

Staging accuracy in resectable esophageal cancer. Observational retrospective study

Exactitud diagnóstica en el cáncer de esófago localizado. Estudio observacional retrospectivo

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Abstract

Objective: To assess the accuracy of the diagnostic tests for a correct clinical tumor staging in localized esophageal cancer (EC).

Method: Retrospective observational study of patients who underwent esophagectomy for cancer in a referral hospital between January 2003 and September 2019. Those patients who received neoadjuvant treatment were excluded in order to avoid bias from downstaging effects. The preoperative stage was compared with the pathological stage of the surgical specimen. Computed tomography (CT), endoscopic ultrasound (EUS) and positron emission tomography (PET) were evaluated. The pT stage was correlated with the tumor length described in the esophagogram (EG). **Results:** Among the 63 patients included, the clinical staging was correct in 16 (global accuracy 25.4%), it was overstaged in 21 (33.2%) and understaged in 26 (41.3%). For cT staging, the accuracy of EUS was higher than that of CT (46.6% and 34.9%, respectively), specially for early stages. EG tumor length correlated with pT stage ($p < 0.05$). For cN staging, PET had the highest sensitivity (50.0%) and negative predictive value (75.0%).

Conclusions: Despite the multiple diagnostic tools used, the global accuracy of clinical staging in localized EC is still a challenge. The lack of a test that stands out significantly from the others reinforces the need to use them in a complementary way.

Keywords: Esophageal cancer. Tumor staging. Diagnostic accuracy.

Resumen

Objetivo: Evaluar la exactitud diagnóstica para el estadiaje clínico del cáncer de esófago (CE) localizado. **Método:** Estudio observacional retrospectivo de los pacientes esofagectomizados por CE en un hospital de referencia entre enero de 2003 y septiembre de 2019. Se excluyeron aquellos que recibieron neoadyuvancia para evitar sesgos de infraestadiaje. Se comparó el estadio preoperatorio con el estadio patológico de la pieza quirúrgica. Se evaluaron la tomografía computarizada (TC), la ecoendoscopia (EUS) y la tomografía por emisión de positrones (PET). El estadio pT se correlacionó con la longitud tumoral descrita en el esofagograma (EG). **Resultados:** De los 63 pacientes incluidos, el estadiaje clínico fue correcto en 16 (exactitud 25.4%), con sobreestadiaje en 21 (33.2%) e infraestadiaje en 26 (41.3%). Para el estadiaje cT, la EUS fue superior a la TC (exactitud 46.6% y 34.9%, respectivamente), en especial para estadios precoces. La longitud tumoral del EG se correlacionó con el estadio pT ($p < 0.05$). Para el estadiaje cN, la PET tuvo la mayor sensibilidad (50.0%) y el mayor valor predictivo negativo (75.0%). **Conclusiones:** A pesar de las múltiples herramientas diagnósticas empleadas, la exactitud diagnóstica en el CE localizado es limitada. La ausencia de una prueba que destaque de manera significativa refuerza la necesidad de emplearlas de forma complementaria.

Palabras clave: Cáncer de esófago. Estadificación tumoral. Exactitud diagnóstica.

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Introduction

The survival of patients with esophageal cancer correlates with the degree of tumor spread at the time of diagnosis. Therefore, to offer optimal treatment and make a reasonable use of health care resources, it is essential to perform accurate clinical staging¹.

Typically, tumor diagnosis is established through upper digestive endoscopy with biopsy. Clinical staging is achieved by combining several diagnostic imaging modalities, such as thoraco-abdominopelvic (TAP) computed tomography (CT) (cervical in case of cervical tumor involvement), esophagogram (EG), positron emission tomography (PET), and ultrasound (US)¹.

Once distant dissemination (cM) has been ruled out, it is important to determine the tumor (cT) and lymph node (cN) stages because these patients will likely be eligible for curative intent treatment. Patients with early tumor stages without lymph node involvement may be eligible for endoscopic or surgical treatment alone, while those with suspected lymph node involvement or more advanced stages of the disease will benefit from a multidisciplinary approach with neoadjuvant treatment (chemotherapy-radiation therapy) and further surgery¹⁻⁴.

The T staging is mainly evaluated using CT and US. CT measures the thickness of the esophageal wall (pathological if > 5 mm) and its asymmetry, as well as possible infiltrations of adjacent structures. On the other hand, the US provides a more precise assessment of tumor infiltration into the different layers of the esophageal wall^{5,6}. Lymph node involvement is also evaluated by these two imaging modalities, mainly based on the size of the lymph nodes (pathological if > 10 mm), but also on their shape or formation of adenopathy clusters.¹ The main objective of PET is to rule out lymph node or metastatic dissemination.

Former studies have already analyzed the performance of various diagnostic tests for the clinical staging of esophageal cancer⁷⁻¹⁰. However there are no studies comparing TAP CT, PET, EG, and US all together.

The objective of this study is to evaluate diagnostic accuracy in the clinical staging of localized esophageal cancer. For this purpose, clinical staging was compared with the anatomopathological staging (8th edition of the TNM classification)¹¹.

Method

This was a retrospective observational study of patients treated with esophagectomy due to neoplasm

at a tertiary referral hospital from January 2003 through September 2019.

The study included patients with localized stages of cancer who underwent surgery as the initial treatment. Patients who received neoadjuvant therapy were excluded to avoid under-staging bias (Fig. 1).

Tumor staging of the patients

All patients with esophageal cancer underwent several diagnostic tests, including TAP CT, upper digestive endoscopy with biopsy, EG, and a full blood test with tumor markers. Also, an US was performed in non-stenotic lesions without distant disease, and a PET in cases where distant disease was suspected. The cytology of lymph nodes through fine-needle aspiration (FNA) was not performed systematically. In case of discrepancies among different imaging modalities, the more advanced stage was considered.

The US was not always performed by the same endoscopist. Nonetheless, they all followed the same diagnostic criteria: for T staging, visualization of a 5-line structure of hypo- and hyperechoic alternations corresponding to the 5 histological layers of the esophageal wall. For N staging, identification of lymph nodes > 10 mm, round, well-demarcated, heterogeneous or hypoechogenic suggestive of malignancy¹².

Patients with stages > cT3 or cN+ were eligible for neoadjuvant therapy with chemotherapy-radiation therapy according to the CROSS scheme. After finishing treatment, a CT was performed to assess the response, and surgery was performed 6-8 weeks later. Tumors staged as cT1-2 cN0 were generally considered eligible for surgery as first-line therapy.

Staging was performed according to the current TNM classification at each time, and later according to the 8th edition for proper comparability.

Surgical technique

A 3-stage esophagectomy (McKeown procedure) was performed for tumors located in the upper and middle thirds of the esophagus, a 2-stage esophagectomy (Ivor-Lewis procedure) for tumors located in the lower third or at the gastroesophageal junction (Siewert I and II), and a two-stage transhiatal esophagectomy (Orringer procedure) in cases of significant cardiac or respiratory comorbidity. A standard two-field lymphadenectomy was performed according to the International Society for Diseases of the Esophagus classification (1994)¹³⁻¹⁵, with a requirement of resecting, at least,

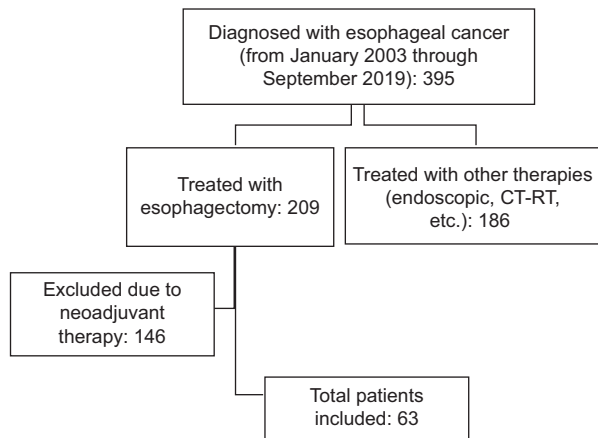


Figure 1. Flowchart of the patient selection process for the studied group. CT: chemotherapy; RT: radiation therapy.

12 lymph nodes for the two-field lymphadenectomy to be considered optimal. Reconstruction was performed using gastropasty or coloplasty in cases of previous gastric surgery.

Surgical approach was minimally invasive, open, or hybrid, with a clear trend towards minimally invasive techniques across the entire study period.

Statistical analysis

Variables were described using the most appropriate statistical measures based on the nature and scale of measurement for each variable: mean and standard deviation for quantitative variables, and absolute and relative frequencies in percentage for qualitative variables.

The preoperative stages cT and cN, as well as their combination (cTNM), were compared to the pathological stage of the surgical specimen (pT, pN, pTNM), which was considered the reference method. CT and US were evaluated for cT and cN, respectively, while PET was only used for cN. Additionally, the pT stage was correlated with the tumor length described in the EG.

Correct staging was considered when cT, cN, or both were confirmed in the surgical specimen (pT, pN), reflected by the accuracy of each test. Over- or under-staging was considered when cT or cN were higher or lower than pT or pN, respectively.

To conduct certain analyses, data were grouped. Specifically, pT1a and pT1b stages were grouped as pT1, and pT4a stages as pT4 to be able to compare them with cT stages, which do not consider these subdivisions. Similarly, pathological stages pIIIA and pIIIB were grouped as pIII, and stages pN1, pN2, and pN3 as pN+.

The performance of the additional tests performed was described using sensitivity (S), specificity (Spe), positive predictive value (PPV), negative predictive value (NPV), and accuracy. Fisher's exact test was used to analyze differences among different diagnostic imaging modalities or tumor stages.

To study the association between tumor length described in the EG and pT stage, the analysis of variance (ANOVA) was used after checking the comparability, normal distribution, and homogeneity of the samples. Additionally, attempts were made to predict pT stage based on tumor length using the receiver operating characteristic (ROC) curves and subsequent contingency tables.

P values < 0.05 were considered statistically significant. Data were collected using the Scientific Package of the Social Sciences 21.0 (SPSS, Chicago, IL, United States) and analyzed using SPSS and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 63 patients were included in the study whose characteristics are shown on table 1. Clinical staging was correct in 16 cases (25.4%). Over- and under-staging occurred in 21 (33.2%) and 26 (41.3%) patients, respectively. Given the low accuracy of clinical staging, the diagnostic performance of the different additional tests for T and N stages was analyzed.

Tumor staging

ULTRASOUND

The US was performed in 43 patients. The contingency table and the corresponding S, Spe, PPV, NPV, and overall diagnostic accuracy are shown on table 2. Tumor staging (uT) was correct in 20 patients (overall accuracy, 46.6%). In 23 patients (53.4%), the uT stage was incorrect, in 30.2% over-staged and in 23.2% under-staged.

To study S and Spe, uT0, uT1a, and uT4 stages were excluded due to the low number of patients. Looking at the table, we should mention that the S for the uT1b stage was low (33%), lower compared to other stages (66.7% and 64.3%, with $p = 0.08$ and $p = 0.10$, respectively). Additionally, Spe was also low (55.9%) for uT2 stage compared to other stages (96.2% and 82.8%), which was statistically significant ($p < 0.001$ and $p = 0.03$, respectively).

Since patients with cT1 stage tumors may be eligible for endoscopic treatment, the ability of US to distinguish

Table 1. Characteristics of the patients (n = 63)

Mean age, years (SD)	61.27 (9.39)
Men (%)	54 (85.7)
BMI, kg/m ² (SD)	26.22 (3.64)
Mean time since diagnosis until surgery, days (SD)*	51.7 (33.09)
Type of cancer	
Squamous (%)	25 (39.7)
Adenocarcinoma (%)	38 (60.3)
Tumor location	
Upper thoracic third (%)	5 (7.9)
Middle thoracic third (%)	7 (11.1)
Lower thoracic third (%) / gastroesophageal junction (%)	51 (81.0)
Imaging modalities	
TAP CT (%)	63 (100)
Upper digestive endoscopy with biopsy (%)	63 (100)
PET (%)	17 (27)
EG (%)	32 (50.8)
US (%)	43 (68.3)
Type of surgical procedure	
Ivor-Lewis (%)	24 (38.1)
McKeown (%)	25 (38.7)
Orringer (%)	14 (22.2)
Resection margins	
R0 (%)	56 (88.9)
R1 (%)	7 (11.1)
Diseased proximal longitudinal margin	3
Diseased circumferential margin	4
Approach	
Open (%)	8 (12.7)
Minimally invasive (%)	39 (61.9)
Hybrid (%)	16 (25.4)
Laparotomy + thoracoscopy (%)	4 (6.3)
Laparoscopy + thoracotomy (%)	12 (19.0)
Lymphadenectomy	
2-field standard (%)	49 (77.8)
Suboptimal lymphadenectomy (%)	23 (36.5)
No lymphadenectomy (%)	14 (22.2)
Number of nodes resected (SD)	15.11 (6.88)
Clinical stage	
I	13 (20.6)
II	36 (57.1)
II	14 (22.2)
Pathological stage	
0	4 (6.3)
I	24 (38.1)
II	9 (14.3)
II	15 (23.8)
IV	11 (17.5)

SD: standard deviation; EG: esophagogram; US: ultrasound; BMI: body mass index; PET: positron emission tomography; TAP CT: thoraco-abdominopelvic computed tomography.

*Considering the diagnostic moment as the day the upper digestive endoscopy was performed.

COMPUTED TOMOGRAPHY

All patients underwent CT scans. The cT staging was correct in 22 patients (overall accuracy, 34.9%), over-staged in 22.2% and under-staged in 42.9%. Table 3 shows that the S of the CT scan was higher in the advanced stage cT3 (68.4%) compared to cT1 and cT2 stages (11.1% and 36.4%, respectively) being the difference with respect to cT1 statistically significant ($p < 0.001$ and $p = 0.13$, respectively).

ESOPHAGOGRAM LENGTH

A total of 32 patients underwent EGs. The data showed a normal distribution ($p = 0.054$), and there was homogeneity in variances ($p = 0.53$). The tumor length (cm) on the EG was greater as the pT stage grew: for pT1, tumor length was 2.5 ± 1.68 cm; for pT2, 4.33 ± 1.21 cm; and for pT3, 4.47 ± 1.35 cm being the differences statistically significant if pT1 was compared to pT3 ($p = 0.006$), and almost statistically significance if pT2 was compared to pT1 ($p = 0.054$).

The diagnostic accuracy of the EG was analyzed using the ROC curve. Therefore, considering the results discussed and that pT1 could be eligible for less invasive treatments, 2 groups were created: those with pT1 stage and those with pT2 or higher stage. The area under the ROC curve was 0.804 (95% confidence interval, 0.633-0.975; $p < 0.004$). The value with the highest discriminative power was 3.5 cm (80% S and 74% Spe). Table 4 shows that using this value, tumors with lengths < 3.5 cm could be predicted—with an accuracy of 78.1%—to be stage T1, while those with greater lengths would be stage T2 or higher.

Nodal staging

The results are shown on table 5.

COMPUTED TOMOGRAPHY

The cN staging was correct in 42 cases (66.7% accuracy). A total of 19 patients (30.2%) were considered cN0 but turned out to be pN+, while in 2 cases (3.2%), nodal involvement was suspected, but they were ultimately pN0.

ULTRASOUND

US was performed on 42 patients. The uN staging was correct in 22 cases (52.4% accuracy). In 18 cases

between T1 and T2 stages was analyzed. The PPV of those categorized as uT1 was 83.35%, compared to 28.6% for those categorized as uT2, with a 42.9% over-staging in the latter.

Table 2. Comparison between the tumor clinical stage by ultrasound (uT) and the pathological one (pT)

pT0	pT						S (%)	Spe (%)	NPV (%)	PPV (%)	Accuracy (%)	
	pT1a	pT1b	pT2	pT3	pT4a	Total						
uT												
uT0	0	0	1	0	0	0	1	-	97.7	100	0	97.7
uT1a	0	0	1	0	0	0	1	0	97.6	97.6	0	95.3
uT1b	0	0	5	1	0	0	6	33.3	96.2	67.6	83.3	69.8
uT2	0	1	8	6	5	1	21	66.7	55.9	86.4	28.6	58.1
uT3	0	0	2	2	9	1	14	64.3	82.8	82.8	64.3	76.7
uT4	0	0	0	0	0	0	0	0	100	95.2	-	93.0
Total	0	1	17	9	14	2	43					46.5%

Spe: specificity; S: sensitivity; NPV: negative predictive value; PPV: positive predictive value.

Table 3. Comparison between the tumor clinical stage by computed tomography (cT) and the pathological one (pT)

	pT					Total	S (%)	Spe (%)	NPV (%)	PPV (%)	Accuracy (%)
	pT0/Tis	pT1	pT2	pT3	pT4						
cT											
cT0	2	13	5	0	0	20	66.7	70	97.7	10	68
cT1	0	3	0	1	0	4	11.1	97.2	59.3	75	60.3
cT2	0	7	4	5	1	17	36.4	75	84.8	23.5	68.3
cT3	1	4	2	13	2	22	68.4	79.6	85.4	59.1	76.2
cT4	0	0	0	0	0	0	0	100	95.2	-	95.2
Total	3	27	11	19	3	63					34.9%

Spe: specificity; S: sensitivity; NPV: negative predictive value; PPV: positive predictive value.

Table 4. Correlation between tumor length and the pathological stage (pT)

	pT			S (%)	Spe (%)	NPV (%)	PPV (%)	Accuracy (%)
	pT1	≥ pT2	Total					
Length (cm)								
< 3.5	9	4	13	80.0%	75.0%	69.2	84.2%	78.1
≥ 3.5	3	16	19					
Total	12	20	32					

Spe: specificity; S: sensitivity; NPV: negative predictive value; PPV: positive predictive value.

Table 5. Comparison between the clinical node stage (cN, uN) and the pathological one (pN)

	pN			S (%)	Spe (%)	NPV (%)	PPV (%)	Accuracy (%)
	pN-	pN+	Total					
CT								
cN0	34	19	53	29.6	94.4	64.1	80.0	66.7
cN+	2	8	10					
Total	36	27	63					
US								
uN0	20	18	38	10.0	90.9	52.6	50.0	52.4
uN +	2	2	4					
Total	22	20	42					
PET								
cN0	9	3	12	50.0	81.8	75.0	60.0	70.6
cN+	2	3	5					
Total	11	6	17					

Spe: specificity; S: sensitivity; NPV: negative predictive value; PPV: positive predictive value.

(42.9%), no nodal disease was suspected, but they turned out to be pN+, while only in 2 cases (4.8%), nodal involvement was suspected without confirmation in the surgical specimen analysis.

POSITRON EMISSION TOMOGRAPHY

Among the 17 patients who underwent PET, nodal staging was correctly predicted in 12 cases (70.6% accuracy). Three cases, however, (17.6%) with nodal involvement were misdiagnosed by the PET, while 2 cases (11.8%) with suspected nodal involvement turned out to be pN0.

The specificity of the 3 imaging modalities was comparable (94.4%, 90.9%, and 81.8%, respectively), while the S (50.0%) and NPV (75.0%) of PET were higher. In the CT scan, and especially in the US, the large number of false negatives resulted in low S (29.6% and 10.0%, respectively) and low NPV (64.1% and 50.0%, respectively).

Discussion

Despite the availability of multiple diagnostic imaging modalities, and consistent with what has been reported in former studies⁹, in our study, clinical staging was correct in only a quarter of the patients, with therapeutic and prognostic implications associated.

Regarding clinical tumor stage (cT), the accuracy of CT and US was 34.9% and 46.6%, respectively, being over-staging more common in the US (30.2% vs 22.2% for the CT) and under-staging more common in the CT (42.9% vs 23.2% for the US).

Former studies have reported CT accuracies of 68.7% to 76.3% for cT staging¹⁶, which is higher than what we obtained. The CT scan cannot distinguish among T1, T2, and T3 stages⁶. However, it is very useful to assess infiltration of adjacent structures, with sensitivity and specificity rates of 85% to 100%, resulting in higher accuracy for T4 stage^{17,18}. However, our study excluded cT4 tumors because they were not eligible for primary surgery, which may have negatively impacted the overall accuracy of this imaging modality.

A meta-analysis that studied the ability of US to establish cT reported S rates of 81% to 90% and Spe rates close to 99%¹⁹. Our data are worse compared to those reported in the medical literature available, being the accuracy rate of the US between 64% to 92%^{7,8,20}.

The pT stage was more advanced as tumor length grew in the EG, suggesting it could be an additional predictive tool. Although literature on this subject is limited, existing studies support its use because it improves the diagnostic accuracy of other imaging modalities²¹.

Regarding nodal staging (cN), PET showed higher diagnostic accuracy (70.6%) compared to CT (66.7%) and US (52.4%). However, all 3 imaging modalities commonly produced tumor under-staging (PET, 17.6%; CT, 30.2%; US, 42.9%), with no statistically significant differences being reported among the three. These results are consistent with former studies published in the medical literature currently available^{7,8}.

The findings of this study, in conjunction with the existing literature, suggest that the clinical staging of esophageal cancer remains challenging despite the availability of various diagnostic imaging modalities. Consistent with former studies, the US appears superior for cT staging, especially regarding T1-T3 stages^{6,19,22-24}. No significant differences in the accuracy of the 3 imaging modalities have been reported regarding nodal staging.

The absence of a clearly superior imaging modality is due to the limitations of each individual modality. Compared to the CT scan, the US provides better visualization of esophageal wall layers and higher sensitivity for nodal staging when combined with FNA of suspicious nodes. However, it does not provide information on distant spread, is invasive, operator-dependent, not feasible in stenosing tumors, and not all adenopathies are accessible through puncture^{19,20,22,25}. On the other hand, the CT scan provides information on disease spread but is limited when it comes to detecting small tumor deposits that do not alter nodal morphology and distinguishing enlarged nodes for other reasons, such as smoking or inflammatory-infectious conditions²⁶. Similarly, the PET cannot identify subcentimeter nodes and may not accurately evaluate proximal nodes due to significant tumor isotope uptake²⁷. However, it has a high S for distant nodal metastases, which is its main advantage⁶. Lastly, the EG, although limited compared to other imaging modalities, provides useful additional information and is a non-invasive, low-radiation, and cost-effective option.

This study has limitations, including its retrospective nature, small sample size, the absence of advanced-stage (T4) patients, and very few patients in very early stages (T1). Additionally, multiple imaging modalities are operator-dependent and not all of them were used in all the patients studied. The extended study period

may have influenced the diagnostic yield of the imaging modalities and the evolution of surgical procedures.

Conclusions

Despite the various diagnostic imaging modalities used, their accuracy in localized esophageal cancer is limited, with the therapeutic and prognostic implications that this entails. The absence of an imaging modality standing out from the rest significantly reinforces the need for using them complementarily.

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None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this study.

Patients' data protection. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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