Staging Accuracy of Computed Tomography and Endoscopic Ultrasound in Preoperative Staging of Esophageal Cancer: Results of an Referral Center

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Abstract

Introduction: *Preoperative staging is the main prognostic factor and is crucial in therapeutic selection of esophageal cancer.*

Aim: *Evaluate computerized tomography and endoscopic ultrasonography accuracy in preoperative esophageal cancer staging.*

Methods: *A retrospective study between 1/1/2010 and 30/9/2015 was performed. Sensibility, specificity, positive and negative predictive values, and accuracy for T and N stage was calculated. Using the Cohen weighted K, the degree of concordance between the exams and anatomopathological results was assessed.*

Results: *Computerized tomography and endoscopic ultrasonography presented an accuracy of 35.7% (95%CI, 17.9-53.4) and 64.3% (95%CI, 46.5-82) for T, and 57.1% (95%CI, 38.8-75.4) and 71.4% (95%CI, 54.6-88.1) for N.*

Computerized tomography presented an sensibility, specificity, positive and negative predictive values of 12.5%(95%CI, 0.32-52.6), 85%(95%CI, 62.1-96.8), 25%(95%CI, 0.63-80.6), 70.8%(95%CI, 48.9-87.4) for T1; 33.3%(95%CI, 4.3-77.7), 68.2%(95%CI, 45.1-86.1), 22.2%(95%CI, 2.8-60), 78.9%(95%CI, 54.4-93.9) for T2; 50%(95%CI, 23-77), 57.1%(95%CI, 28.9-82.3), 53.8%(95%CI, 25.1-80.8), 53.3%(95%CI, 26.6-78.1) for T3; 30%(95%CI, 6.67-65.25), 72.2%(95%CI, 46.5-90.3), 37.5%(95%CI, 8.5-75.5), 65%(95%CI, 40.8-84.6) for N. For endoscopic ultrasonography: 62.5%(95%CI, 0-40.96), 95%(95%CI, 75.1-99.9), 83.3%(95%CI, 35.9-99.6), 86.4%(95%CI, 65.1-97.1) for T1; 50%(95%CI, 11.8-88.2), 77.3%(95%CI, 54.6-92.2), 37.5%(95%CI, 8.5-75.6), 85%(95%CI, 62.1-96.8) for T2; 71.4%(95%CI, 41.9-91.6), 71.4%(95%CI, 41.9-91.6), 71.4%(95%CI, 41.9-91.6), 71.4%(95%CI, 41.9-91.6) for T3; 90%(95%CI, 55.5-99.7), 61.1%(95CI, 35.7-82.7), 56.2%(95%CI, 29.9-80.2), 92%(95%CI, 62.5-99.8) for N.

Concordance was poor for computerized tomography and moderate for endoscopic ultrasonography.

Conclusions: *Endoscopic ultrasonography has a better accuracy in esophageal cancer staging, for T and N, showing a high sensibility, specificity, positive and negative predictive values, with a better accuracy for T3. Only endoscopic ultrasonography showed a significant relationship with an atom pathological results (p<0.05).*

Keywords: *esophageal cancer, staging accuracy, endoscopic ultrasonography, computerized tomography.*

1. INTRODUCTION

According to the latest report from the World Health Organization (WHO), the oncologic diseases incidence rate, presents a concerning rising trend. In 2012, the incidence was almost 14 million, and an increase of 22 million per year is expected over the next two decades.[1] This disturbing increase includes the esophageal cancer (EC), which is in eighth place in the list of most frequent cancers worldwide, and in sixth place regarding mortality.[2] In 2012, approximately 456 1000 new diagnoses (3.2% of the total) of EC were carried out, and approximately 400 1000 deaths (4.9% of the total) were attribute to it[1], and this number is expected to grow 140% by 2025.[3]

There are essentially two histological types of EC, adenocarcinoma and squamous cell carcinoma (SCC). Despite the last one being the more common worldwide, there was a marked increase in the incidence of adenocarcinoma in the last two decades.[4,5]

Currently, at the time of diagnosis, 50% of patients already present metastatic disease, about 30% have locally advanced disease and less than 20% present an initial staging, compatible with curative treatment.[6] Corporately, the factor with the greatest impact on the prognosis, as well as in the selection of therapeutics, is the preoperative staging. [4,5,7]

Several imaging modalities can be used for preoperative staging, namely Computerized Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and esophageal Endoscopic Ultrasound (EUS).[5] The information obtained from these tests is then grouped according to the classification system Tumour-Node-Metastasis (TNM) of the American Joint Committee on Cancer.[8]

At the Braga Hospital (BH), the exams used for EC staging are thoracic CT and EUS, so it becomes pertinent to assess the accuracy of these exams, comparing it with the histopathological result of the surgical specimen.

2. METHODS

The study population included patients with histological diagnosis of CE treated in the Esophagogastric Unit of BH, between January 1st, 2010 and September 30th, 2015.

2.1. Inclusion criteria:

For this study were: patients with histological diagnosis of esophageal adenocarcinoma and CCE of the esophagus; patients with a conclusive preoperative staging by CT and EUS and patients with pathology staging results based on the surgical specimen.

2.2. Exclusion criteria where the following

Patients with histological diagnosis differing from the above; patients who did not undergo CT, EUS or for whom these tests were inconclusive; patients not submitted to surgical treatment or submitted to palliative surgery with and patients without results from pathology staging.

A convenience sample of 28 patients who meet the previously defined criteria, was studied.

Clinical and staging data collected include: age, gender, tumour location, adjuvant therapeutic and T/N staging by CT and EUS. Pathological data comprise the histological type, T/N staging, and lymphatic and venous invasion.

The collected data were organized in an Excel (Microsoft Office 2010) database, and the Statistical Package for Social Sciences (SPSS) version 24.0 was used.

A descriptive analysis of the variables under study was performed, providing frequencies, means (M) and standard deviations (SD). Sensitivity, specificity, positive and negative predictive values (PV) of CT and EUS staging, related to T and N, were compared with pathology results. For this purpose, the online tool MedCalc, available in http://www.medcalc.org/calc/diagnostic_test.php was used. Efficacy was calculated by the formula (TP+TN/n) and the confidence interval (CI) by the formula P-Z×√P(1-P)/ √n; P+Z×√P(1-P)/ √n.

The agreement between the staging results obtained by CT and EUS with anatomo-pathological study was assessed by calculating the value of Cohens's Kappa (Kw); for this purpose, the online tool VassarStats, available in http://vassarstats.net/kappa.html. Value of Kw between 0.00-0.20 indicates poor agreement; between 0.21-0.40 points to a considerable agreement; between 0.41-0.60, reveals a moderate agreement; between 0.61-0.80 indicates a good agreement; and between 0.81-1.00 shows an excellent agreement.[9]

For all testes, it was assumed a significance of 0.05 and a confidence interval (CI) of 95%.

This project was approved by HB's Ethics Committee and also by Ethics Subcommittee for Life and Health Sciences.

3. RESULTS

3.1. Patient's Data

The casuistic included 28 patients, 68% (n=19) males and 32% (n=9) females, aged between 40 and 85 years (M=65; SD=12). 10.7% (n=3) of the tumours, were located in the esophagus upper third, 21.6% (n=6) in the middle third and 67.9% (n=19) in the lower third of the esophagus. Lower third of esophagus was the most common localization in both genders, 77.8% and 63% on female and male gender, respectively.

According to pathological analyse, 39.3% (n=11) of tumours was adenocarcinomas and 60.7% (n=17) was CCE. Vascular venous invasion was present in 32.1% (n=9) of patients, and lymphatic invasion in 17.9% (n=5).

Of the 28 patients, 10.7% (n=3) and 3.6 % (n=1) performed, respectively, chemotherapy and radiotherapy as adjuvant therapeutic.

Follow-up data demonstrate 37.5% (n=10) deaths.

3.2. T and N Staging

Regarding T staging by CT, 14.3% (n=4); 32.1% (n=9); 46.4% (n=13) and 7.1% (n=2) was staged as T1, T2, T3 and T4, respectively. With respect to N staging, by CT, 71.4% (n=20) of the cases, do not have lymph node involvement (N0), and 28.6% (n=8) have lymph node involvement (N+).

When staging was accomplished by EUS, 21.4% (n=6); 28.6% (n=8) and 50% (n=14) was staged as T1, T2 and T3, 42.9% (n=12) as N0 and 57.1% (n=16) as N+.

According to pathological results 28.6% (n=8); 21.4% (n=6) and 50% (n=14) was staged as T1, T2 and T3; 64.3% (n=18) as N0 and 35.7% (n=10) as N+.

3.3. Comparison between CT and an atomopa -thological Staging

Comparing CT staging versus anatom - opathological results based on surgical specimen, we noted a substaging in 10.7% of cases (n=3) staged as T1 and in 14.3% (n=4)

staged as T2 by CT; an overstaging was observed in 10.7% (n=3) of the cases staged as T2 and in 21.4% (n=6) staged as T3. We also observed that all the cases classified as T4 by CT was overstaged (7.1%, n=2).

According to N staging, obtained by CT and by anatomopathological results, a substaging was noted in 25% (n=7) of the cases staged as N0, and an overstaging was noted in 17.8% (n=5) of the cases staged as N+ by CT.

The sensitivity of CT in pre-operative staging of EC was calculated, and it was 12.5% (95% *CI*, 0.32-52.6) for T1, 33.3% (95% *CI*, 4.3-77.7) for T2 and 50% (95% *CI*, 23-77) for T3. As for specificity, this parameter is 85% (95% *CI*, 62.1-96.8) for T1, 68.2% (95% *CI*, 45.1-86.1) for T2 and 57.1% (95% *CI*, 28.9-82.3) for T3.

In relation to efficacy, CT shows efficacy of 35.7% (95%CI, 17.9-53.4) for T staging, 64.3% (95% *CI*, 46.5-82) in particular for T1 staging, 60.7% (95% *CI*, 42.6-78.8) for T2 staging and 53.6% (95% *CI*, 35.1-72) for T3 staging.

According to N staging, the sensitivity, specificity and efficacy in preoperative staging was 30% (95% *CI*, 6.67-65.25), 72.2% (95% *CI*, 46.5-90.3) and 57.1% (95% *CI*, 38.8-75.4), respectively.

In order to determine the correlation between CT versus anatomopathological staging, Kw was calculated. Kw was 0.11 (95%*CI*, 0-0.36) For T staging and 0.02 (95%*CI*, 0-0.44) for N staging.

3.4. Comparison between EUS and anatomo - -pathological Staging

Comparing EUS staging versus anatomopathological results based on surgical specimen, we noted a substaging in 3.6% of cases (n=1) staged as T1 and in 10.7% (n=3) staged as T2 by EUS; an overstaging was observed in 7.1% (n=2) of the cases staged as T2 and in 14.3% (n=4) staged as T3.

According to N staging, obtained by EUS and by anatomopathological results, a substaging was noted in 3.6% (n=1) of the cases staged as N0, and an overstaging was noted in 25% (n=7) of the cases staged as N+ by EUS.

The sensitivity of EUS in pre-operative staging of EC was calculated, and it was 62.5% (95% *CI*, 0-40.96) for T1, 50% (95% *CI*, 11.8-88.2) for T2 and 71.4% (95% *CI*, 41.9-91.6) for T3. As for specificity, this parameter is 95% (95%

CI, 75.1-99.9) for T1, 77.3% (95% *CI*, 54.6-92.2) for T2 and 71.4% (95% *CI*, 41.9-91.6) for T3.

In relation to efficacy, EUS shows efficacy of 64.3% (95%CI, 46.5 -82) for T staging, 85.7% (95% *CI*, 72.7-98.7) in particular for T1 staging and 71.4% (95% *CI*, 54.7-88.1) for T2 and T3 staging.

4. DISCUSSION

Currently therapeutic approach of EC is multidisciplinary and individualized. Therefore, a correct preoperative staging is essential to the selection of the best therapeutic option, with a clear impact on the patient's prognosis.[5,7]

From the various methods available for preoperative staging, CT and EUS, are the most commonly used.[10] Despite, literature results are not consensual, EUS seems to present a better definition for T staging when compared with the CT.[11] Napier JK et al documents a higher capacity in the differentiation between T1, T2 and T3, of EUS compared with the CT, showing efficacies of 76-89% and 49-59% respectively on T staging.[4] However, the EUS presents some limitations, these being more evident in lesions locally more advanced. These are not only due to the loss of definition that occurs when there is local compression, but also to the impossibility of progression of the probe in case of stenosis lesions.[10]

In relation to CT, this exam stands out for its easy way to be accessed, as well as the usefulness in establishing invasion of adjacent structures by the tumour, showing specificity in the determination of mediastinum invasion around 100%.[12]

In this study, results obtained by CT and EUS were compared with pathological results, aiming to analyze the accuracy of these exams. Only, for EUS, significant results were found (*p*=0.009), the number of sub and overstaging were higher for CT compared with EUS.

A sub-staging in 25% (n=7) of cases staged by CT and 14.3% (n=4) staged by EUS, were observed as well as an overstaging of 39.2% (n=11) and 21.4% (n=6), when using the CT and EUS, respectively. To exclude that overstaging cases were due to a downstaging of primary therapeutic effect, patients submitted to primary therapy were analysed and we concluded that only in one case (the same for CT and EUS) it was not possible to exclude the effect of primary therapy downstaging, being the remaining cases, clearly, overstaging cases. It was also found that all cases classified as T4 by CT, (7.1%, n=2), were overstaging cases. This result, can be explained by loss of definition of the fat between the primary tumour and adjacent structures, which seems to occur in locally advanced tumours.[4] This result has clear impact on therapeutic approach decision, if this decision is taken only based on CT preoperative results.

In this study, the sensitivity values calculated for EUS were clearly superior to CT, for T1, T2 and T3, in particular, 62.5% (95% *CI*, 0-40.96), 50% (95% *CI*, 11.8-88.2) and 71.4% (95% *CI*, 41.9-91.6), respectively. Jin Woong Cho,[13] presents values of 81.6%, 81.4% and 91.4%, respectively, however, we cannot forget that this exam is operator dependent, being important to point out the fact that, as described in other studies, the sensitivity of the EUS is higher in more advanced stages.[14,15]

For specificity, the documented values were also superior for EUS, in particular, of 95% (95% *CI*, 75.1-99.9) to T1, 77.3% (95% *CI*,54.6-92.2) for T2 and 71.4% (95% *CI*, 41.9-91.6) to T3 compared with 85% (95% *CI*, 62.1-96.8) to T1, 68.2% (95% *CI,* 45.1-86.1) for T2 and 57.1% (95% *CI*, 28.9-82.3) for T3 for CT. These results are consistent with those described in other studies to the extent that present the EUS as being a more specific exam in definition of the T staging.[13] However, EUS values are slightly lower than those presented by Jin Cho, which presents values of specificity greater than 94%, namely 99.4% 96.3% for T1, T2 and 94.4% for T3.[13]

As documented in literature, effectiveness result, were better for EUS when compared to TC,[4,13,16] although results, 35.7% (95% CI, 17.9-53.4) and 64.3% (95% CI, 46.5-82), for CT and EUS respectively, were lower than those described, 59% for CT and 85% for EUS.[4]

For TC and EUS, T staging, an Kw=0.11 (95% *CI*, 0-0.36) and Kw=0.51 (95% *CI*, 0.24-0.78) was observed respectively, which according to Fleiss, indicate a poor association in the case of CT and moderate in the case of EUS.[9] These results reinforce, in this study, that EUS is a most appropriate means for T staging when compared with the CT, in EC.

Regarding N staging, significant results were observed for staging by EUS (p=0.016). Kw of 0.02 (95% *CI*, 0-0.44) and 0.45 (95% *CI*, 0.13-0.77), for TC and EUS respectively, were documented, that according to Fleiss indicates a poor agreement between the two tests.[9]

When evaluated the sensitivity, specificity and effectiveness of CT in N staging, values obtained were 30% (95% *CI*, 6.67-65.25), 72.2% (95% *CI*, 46.5-90.3) and 57.1% (95% *CI*, 38.8-75.4), therefore, this is a better test to exclude than to confirm lymph node invasion. This finding can be explained by the fact that the lymph node involvement by CT is dependent on the size of the ganglion, lacking sensitivity in situations where the ganglion is increased by inflammatory or other reasons.[17] The results obtained are in agreement with studies already published, presenting values of sensitivity, specificity and effectiveness for the CT of 29%, 60-80% and 58%, respectively.[4,18]

Regarding the EUS, sensitivity results for N staging, was 90% (95% *CI*, 55.5-99.7), higher than observed in literature, that refers values between 68-73%.[19] Specificity results observed, 61.1% (95% *CI*, 35.7-82.7), were lower than the documented by Sequeiros E, 79%, and slightly lower than the values documented for CT, which seems to be a better method for exclusion of lymph node involvement.[18] Effectiveness values, 71.4% (95% CI, 54.6-88.1), matches with that described by other studies, namely Kyle Napier, which presents values of efficiency of 72%.

Superior sensitivity and effectiveness results of EUS in N staging, were documented, although, as documented in literature this results can be improved by the use of endoscopic ultrasound guided aspiration biopsy, allowing an increase from 85% to 97% of sensitivity and from 85% to 96% of specificity.[16]However it is a method not yet commonly used, being held in reserve for cases in which the level of suspicion of ganglionic involvement is high.

5. CONCLUSION

Preoperative staging is the factor with the greatest impact on EC patient, being decisive in selection individualized therapeutic approach.

Currently there are several exams available for preoperative staging of EC, being CT and EUS the most frequently used.

EUS staging accuracy, compared to CT, presents a better effectiveness, sensitivity and specificity, for T staging. A better specificity and effectiveness for T1 and a greater sensitivity for T3, were observed. Also, for N staging, EUS presents better sensitivity and effectivity results. On the other hand, CT offers a better specificity, that is, it seems to be a better test to exclude lymph node invasion.

We conclude that to the current knowledge, despite the best results for the EUS in local staging, CT has a place in local and distant staging, so EUS and CT must be considered as complementary and not as competitors in EC staging.

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