UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

DOCTORAL SCHOOL

DOCTORAL THESIS

THE ROLE OF NON-INVASIVE EXPLORATIONS IN THE DIAGNOSIS AND STAGING OF ESOPHAGEAL CANCER

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INTRODUCTION

Among the reasons that made me choose the subject for my doctoral thesis "The role of non invasive explorations in the diagnosis and staging of esophageal cancer" I should mention: the growth in incidence of the esophageal cancer in the last 20-30 years, the problems regarding the diagnosis and the treatment of this disease that affects an organ which is located profoundly, having poor clinical objective signs, being very difficult to approach and with a resecability rate of under 50% associated with high postoperatory morbidity and low rate of long term survival .

Establishing a diagnosis as soon as possible is the main element for a favorable postoperatory prognosis; thus , in stages I and IIA the surviving rate is about 40-62% whereas in stages IIB and III is about 18-25%.

Another important aspect is accurately establishing the stage of this disease and it represents the main element in choosing the right therapeutic method for each patient. From this point on, the various medical imaging methods are able to establish the loco-regional extension as well as the distant metastasis in esophageal cancer.

Medical imaging techniques have improved significantly over the last years. Initially, the contrast barium enema associated with endoscopy and biopsy were successfully used to diagnose high grade dysplasia and early stages of esophageal cancer. However, a radiological examination is able only to suggest the evolutive stage of the disease by measuring the degree of esophageal lumen involvement and the extension of the tumor in the organs' axis.

Nowadays, computed tomography (CT), positron emission tomography (PET) and echoendoscopy (EUS) are considered standard methods (standard imaging explorations) in establishing the loco-regional evolutive stage as well as distant extension in esophageal cancer. These imaging techniques are complementary, their singular being insufficient for the correct staging diagnosis of esophageal tumors.

CLINICAL, IMAGING AND THERAPEUTIC STUDY IN ESOPHAGEAL CANCER
- GENERAL PROBLEMS -

MATERIAL AND METHOD

Patients. This study involved a lot of 103 patients diagnosed with esophageal neoplasm and types 1 and 2 Siewert esogastric neoplasm that were admitted in the Second Surgical Clinic from the Emergency Clinical Hospital in Craiova between 1st of January and 31 December 2016. Type 3 Siewert esogastric neoplasm was not included in the studied lot.

6 cases of cervical esophageal cancer were admitted with locally advanced tumors, inoperable and with an extremely severe general status, strictly in order to obtain nutritional support(gastrostomy); the explorations in these cases were limited and these patients were excluded from the study.

Ultimately, the studied lot was represented by 97 cases of esophageal cancer confirmed by histopathological examinations.

Depending on the diagnostic possibilities the patients had, they were divided into 2 lots: the first one was composed by patients admitted between January 2007-December 2011, when imaging methods were limited and another lot with patients admitted between January 2012-December 2016 where the diagnosis protocol was entirely respected.

RESULTS

The esophageal cancer was diagnosed in 86 men (88.65%) and 11 women (11.34%).

The age of the patients was between 51 and 89 years old, with a mean of 65.44 ± 7.23 years; the mean age in men was 64.93 ± 9.27 years, while in women the mean age was 69.45 ± 5.86 years. Despite the fact that in women the esophageal cancer appeared at a later age, there is no statistical significant difference from this point of view (*p=0.051*).

	Globally N (%)	Squamous carcinoma n (%)*	Adenocarcinoma n (%)*
smoking	78 (80,41%)	62(91,17%)	16(55,17%)
alcohol	37(38,14%)	31(45,58%)	6(20,68%)
obesity	19(19,58%)	2(2,94%)	17(58,62%)
RGE	6(6,18%)	1(1,47%)	5(17,24%)

% is reported to the number of the same type of carcinoma (68 squamous carcinomas and 29 adenocarcinomas)

Risk factors involved in the apparition of esophageal cancer in the studied lot

Principal clinical aspects in the studied lot

Signs and symptoms	n	%
disfagia	97	100
regurgitations	14	14,43
sialorrhoea	2	2,06
heartburn	7	7,21
retrosternal pain	8	8,24
epigastric pain	11	11,34
vomit	4	4,12
palpable tumor	1	1,03
UGIB	1	1,03
weight drop	62	63,91
fatigue	10	10,3
anemia	35	36,08
hypoproteinemia	63	64,94

Main symptoms, clinical and biological sign in the studied lot

The evaluation of the patients' background and the risk of surgery involves, most of all, the evaluation of the cardiac, respiratory, hepatic functions and the nutritional status. All these elements determine the operatory risk. Most opstoperatory complications are represented especially by the cardio-respiratory and anastomotic ones. They are associated with changes in these functions. The evaluation of the preoperatory risk is based on the quantification of these parameters and the results of these risk indicators can be contradictory and do not always correlate with the immediate postoperatory evolution of the patient.

Detecting other associated conditions with an influence on the therapeutic strategy refers especially to detecting other concurrent neoplasms with the squamous esophageal carcinoma which is known to associate synchronous or metachronous malignant sites. These occur with an incidence of about 7% and even higher if in the initial diagnosis protocol PET-CT is used.

It is well known the association of squamous carcinoma with primitive pulmonary, renal and colonic malignant sites; in the studied lot 5 cases associated concurrent or metachronous malignancies with the esophageal squamous carcinoma: a synchonous urothelial renal carcinoma, one synchronous colonic adenocarcinoma, one metchronous colonic carcinoma, a synchronous prostate carcinoma and a synchronous cutaneous basocelullar carcinoma. If in the last 3 cases the therapeutic influence was not signifcant, for the first 2 cases the association of those two neosplasms determined changes in the surgical strategy and have raised the postoperatoy mortality risk. Abdominal ultrasound, simple thoracic radiography and most of all computed tomography of the thorax and abdomen and PET-CT play an important role in the preoperatory diagnosis of these neoplasic associations.

THE EVALUATION OF THE PRIMARY TUMOR AND THE GANGLIONARY LYMPHATIC DISEMINATION IN ESOPHAGEAL CANCER
- IMAGING AND HISTOLOGICAL COMPARED STUDY-

RESULTS

The results of the histopathological exam in evaluating the primary tumor and the regional lymph ganglions in the studied lot

Apart from the diagnostic, therapeutic and prognostic implications, the histopathological examination represents the starting point for the analysis of the preoperatory evaluation techniques in esophageal cancer. For this reason, the analysis of the main aspects of the imaging explorations (accuracy, sensitivity, specificity) used in the studied cases will begin with elements of morphopathology even though, in current practice, the morphopathological results are known only after imaging and therapeutic protocols have been performed.

The purpose of analyzing the pathological examination results is to point out some significant differences between various morphological and histological parameters that belong to the two main histopathological forms (squamous esophageal carcinoma and adenocarcinoma) which could influence the results of the imaging study of the primary esophageal tumor and the regional lymphatic draining territory.

In addition, the morhopathological examination brings clarifications regarding some fundamental aspects in esophageal cancer starting with the main morphological elements of the tumor and continuing with data regarding its' microscopic structure.

The role of echoendoscopy and esophagography in establishing a positive and stage diagnosis in esophageal cancer

Apart from establishing a positive diagnosis, the endoscopy allows to appreciate some morphological tumoral characteristics which influence the use of subsequent imaging methods: establishing the tumoral topography (cervical esophagus, superior,

medium or inferior thoracic esophagus), the morphology of the primary tumor, the degree of obstruction it generates and the length of the tumor.

The degree of the stenosis generated by the esophageal cancer appears to correlate with the long-term survival: patients with endoscopically diagnosed tight stenosis have a lower surviving rate compared to those without esophageal stenosis.

Also, the endoscopy allows the diagnosis of associated lesions which can be risk factors for the apparition of esophageal cancer (reflux esophagitis, post-caustic esophagitis, benign of malign synchronous lesions) and, on the other hand, can influence the therapeutic decision.

In addition, endoscopy can establish the macroscopic aspect of the primary tumors and, consequently, it can partially anticipate the possibility of tumoral resection.

In the case of stenotic associated lesions, esophagography with contrast agents is the method that brings information about the length of the tumor and about the possible underlying associated lesions.

Currently, this method keeps its' value especially in the cases of stenotic tumors where the endoscopic passage is not possible, allowing to visualize the length of the tumor and the underlying associated lesions. However, the value of esophagoscopy with contrast agents is tied mainly to monitoring the response to the neo-adjuvant therapy. Thus, in numerous situations, it remains the imaging investigation of first choice in the esophageal cancer.

The malignancy of the stenotic lesion was suggested by the radiologic exam in 95.8% of the cases.

Computed tomography in preoperatory evaluation of the primary esophageal tumor and of the regional lymphatic ganglions

Practically, computed tompgraphy is not able to diferentiate a T1 tumor from a T2 tumor, so is not able to contribute to the decision of endoscopic resection of an early-stage tumor with the exception when it reveals the existence of regional adenopathies that could be invaded and which will advise against endoscopic resection.

Stage T3 is characterized on the CT through the invasion in the periesophageal mediastinal fat tissue, even though many studies have drown the attention regarding the CT's inability to appreciate or exclude a minimal periesophageal invasion. The

accuracy of tomographic staging a T3 tumor is about 74%, varying between 59 and 82%.

In the current study the accuracy, sensitivity and specificity of the CT in diagnosing T3 stages were 32.55%, 40% and 15.38%.

In the studied lot, the CTs' accuracy of appreciating a T4 stage matches the data from literature, with a value of 74.41% but with a sensitivity of only 40%. Problems occur when we refer to cases where a resection was not performed and that benefited from a nonconclusive tomography before surgery. In these cases, the accuracy drops at about 61.22% with a sensitivity of only 9.09%. Also, the CTs' accuracy drops when it comes to differentiating between stages T4a and T4b, but because of the small numer of cases we could not make any appreciations regarding the differences reported on invaded organs.

In predicting the tumoral resecability, CT had an accuracy of 64.1%, a sensitivity of 67.3% and a specificity of 57.69%.

Another important role of CT is that it is able to detect regional ganglionary extension.

In the presented study, CT had an accuracy, sensitivity and specificity of 55.81, 47.61 and 63.63%. The results match the ones from literature which show a relatively low value in evaluating ganglionary status in esophageal cancer.

Echoendoscopy in preoperatory evaluation of the primary esophageal tumor and of the regional lymphatic ganglions

The endoscopic ultrasonography (echoendoscopy – EUS) represents the only imaging method that can differentiate the esophageal wall layers; because of this, currently, echoendoscopy is indispensable in establishing T category of the esophageal cancer and especially in differentiating T1 from T2-T4 stages, if the endoscopic treatment is desired.

In the analyzed lot, the global accuracy of echoendoscopy for establishing T stage was 65.51%, relatively similar to Räsänen et al.'s study, but with a rate of over-staging of 13.79% and a rate of under-staging of 20.68%; this is probably due to the fact that it can detect muscular invasion but with a low accuracy for tumors with extension in periesophageal fat (T3).

In T2 tumors, echoendoscopy had an accuracy of 79.3% with a sensitivity of 66.67% and a specificity of 82.6%, evidently being far superior to CT in the diagnosis of this category becasue tomography is unable to differentiate T2 from T3 tumors.

For T3 tumors, the accuracy of echoendoscopy dropped to 68.96%, with a sensitivity of 63.15% and a specificity of 80%, still being superior to CT (accuracy 32.55%, sensitivity 40% and specificity 15.38% for CT). The drop in the echoendoscopies' value for T3 stages is due to the fact that these tumors generate a greater degree of obstruction.

Finally, for T4 tumors, echoendoscopy is yet again influenced by the stenosis of the esophageal lumen which is usually determined by a large mass that does not allow the endoscope to pass; consequently, the methods' accuracy is diminished. To this fact it must also be added the risk of under-staging for tumors that exceed the endoscopes' penetration limits. Nevertheless, for a T4 stage in our study, we have recorded an accuracy for echoendoscopy of 86.2% with a sensitivity of 75% and a specificity of 88%, values that be statistically influenced by the small number of cases with this type of tumors that were examine using echoendoscopy.

The evaluation of lymphatic ganglion extension with the aid of echoendoscopy is based on a series of morphological criteria: size above 10 mm, roundly shaped, hypoechogenic and with nete margins.

Fine needle aspiration biopsy in a suspect adenopathy and the elastography represent two methods that were used in the studied lot which can contribute to a raise in value for accuracy, sensitivity and specificity of this method.

In the analyzed lot, the accuracy of echoendoscopy in identifying invaded lymph nodes was 68.96%, with a sensitivity of 78.57% and a specificity of 60%, relatively similar to those in Choi et al.'s published study: 66% accuracy, 42% sensitivity and 91% specificity.

Echoendoscopy remains an extremely useful investigation even in the case of stenotic tumors, just like Räsänen et al. noticed, becasue these are, in the majority of cases, T3 or T4 tumors with a very probable regional lymphatic invasion.

PET-CT in preoperatory evaluation of the primary esophageal tumor and of the lymphatic ganglions

PET-CT is a modern investigation based on the high metabolism of tumoral cell compared to normal ones; presently, PET-CT remains an expensive and largely

unavailable investigation. In addition, there are some limitations of this method in diagnosing the primary tumor and the regional lymph nodes in esophageal cancer. All these elements lead to the conclusion that PET-CT is an additional staging method, its' main purpose being not to diagnose the primary tumor but to identify ganglionary invasion and distant metastasis.

In the studied lot, PET-CT was used only to identify a series of metastasis that were suspected on CT in a limited number of cases in which we were not able to asses the value of PET-CT in the diagnosis of T and N categories of the TNM classification.

All things considered, even though the main indication was to confirm or deny the presence of distant metastasis, PET was able to detect some metastasis in cervical nodes and also to detect the primary tumor. Because of the small number of cases, these elements could not pe analyzed in our lot.

THE ROLE OF NON-INVASIE IMAGING TECHNIQUES IN DIAGNOSING DISTANT METASTASIS AND SYNCHRONOUS MALIGNAT LESIONS TO PRIMARY TUMOR IN ESOPHAGEAL CANCER. NON-INVASIVE IMAGING STAGING INVESTIGATIONS SEQUENCE

The clinical diagnosis of the metastasis is inefficient, and it is possible only for certain accessible sites but usually for patients for which a therapeutical course of action is no longer an option. As a result, an important role is held by the non-invasive imaging investigations from which CT and PET-CT are currently most commonly used.

The incidence of distant metastasis in patient from the studied lot

At the moment of clinical diagnosis and/or after a toracotomy and/or laparotomy were performed, 19 patients (19,58%) presented distant metastasis.

CT of the thorax and abdomen has diagnosed 16 cases in stage IV (presence of metastasis); 7 cases were false positives.

In 9 cases the CT failed to identify distant metastasis.

PET-CT was available only for 4 cases. In one case the PET-CT excluded a pulmonary metastasis that was suspected on CT and in other two cases it identified metastasis in the left adrenal gland, supraclavicular nodes, liver and abdominal wall which were not identified on the CT.

The incidence of synchronous or metachronous malignant lesions with esophageal cancer in patient from the studied lot

There were 5 cases (5,15% incidence) of malignant lesions associated with the squamous esophageal carcinoma in the patients from the studied lot:
- One case of synchronous cutaneous basocellular carcinoma;
- One case in which a prostate carcinoma was present in the patient's history;
- 2 cases in which the squamous esophageal carcinoma was associated with a colonic adenocarinoma: one synchronous and one in which the colonic neoplasia was previously operated on;

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-   One case of synchronous urothelial renal carcinoma with the esophageal squamous cancer.

The imaging studied played an essential role in the diagnosis of the synchronous colonic adenocarcinoma and the urothelial renal carcinoma.

The urothelial renal carcinoma was asymptomatic, being accidentally discovered in the course of an abdominal ultrasound examination that was followed by a CT.

CT failed in identifying the asymptomatic colonic adenocarcinoma.

The imaging investigations had a limited role in the case of the other malignant lesions, but CT was used to detect possible metastasis of the squamous esophageal carcinoma and of the prostatic carcinoma.

CONCLUSIONS

1. The stage diagnosis of esophageal cancer represents a vital component in the diagnostic procedure with direct implications on the teraputical strategy.

2. The upper digestive endoscopy represents the main imaging method of diagnosis allowing the retrival of a biopsy and determining a positive certain diagnosis.

3. The barium esophagography (or using hydrosoluble contrast agents in the case of a suspected tumoral invasion of the airways) keeps its' value in appreciating the lenght of the primary tumor, localising the cancer on the esophageal segments and in appreciating the size of the tumor under neo-adjuvant treatament (radio/chemotherapy).

4. CT of the thorax and abdomen represents the most frquently used imaging technique for determining the evolutive stage of the primary tumor and of the lymph nodes invasion and for establishing the resecability of the tumor. In the studied lot CT had an accuracy of 64.1% in determining the prediction of resecability with a sensitivity of 67.3% and a specificity of 57.69%.

5. Esophageal echoendoscopy remains the main imaging method in establishing the T tumoral stage but with a global accuracy of 65.51% and a rate of under-staging of 20.68% and over-staging of 13.79%.

6. PET-CT represents a seldomly available method in the staging of esophageal cancer but data from literature indicate values similar with CT and esophageal echoendoscopy regarding accuracy, sensibility and specificity for staging categories T and N.

7. CT represents the most frequently used imaging investigation in the diagnosis of distant metastasis; PET-CT, even though more efficient, is rarely available.

8. The detection of synchronous of primary malignancies can only be accomplished imagisticaly, most of them being asymptomatic at the moment of diagnosis.

Keywords: esophageal carcinoma, computed tomgraphy, echoendoscopy, PET-CT