first was a 59-year-old man with two proliferations, one protrusive in the cervical segment, measuring 1 cm in diameter and the other in the middle thoracic segment, measuring 7 cm, with infiltrating appearance. Both tumors were ESCCs. Surgeons discovered a node of around 1 cm in diameter in the inferior lobe of the right lung that they have resected. HP examination revealed the presence of a lung metastasis of the esophageal squamous tumors.

The second case was a 63-year-old woman with a mixed protruding and infiltrating ulcerated tumor of around 5 cm in its long diameter, placed in the EGJ segment, extended to the pancreatic parenchyma that proved at the HP examination a moderately differentiated adenocarcinoma. Surgeons discovered intraoperatively also an irregular node in the hepatic left lobe, which they resected. HP examination revealed a metastatic adenocarcinoma migrated from the esophageal tumor.
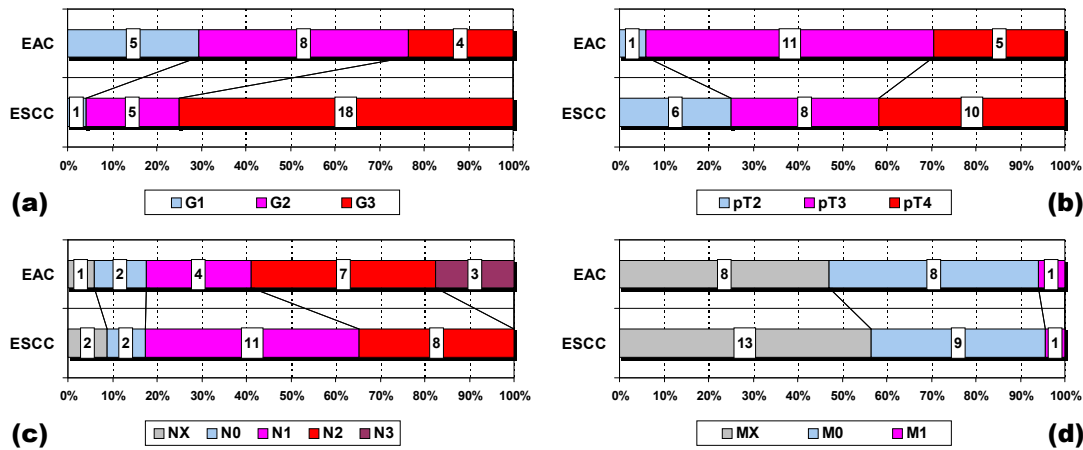

Figure 7 – *(a–d) Comparative distribution of the morphological microscopic parameters in the two main groups. EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma.*

Table 6 – *Statistical assessment of morphological gross parameters comparisons*

Statistical assessment	(a) Tumor grading	(b) Tumor T staging	(c) Tumor N staging	(d) Tumor M staging	(e) Overall staging
Chi-squared (observed value)	11.4054	4.6523	5.8994	0.3573	6.6301
Degrees of freedom (DF)	2	2	4	2	6
p-value	**0.0033**	*0.0977*	0.2068	0.8364	0.3564
Alpha	0.05	0.05	0.05	0.05	0.05

Overall staging

Final assessment of the overall staging showed similar trends in the distribution of stages in both groups, with between half and two thirds of the cases being in stage III and another one third being in stage IV (Figure 8; Table 6e).
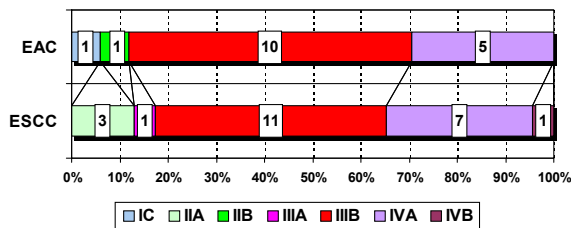

Figure 8 – *Comparative distribution of the overall staging in the two main groups. EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma.*

The group of other types of carcinoma

The four carcinomas of other type than the two main types analyzed above had characteristic, some of which were common for all of them. Thus, two patients were men but the other two were women. Two patients were mature adults (P3), and the other were elderly (P4). All tumors were placed in the fifth esophageal segment (EGJ) and were medium to large in size. The gross aspect was either protruding or infiltrating or a combination between the two aspects, two of them causing stenosis but no one with circumferential extension. All of them had a poorly differentiated appearance. All of them were invasive locally, reaching the adventitia in three cases and surpassing it in the fourth. Somewhat surprisingly, one "signet ring cell" carcinoma, the one that surpassed the adventitia in the neighboring structures, had no lymph node extension. In turn, all the other three tumors extended in at least one

or two regional lymph nodes. Distance metastases could not be assessed histologically in three cases and were not present in the fourth case. As overall staging, all tumors were in stage IIIB.

⊟ Discussions

Profiles of the two main types of EC

The second step in our analysis as to check if there are really significant differences between the morphological profiles especially of the two main types of EC.

Our data highlighted the contouring of distinct profiles of ESCC and EAC although we have to mention that none of our groups had a significant number of cases (Table 7).

ESCCs

Thus, the tumors of squamous type were observed only in men older than 50 years but with a mean age lower than 60 years, in other words, adult mature active people.

Tumors were harbored usually by the lower and middle thoracic parts of the esophagus but, as compared with EACs, some of them were large tumors, overlapping at least two segments.

The infiltrating pattern was present most frequently but there were also a significant number of cases with protruding appearance. The long diameter varied usually between 5 cm and 10 cm but, as we mentioned before, tumors larger than 10 cm were not so rare.

Tumors were slightly more stenosing and circumferential than tumors of glandular origin.

From histological point of view, squamous tumors were mostly poorly differentiated and most often invasive beyond the esophageal wall in the neighboring tissues but with a less extended lymph node invasion. However, the overall staging (pTNM), assessed mostly on pT and pN aspects, was usually very high, namely stage IV.

EACs

Tumors with glandular origin, in turn, occurred also in women; patients were older than 50 years but with a mean age higher than 64 years, in other words, elderly people.

The seat of predilection was the last esophageal segment, namely the EGJ.

The infiltrating pattern of appearance was almost the rule and dimensions larger than 10 cm were the exception.

Table 7 – *Synopsis of clinical and morphological profiles of ESCC and EAC*

Parameter	ESCC	EAC
Clinical		
Gender	Only men	Also women
Mean age [years]	<60	*>64*
Morphological gross		
Site	Lower + middle thoracic segments + overlaps	*Mostly EGJ segment*
Gross aspect	Protruding twice frequently	*Usually infiltrating*
Dimension	*More frequently large* (16%)	Rarely large (6%)
Lateral extension	*Slightly more circumferential*	Less circumferential
Stenosis	*Slightly more stenotic* – half of the tumors	Almost half of the tumors
Histopathology		
Grading	*Mostly poorly differentiated*	Most often moderately differentiated
Local Invasion	*More frequently T4*	Most often T3
Regional lymph nodes	Most often N1	*Most often N2 and N3*
Metastases	One case in each group	
Staging	*Slightly more IV*	Mostly III and higher

EAC: Esophageal adenocarcinoma; EGJ: Esophagogastric junction; ESCC: Esophageal squamous cell carcinoma.

Although almost half of the tumors produced stenosis, they were circumferential less frequently than squamous tumors.

From histological point of view, tumors of glandular origin were most often moderately differentiated, with local extension till the limits of esophageal wall but with a larger extension in the regional lymph nodes than squamous tumors. Therefore, the overall staging (pTNM), assessed also mostly on pT and pN aspects, was usually high but lower than in squamous tumors, namely stage III.

EACs

The small group formed by other histological types of EC, described above, had a profile almost similar to that of the esophageal tumors of glandular origin we studied.

Comparisons with other studies

Comparison with literature data was not so easy, as we mentioned above, because the lack in the homogeneity in covering the entire set of parameters.

Gender

The M/F ratio had large variations whether it was squamous tumors only, glandular tumors only or esophageal tumors as a whole.

The widest range of variation was in squamous tumors (Figure 9 – red dashed line). Thus, in an American study [29] and a Swedish study [25], M/F ratio had the lowest value, namely 1.9. The highest ratio was of 21.3 and was reported by a Chinese group of researchers [33]. Our group of squamous tumors had the specific feature of including only men.

The M/F ratio of glandular tumors varied in a narrower range of variation, starting also from 1.9 in a Tanzanian study [24] but stopping at 6.5 in the Swedish study mentioned above [25]. Our value was inside this range of variation (Figure 9 – green dashed line).

The range of variation of M/F ratio of ECs taken as a whole was also large, between 1 in a Malawian study [22] and 12.5 in a Korean study [26]. Our value was placed a

little above the middle of this range (Figure 9 – black dashed line).

In studies that analyzed both ECs and their subtypes [25, 27–29], the values of EACs M/F ratio were higher than those of ESCCs and the values of ECs taken as a whole were placed between the values of the two main types. However, there were two exceptions: our study and the Korean study [26] in which the M/F ratio value of ESCCs was higher than that of EACs.

So, as a concluding remark, it is very difficult to establish a pattern of gender distribution either for ECs as a whole or for their subtypes. The only sure thing is that EC and their subtypes are more frequently observed in men.
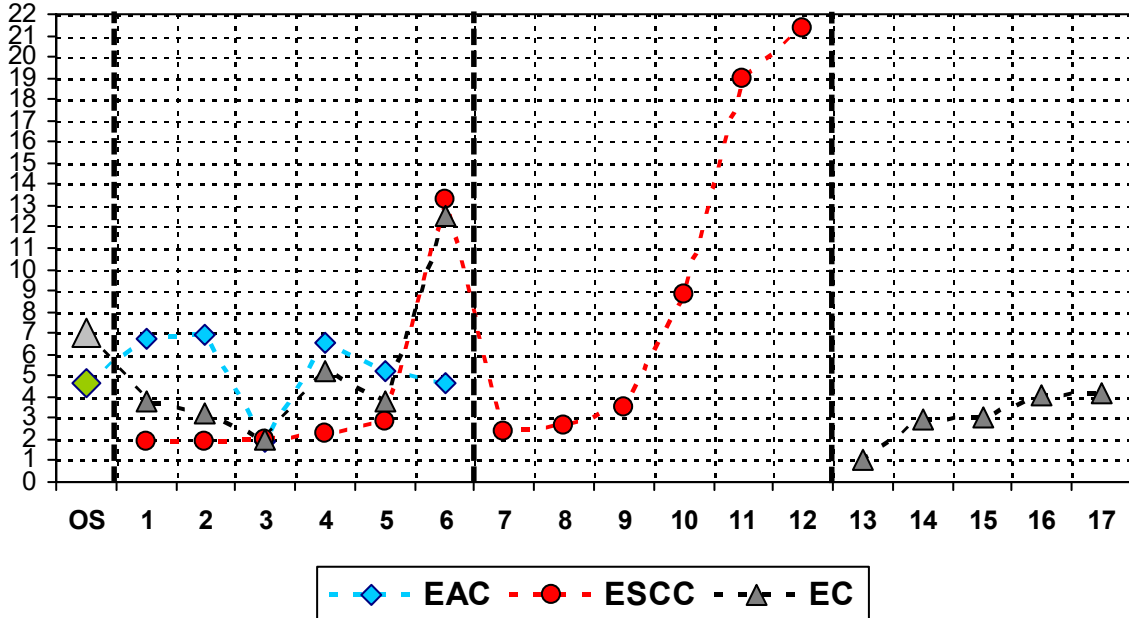
Figure 9 – *Comparison of M/F ratio with other studies. EC: Esophageal cancer; EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; M: Male; F: Female; OS: Our study; 1: [29]; 2: [25]; 3: [24]; 4: [27]; 5: [28]; 6: [26]; 7: [32]; 8: [30]; 9: [31]; 10: [35]; 11: [34]; 12: [33]; 13: [22]; 14: [21]; 15: [5] all cases; 16: [5] surgery; 17: [23].*

Age

The comparison of age distributions was much more difficult. The main reason is the total lack of a general rule of establishing the age groups. Another reason was the way of reporting (numerical, percentage, median value).

Some studies (Figure 10) reported the median age of patients. Four of these analyzed only patients with ESCCs [23, 30, 32, 34].

Figure 10 – *Comparison of median age with other studies. EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; 1: [30]; 2: [34]; 3: [32]; 4: [27]; 5: [23].*

The values varied between 55 years (a Chinese study) [30] and 63 years (an Italian study) [23]. Our median value (58 years) was included in this range of variation.

Only an American study [27] that reported the median value of the patients' age analyzed both types of EC. This study revealed that median age of patients with EACs is higher than that of patients with ESCCs, situation observed also in our study, except that the difference between the two median values is significantly larger in our study.

There were only few studies that analyzed ECs only as a whole (Table 8). However, differences were present. Moreover, even in the same study [5] differences were observed between subgroups.
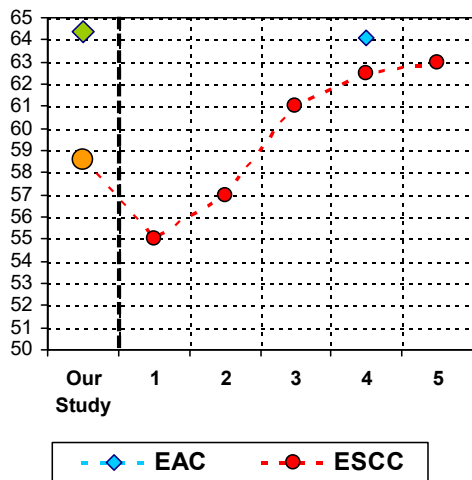
Table 8 – *Comparison of age distribution with other studies of esophageal cancer*

Age group [years]	Our study	[5] All	[5] Surgery	[24]	[26]
<35				79	
35–39	3	165	113	141	
40–44					
45–49				246	7016
50–54	16	649	449		
55–59				374	
60–64	16	1188	810		
65–69					6898
70–74	9	1256	767	498	
75–79					3937
>80		1047	309		

Thus, patients admitted with EC were most often elderly (over 70 years) whereas patients undergoing surgery were most often in the 7th decade of life (60–69 years).

In a Tanzanian study [24], the situation was somehow similar to that of the Chinese first group.

In our study, most of the patients were younger (between 50 and 69 years), a situation similar somehow with that of the Korean group [26].

Other studies analyzed either both subtypes of EC or only the ESCCs (Table 9).

Regarding the ESCCs, most of these studies [24, 28, 31, 35] revealed a higher incidence of squamous tumors in elderly persons. Only the Swedish study [25] reported younger ages for patients with ESCCs – many patients in the 7th decade of life (60–69 years) but followed by the 8th decade (70–79 years).

The situation was the same for the patients with EACs as compared with those with ESCCs in each of the mentioned studies excepting our study, where patients with EACs were older than those with ESCCs.

As a concluding remark, it seems that in terms of age, a rule of tumor distribution is not clearly outlined according to the histological type. The only general rule is that EC, is the prerogative of the transition period from mature adult to elderly, regardless of the histological type.

Table 9 – *Comparison of age distribution with other studies of both ESCCs and EACs or only squamous cell carcinomas*

Age group [years]	Our study		[24]		[25]		[28]		[31]	[35]
	ESCC	EAC	ESCC	EAC	ESCC	EAC	ESCC	EAC	ESCC	ESCC
<35	0	0	34	4	317	286	120	108	1%	105
35–39			64	1						
40–44	3									
45–49			111	9					48%	
50–54	11	4								
55–59			139	15						
60–64	6	7			443	423				130
65–69			221	28						
70–74	3	6			328	370	231	172	51%	
75–79										
>80	0				28	52				

EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma.

Morphological gross parameters

The papers we could access and consult included not too many data concerning the macroscopic features of esophageal tumors observed either in preoperative investigations or in operating room or in the pathology laboratory. The only parameter mentioned in some of these consulted studies was the tumor site.

Site

There were only two studies where the tumor location was analyzed for both ECs and their main histological types: an American study [29] and an Italian study [23] (Figure 11a).

In both studies, ESCCs seem to be placed in an upper position than EACs, situation observed in our group too. However, in the American study [29], EACs were in an upper position than in the Italian study [23].

The American study [29] reported also in both subgroups, as we found but only in our ESCC subgroup too, a significant number of cases with large tumors overlapping at least two esophageal segments.

In our study, the situation of EACs was similar to that of the Italian study but ESCCs were placed more often in lower positions than in the foreign studies (Figure 11a).

In all studies, the number and the distribution of EACs influenced obviously the distribution of tumor site in the whole group of ECs.

There were another two studies that analyzed only the ECs as a whole [5, 21]. The Swiss study [21] revealed a trend towards an upper placement of EC tumors but also a significant number of large tumors overlapping at least two esophageal segments. In turn, in both subgroups of the Chinese study of Qiu *et al.* [5], the trend was more oriented toward the lower positions. In our study, due to the influence of EAC subgroup, the trend was clearly oriented towards lowest esophageal segments (Figure 11b).

Finally, there were four studies dedicated only to ESCCs [30, 31, 32, 35]. The trend of tumor site distribution varied significantly, from the tendency to locate more proximal in one Chinese study [30] to the tendency of more distal placement in another Chinese study [32]. Our ESCC tumors had a somehow uniform distribution along the esophagus, without neglecting cases stretching over at least two esophageal segments.

As a concluding remark, it seems that even in terms of location, a rule of tumor distribution is not clearly outlined according to the histological type.

Histological parameters

Histological type

The main histological parameter is the tumor type. The consulted papers showed us that another reason that makes difficult any comparison between data is the wide heterogeneity of tumor type distribution.

Even if we are talking about large groups of cases [5, 21, 26, 27], differences are very large. For instance, the Korean study of Shin *et al.* [26] is clearly dominated by the squamous tumors. At the opposite pole, the American study of Salem *et al.* [27] is clearly dominated by the glandular tumors. In between are the European studies of Castoro *et al.* (Italy) [23] and Jacobsen *et al.* (Germany) [28], with a slight predominance of EACs in both. Our study is placed in the European trend, but with a slight predominance of squamous tumors (Figure 12).
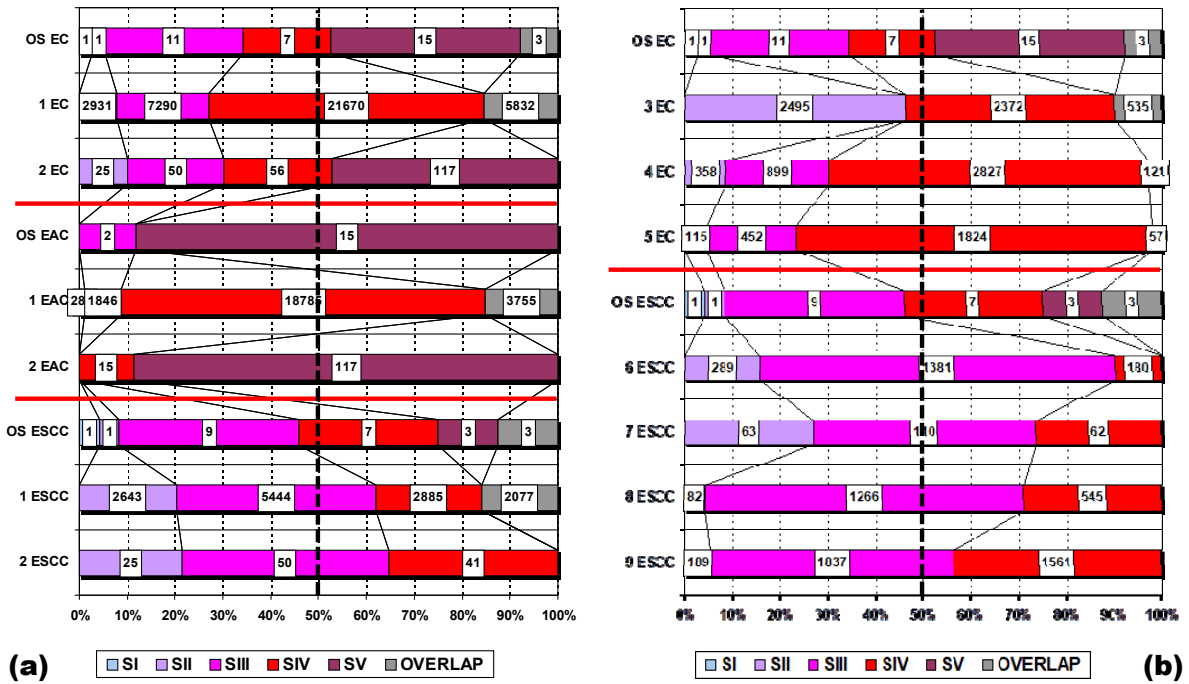
Figure 11 – *Comparison of tumor site between our study and (a) studies that assessed both EC and its subtypes or (b) studies that assessed only ECs or ESCCs. EAC: Esophageal adenocarcinoma; EC: Esophageal carcinoma; ESCC: Esophageal squamous cell carcinoma; SI: Cervical segment; SII: Upper thorax; SIII: Middle thorax; SIV: Lower thorax; SV: Abdominal segment/esophagogastric junction (EGJ); OS: Our study; 1: [29]; 2: [23]; 3: [21]; 4: [5] all cases; 5: [5] surgery; 6: [30]; 7: [35]; 8: [31]; 9: [32].*
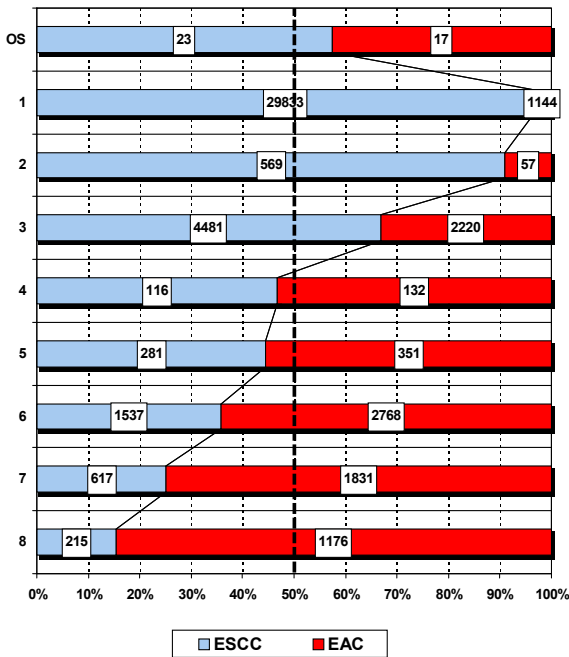
Figure 12 – *Comparison of histological type distributions between our study and other studies. EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; OS: Our study; 1: [26]; 2: [24]; 3: [21]; 4: [23]; 5: [28]; 6: [5] all cases; 7: [35] surgery; 8: [27].*

Grading

We found data about the degree of differentiation in only three studies [5, 28, 29] that presented variations from one study to another and from one histological type to the other.

From the three studies about ECs as a whole, the Chinese study revealed in both its groups a trend toward a better differentiation of tumor proliferations whereas the American study revealed a trend toward a less differentiated appearance of tumor proliferations. Our study was closer to the American pattern of distribution (Figure 13 – top).

The assessment of the degree of differentiation of the two types of carcinoma was present only in the American study mentioned above and in the German study of Jacobsen *et al.* [28]. In both studies the trend was somehow balanced, more inclined toward poorly differentiated pattern in the American study [29], trend that was also present but more pronounced in our study.

Regarding the ESCCs, the difference was more obvious between the foreign studies, with many moderately differentiated cases in the German study [28].

Our study made a special note again, with most of the tumors revealing a poorly differentiated appearance (Figure 13 – middle).

Almost the same situation was present in the case of EACs. Thus, in both foreign studies there was a trend toward poorly differentiated appearance, more obvious in the American group, whereas in our study the trend was totally opposite, with an obvious trend toward better differentiated aspects (Figure 13 – bottom).

T staging

Local invasion was assessed for both ECs as a whole and their main histological variants only in the German and American studies mentioned above [28, 29]. In both studies, both ECs and their types showed a trend toward an invasion limited to the esophageal wall (pT3), more pronounced in the German study [28].
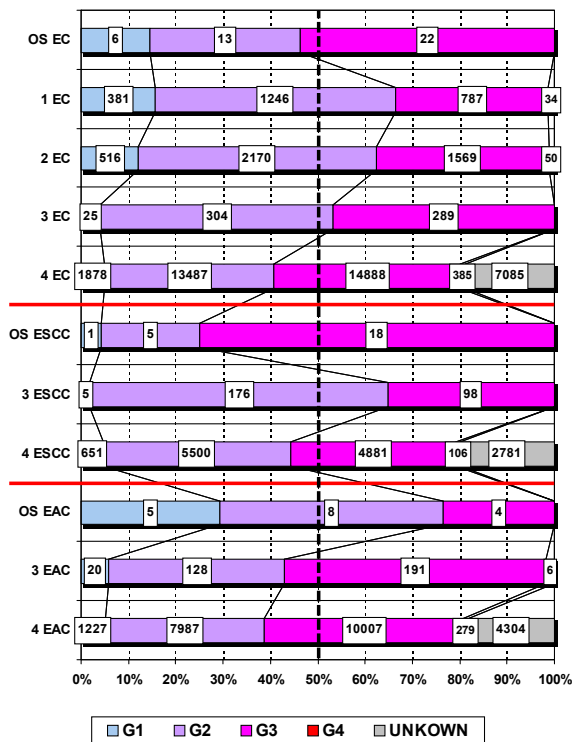
Figure 13 – *Comparison of histological type distributions between our study and other studies. EAC: Esophageal adenocarcinoma; EC: Esophageal carcinoma; ESCC: Esophageal squamous cell carcinoma; OS: Our study; 1: [5] all cases; 2: [5] surgery; 3: [28]; 4: [29].*

In our study, the situation was somehow different, with a more obvious trend toward the aggressive stages (T4) for both ECs and the two histological types (Figure 14a).

In two other studies already mentioned [5, 23], that assessed series of EC in general, the differences of the local invasion distribution are obvious. In the Chinese study of Qiu *et al.* [5], in both subgroups dominated the

tumors that invaded in the worst-case submucosa (T1b). In turn, in the Italian study of Castoro *et al.* [23] dominated the tumors that invaded the entire esophageal wall (T3). Our study was at the opposite pole, with one third of tumors invading beyond the esophageal wall (T4) (Figure 14b – top).

Other three studies, all Chinese [30–32], assessed only ESCCs. In all of them, the local invasion was limited to the thickness of esophageal wall in most of the cases, whereas in our study, the tumors invaded more frequently the esophageal neighboring structures (T4) (Figure 14b – bottom).

As a concluding remark, our tumors were more aggressive as compared with other studies, whether it was ECs as a whole or their histological types.

Regarding the particular aspects of local invasion, we found only one Chinese study on ESCCs only that referred to this aspect (Figure 15). In the Chinese study, vascular invasion was almost a rule whereas in our group of ESCCs, only a small percentage (15%) of the tumors revealed this aspect. However, the glandular tumors revealed this aspect almost three times more frequently (as we already mentioned) but still not so frequently as in the Chinese study (Figure 15).

N staging

Regional lymph node invasion was assessed for both ECs as a whole and their main histological variants in three studies. Regarding the ECs as a whole, the Italian and the American studies [23, 29] showed in almost half and slightly more than half of the cases invasion in one or two regional lymph nodes (pN1).

The German study of Jacobsen *et al.* [28] revealed in turn a more aggressive behavior of studied tumors, with almost two thirds of the cases presenting lymph node invasion and almost 20% of the cases with seven or more regional lymph nodes involved (Figure 16a – top).
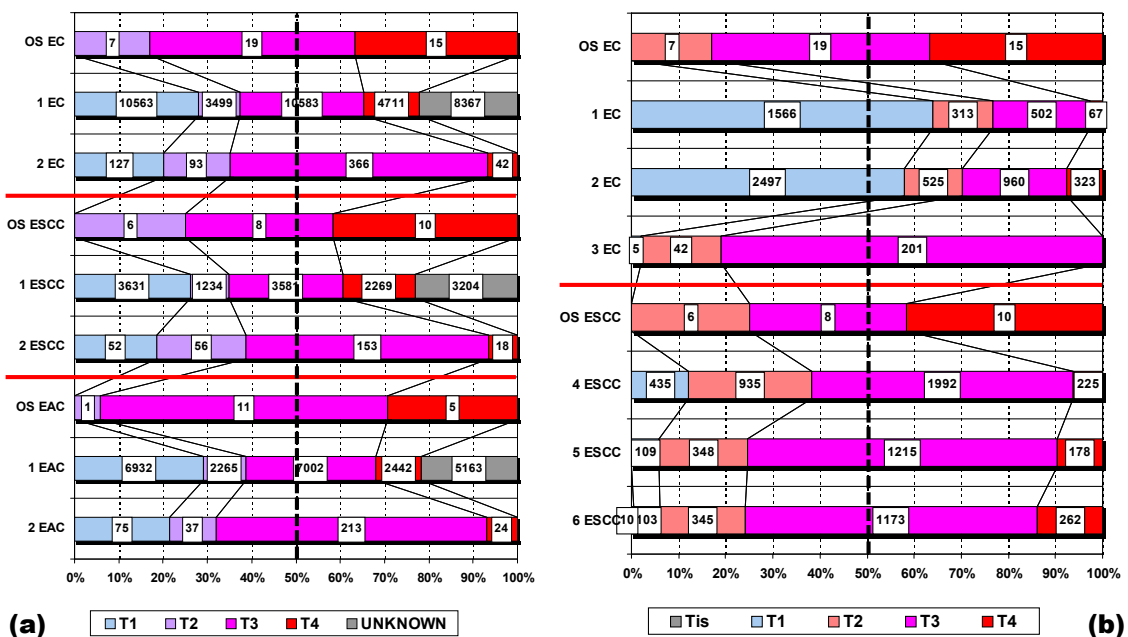

Figure 14 – *Comparison of tumor local invasion (pT) between our study and (a) studies that assessed both EC and its subtypes or (b) studies that assessed only ECs or ESCCs. EAC: Esophageal adenocarcinoma; EC: Esophageal carcinoma; ESCC: Esophageal squamous cell carcinoma; OS: Our study; (a) – 1: [29]; 2: [28]; (b) – 1: [5] surgery; 2: [5] all cases; 3: [23]; 4: [32]; 5: [30]; 6: [31].*
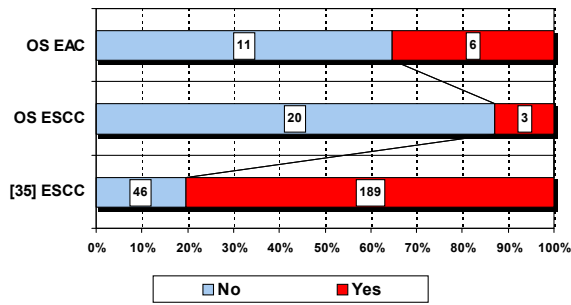
Figure 15 – *Comparison of vascular invasion distribution between our study and other studies. EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; OS: Our study.*

Similar situations were observed when ESCCs and EACs were analyzed separately with some notable differences. ESCCs of the German group were less aggressive than those from the Italian group whereas EACs from the Italian group were less aggressive than those from the German group.

Also, Italian ESCCs were slightly more aggressive than EACs of the same study whereas German ESCCs were less aggressive than EACs of the same study (Figure 16 – middle and bottom) [23, 28].

Our tumors had, both taken as a whole or separately, an invasive behavior closer but more pronounced to the German tumors.

In the Chinese study of Qiu *et al.* [5], who assessed ECs in general, the lymph node invasion was present in around 20% of the cases an in N1 stage, whereas in our study it was in total opposition, with almost 20% of cases without lymph node invasion (Figure 16b – top).

We compared also the lymph node invasion of our ESCC group with the results of the three Chinese studies that assessed only ESCCs [30–32]. All of them had no lymph node involvement in percentages varying from more

than 40% to more than 60%, in evident opposition to our data where regional lymph node invasion was almost the rule (Figure 16 – bottom).

As a concluding remark, our results concerning the regional lymph node invasion were closer to those of the European studies and in more or less evident opposition with Asian or American studies.

M staging

We did not intend to assess the distant metastases on the one hand because we had a large percentage of cases in which metastasis could not be assessed histopathologically and on the other hand because we found but one German study [28] that referred to this aspect. However, even in this study, the percentage of tumor distant spread was much reduced (less than 20%), more pronounced in ESCCs than in EACs (Figure 17).

As a concluding remark, distant metastases are difficult to confirm histopathologically unless they are accessible in the operating field so that samples of tumor tissue can be taken.

Overall staging

Finally, we compared our results related to overall staging with those of the same studies we used for the assessment of TNM staging parts.

Thus, the Chinese study of Qiu *et al.* [5] reported the best staging distribution, with more than half of cases being included in stage I (Figure 18 – top). Likewise, almost 60% of ESCC cases from another Chinese study [35] had stage II or less.

In turn, more than half or even than two thirds of cases of German study of Jacobsen *et al.* [28] and American study of Then *et al.* [29] were included in stage III of higher (Figure 18). It should also be mentioned that ESCCs had a more pronounce trend to higher stages than EACs in both American and German studies (Figure 18 – middle and bottom).
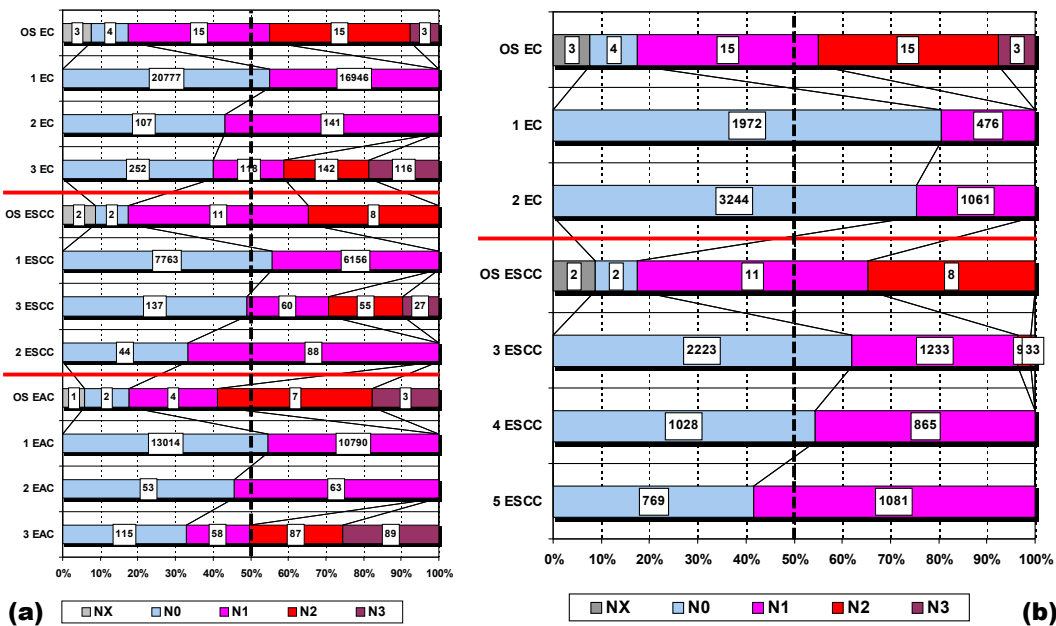

Figure 16 – *Comparison of regional lymph node invasion (pN) between our study and (a) studies that assessed both EC and its subtypes or (b) studies that assessed only ECs or ESCCs. EAC: Esophageal adenocarcinoma; EC: Esophageal carcinoma; ESCC: Esophageal squamous cell carcinoma; OS: Our study; (a) – 1: [29]; 2: [23]; 3: [28]; (b) – 1: [5] surgery; 2: [5] all cases; 3: [32]; 4: [31]; 5: [30].*
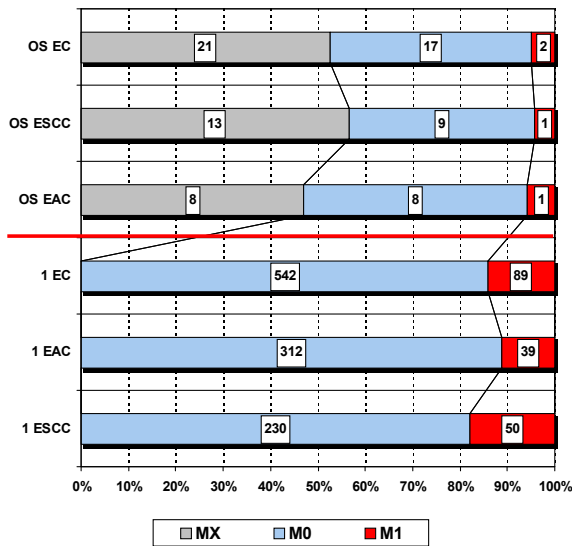
Figure 17 – *Comparison of distant invasion (pM) between our study and other studies. EAC: Esophageal adenocarcinoma; EC: Esophageal carcinoma; ESCC: Esophageal squamous cell carcinoma; OS: Our study; 1: [28].*
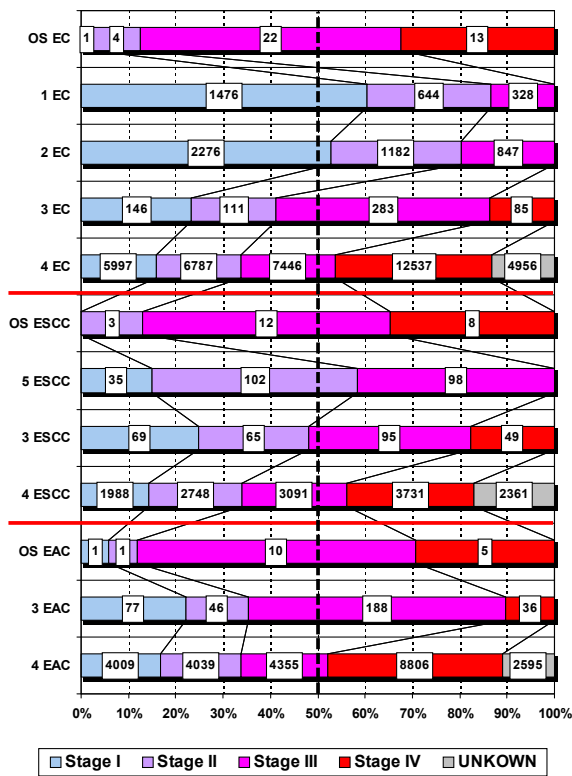

Figure 18 – *Comparison of overall staging (pTNM) between our study and other studies that assessed both EC and its subtypes. EAC: Esophageal adenocarcinoma; EC: Esophageal carcinoma; ESCC: Esophageal squamous cell carcinoma; OS: Our study; 1: [5] surgery; 2: [5] all cases; 3: [28]; 4: [29]; 5: [35].*

Our results were closer but more pronounced than those of the American study.

As a concluding remark, there is a significant variability of overall staging in ECs, dictated by the convergent influence of local invasion, regional lymph node involvement and proved existence of distant metastases.

However, our observations indicate more pronounced trend to high stages of ESCCs as compared with EACs.

⬛ Conclusions

In general, studied tumors were aggressive tumors, usually diagnosed in a late stage of evolution. The two main histological types of carcinomas, namely squamous cell carcinomas and adenocarcinomas proved to have distinct morphological and behavioral profiles. Our observations were within the limits of variation of different morphological and behavioral features found in the literature whether it was EC in general or its main histological types.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018, 68(6):394–424. https://doi.org/10.3322/caac.21492 PMID: 30207593

[2] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. CA Cancer J Clin, 2016, 66(2):115–132. https://doi.org/10.3322/caac.21338 PMID: 26808342

[3] Recio-Boiles A, Babiker HM. Cancer, esophageal. In: ***. StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL, USA, last updated: Aug 10, 2020. https://www.ncbi.nlm.nih.gov/books/NBK459267/

[4] Feng RM, Zong YN, Cao SM, Xu RH. Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics? Cancer Commun (Lond), 2019, 39(1):22. https://doi.org/10.1186/s40880-019-0368-6 PMID: 31030667 PMCID: PMC6487510

[5] Qiu MJ, Yang SL, Wang MM, Li YN, Jiang X, Huang ZZ, Xiong ZF. Prognostic evaluation of esophageal cancer patients with stages I–III. Aging (Albany NY), 2020, 12(14):14736–14753. https://doi.org/10.18632/aging.103532 PMID: 32701062 PMCID: PMC7425498

[6] Napier KJ, Scheerer M, Misra S. Esophageal cancer: a review of epidemiology, pathogenesis, staging workup and treatment modalities. World J Gastrointest Oncol, 2014, 6(5):112–120. https://doi.org/10.4251/wjgo.v6.i5.112 PMID: 24834141 PMCID: PMC4021327

[7] Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. Lancet, 2017, 390(10110):2383–2396. https://doi.org/10.1016/S0140-6736(17)31462-9 PMID: 28648400

[8] Gupta B, Kumar N. Worldwide incidence, mortality and time trends for cancer of the oesophagus. Eur J Cancer Prev, 2017, 26(2):107–118. https://doi.org/10.1097/CEJ.0000000000000249 PMID: 27014938

[9] Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. Gut, 2015, 64(3):381–387. https://doi.org/10.1136/gutjnl-2014-308124 PMID: 25320104

[10] Abnet CC, Arnold M, Wei WQ. Epidemiology of esophageal squamous cell carcinoma. Gastroenterology, 2018, 154(2):360–373. https://doi.org/10.1053/j.gastro.2017.08.023 PMID: 28823862 PMCID: PMC5836473

[11] Tramontano AC, Nipp R, Mercaldo ND, Kong CY, Schrag D, Hur C. Survival disparities by race and ethnicity in early esophageal cancer. Dig Dis Sci, 2018, 63(11):2880–2888. https://doi.org/10.1007/s10620-018-5238-6 PMID: 30109578 PMCID: PMC6738563

[12] Wang QL, Xie SH, Wahlin K, Lagergren J. Global time trends in the incidence of esophageal squamous cell carcinoma. Clin Epidemiol, 2018, 10:717–728. https://doi.org/10.2147/CLEP.S166078 PMID: 29950901 PMCID: PMC6016013

[13] Liang H, Fan JH, Qiao YL. Epidemiology, etiology, and prevention of esophageal squamous cell carcinoma in China. Cancer Biol Med, 2017, 14(1):33–41. https://doi.org/10.20892/j.issn.2095-3941.2016.0093 PMID: 28443201 PMCID: PMC5365188

[14] Halland M, Katzka D, Iyer PG. Recent developments in pathogenesis, diagnosis and therapy of Barrett's esophagus. World J Gastroenterol, 2015, 21(21):6479–6490. https://doi.org/10.3748/wjg.v21.i21.6479 PMID: 26074687 PMCID: PMC4458759

[15] Palethorpe HM, Drew PA, Smith E. Androgen signaling in esophageal adenocarcinoma cell lines *in vitro*. Dig Dis Sci, 2017, 62(12):3402–3414. https://doi.org/10.1007/s10620-017-4794-5 PMID: 29052817 PMCID: PMC5694516

[16] Tiasto V, Mikhailova V, Gulaia V, Vikhareva V, Zorin B, Kalitnik A, Kagansky A. Esophageal cancer research today and tomorrow: lessons from algae and other perspectives. AIMS Genet, 2018, 5(1):75–90. https://doi.org/10.3934/genet.2018.1.75 PMID: 31435514 PMCID: PMC6690251

[17] Lagergren J. Adenocarcinoma of oesophagus: what exactly is the size of the problem and who is at risk? Gut, 2005, 54(Suppl 1):*i1–i5*. https://doi.org/10.1136/gut.2004.041517 PMID: 15711002 PMCID: PMC1867797

[18] Wang RH. From reflux esophagitis to Barrett's esophagus and esophageal adenocarcinoma. World J Gastroenterol, 2015, 21(17):5210–5219. https://doi.org/10.3748/wjg.v21.i17.5210 PMID: 25954094 PMCID: PMC4419061

[19] Rice TW, Kelsen D, Blackstone EH, Ishwaran H, Patil DT, Bass AJ, Erasmus JJ, Gerdes H, Hofstetter WL. Esophagus and esophagogastric junction. In: Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR (eds). AJCC Cancer Staging Manual. 8th edition, American College of Surgeons (ACS), Springer International Publishing, 2017, 185–234.

[20] Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. Ann Cardiothorac Surg, 2017, 6(2):119–130. https://doi.org/10.21037/acs.2017.03.14 PMID: 28447000 PMCID: PMC5387145

[21] Feller A, Fehr M, Bordoni A, Bouchardy C, Frick H, Mousavi M, Steiner A, Arndt V, Clough-Gorr KM; Nicer Working Group. Trends in incidence of oesophageal and gastric cancer according to morphology and anatomical location, in Switzerland 1982–2011. Swiss Med Wkly, 2015, 145:w14245. https://doi.org/10.4414/smw.2015.14245 PMID: 26661828

[22] Mukhula V, Sibale D, Tarmahomed L, Dzamalala C, Msyamboza K, Chasimpha S. Characterising cancer burden and quality of care at two palliative care clinics in Malawi. Malawi Med J, 2017, 29(2):130–135. https://doi.org/10.4314/mmj.v29i2.10 PMID: 28955420 PMCID: PMC5610283

[23] Castoro C, Scarpa M, Cagol M, Ruol A, Cavallin F, Alfieri R, Zanchettin G, Rugge M, Ancona E. Nodal metastasis from locally advanced esophageal cancer: how neoadjuvant therapy modifies their frequency and distribution. Ann Surg Oncol, 2011, 18(13):3743–3754. https://doi.org/10.1245/s10434-011-1753-9 PMID: 21556952

[24] Gabel JV, Chamberlain RM, Ngoma T, Mwaiselage J, Schmid KK, Kahesa C, Soliman AS. Clinical and epidemiologic variations of esophageal cancer in Tanzania. World J Gastrointest Oncol, 2016, 8(3):314–320. https://doi.org/10.4251/wjgo.v8.i3.314 PMID: 26989467 PMCID: PMC4789617

[25] Kauppila JH, Mattsson F, Brusselaers N, Lagergren J. Prognosis of oesophageal adenocarcinoma and squamous cell carcinoma following surgery and no surgery in a nationwide Swedish cohort study. BMJ Open, 2018, 8(5):e021495. https://doi.org/10.1136/bmjopen-2018-021495 PMID: 29748347 PMCID: PMC5950652

[26] Shin A, Won YJ, Jung HK, Kong HJ, Jung KW, Oh CM, Choe S, Lee J. Trends in incidence and survival of esophageal cancer in Korea: analysis of the Korea Central Cancer Registry Database. J Gastroenterol Hepatol, 2018, 33(12):1961–1968. https://doi.org/10.1111/jgh.14289 PMID: 29802647 PMCID: PMC6334276

[27] Salem ME, Puccini A, Xiu J, Raghavan D, Lenz HJ, Korn WM, Shields AF, Philip PA, Marshall JL, Goldberg RM. Comparative molecular analyses of esophageal squamous cell carcinoma, esophageal adenocarcinoma, and gastric adenocarcinoma. Oncologist, 2018, 23(11):1319–1327. https://doi.org/10.1634/theoncologist.2018-0143 PMID: 29866946 PMCID: PMC6291329

[28] Jacobsen F, Kohsar J, Gebauer F, Kluth M, Hube-Magg C, Simon R, Bockhorn M, Hinsch A, Burandt E, Lübke AM, Steurer S, Tachezy M, Sauter G, Izbicki JR, Wilczak W, Melling N. Loss of p16 and high Ki67 labeling index is associated with poor outcome in esophageal carcinoma. Oncotarget, 2020, 11(12):1007–1016. https://doi.org/10.18632/oncotarget.27507 PMID: 32256975 PMCID: PMC7105162

[29] Then EO, Lopez M, Saleem S, Gayam V, Sunkara T, Culliford A, Gaduputi V. Esophageal cancer: an updated surveillance epidemiology and end results database analysis. World J Oncol, 2020, 11(2):55–64. https://doi.org/10.14740/wjon1254 PMID: 32284773 PMCID: PMC7141161

[30] Chen J, Liu S, Pan J, Zheng X, Zhu K, Zhu J, Xiao J, Ying M. The pattern and prevalence of lymphatic spread in thoracic oesophageal squamous cell carcinoma. Eur J Cardiothorac Surg, 2009, 36(3):480–486. https://doi.org/10.1016/j.ejcts.2009.03.056 PMID: 19502077

[31] Cheng J, Kong L, Huang W, Li B, Li H, Wang Z, Zhang J, Zhou T, Sun H. Explore the radiotherapeutic clinical target volume delineation for thoracic esophageal squamous cell carcinoma from the pattern of lymphatic metastases. J Thorac Oncol, 2013, 8(3):359–365. https://doi.org/10.1097/JTO.0b013e31827e1f6d PMID: 23263689

[32] Dong Y, Guan H, Huang W, Zhang Z, Zhao D, Liu Y, Zhou T, Li B. Precise delineation of clinical target volume for crossing-segments thoracic esophageal squamous cell carcinoma based on the pattern of lymph node metastases. J Thorac Dis, 2015, 7(12):2313–2320. https://doi.org/10.3978/j.issn.2072-1439.2015.12.10 PMID: 26793353 PMCID: PMC4703650

[33] Chen CY, Li CC, Chien CR. Does higher radiation dose lead to better outcome for non-operated localized esophageal squamous cell carcinoma patients who received concurrent chemoradiotherapy? A population based propensity-score matched analysis. Radiother Oncol, 2016, 120(1):136–139. https://doi.org/10.1016/j.radonc.2016.04.042 PMID: 27207358

[34] Chang CL, Tsai HC, Lin WC, Chang JH, Hsu HL, Chow JM, Yuan KS, Wu ATH, Wu SY. Dose escalation intensity-modulated radiotherapy-based concurrent chemoradiotherapy is effective for advanced-stage thoracic esophageal squamous cell carcinoma. Radiother Oncol, 2017, 125(1):73–79. https://doi.org/10.1016/j.radonc.2017.08.025 PMID: 28923576

[35] Meng J, Zhang J, Xiu Y, Jin Y, Xiang J, Nie Y, Fu S, Zhao K. Prognostic value of an immunohistochemical signature in patients with esophageal squamous cell carcinoma undergoing radical esophagectomy. Mol Oncol, 2018, 12(2):196–207. https://doi.org/10.1002/1878-0261.12158 PMID: 29160958 PMCID: PMC5792740

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