University of Medicine and Pharmacy Craiova

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DOCTORAL THESIS

ABSTRACT

DIAGNOSTIC AND THERAPEUTIC ALGORITHM IN ESOPHAGEAL NEOPLASM

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KEY WORDS: *esophageal cancer, risk factors,diagnosis,staging ,treatment, diagnostic and therapeutic algorithm*

INTRODUCTION

Esophageal cancer, the 8th most common cancer in the world (about 1% of all cancers and 6% of gastrointestinal cancers) is one of the most severe forms of digestive cancer with a mortality level still very high (6th death cause by cancer), because the diagnosis is made in advanced stages in 50% of cases, despite dysphagia, a sign revealing the disease that appears relatively early and despite the esophagus being one of the more accessible segments of the digestive tract to imaging and endoscopic investigations.

Diagnosis is complex, clinical, biological and morphological. The esophageal syndrome, dominated by dysphagia, is the main element of the clinical diagnosis, while biological investigations show no specificity for diagnosis, being only used for monitoring. Endoscopic and imaging tests are the primary means of preoperative diagnosis, useful not only for the positive diagnosis but also for pre-therapeutic staging; the upper digestive endoscopy and echo endoscopy are the primary means of preoperative morphological evaluation, while the endoscopic biopsy confirms the diagnosis by histopathological examinations, elements that are extremely important for establishing a therapeutic conduct.

The treatment of esophageal cancer is complex and multimodal, the main criteria in choosing the therapeutic methods and sequencing them in the therapeutic algorithm being the evolutionary stage of disease, age, general condition and biological parameters of the patient. Radical surgery (esophagectomy with lymphadenectomy) is the "gold standard" treatment for cancers at stage I and II and for resectable tumors in locally advanced stages; tumor topography, the degree of parietal invasion and regional extension are the criteria for choosing the type of approach, the type and extent of resection and the way to restore continuity of the digestive tract. Palliative procedures (surgical or endoscopic) together with radiotherapy and adjuvant chemotherapy are the standard treatment for non-resectable and locally advanced cancers and for systemic disease.

The steadily increasing incidence of esophageal cancer (8th in the world) both worldwide and in our country, and the special problems of diagnosis, staging and treatment the surgeon faces, fully justify the choice of this research theme for this thesis; the experience gained in Surgical I Clinic Craiova offered me the possibility to conduct a retrospective study, whose objectives were the evaluation of the incidence and population groups at risk, the study of risk factors and current ethiopatogenic elements, setting a clinical and paraclinical diagnostic algorithm and pre-therapeutic

staging criteria, establishing therapeutic strategies depending on the stage of disease and comparing the results with the literature.

A.OVERVIEW

CHAPTER I

ANATOMY AND PHYSIOLOGY

The esophagus is a muscular and membranous pipeline, which is designed to transport the food from the oropharynx to the stomach; it is the only viscera that spreads along three body segments. In adults the esophagus is 25 cm long and 15 to 25 mm in diameter on average, with variations depending on: constitutional type, gender, age, anatomical factors. The upper limit that separates it from the hypopharynx, corresponds to a horizontal plane passing through the cricoid cartilage in the front and the C5 vertebra in the back, and lower limit, located at the cardia, is projected on the X or XI thoracic vertebra. [1]

Depending on the region it crosses and the relations with the surrounding organs, there are four distinct parts of the esophagus described: [1, 2]

- The cervical part (6-8 cm) ends at the horizontal plane passing through C6 and T2 vertebrae;
- The chest part spreads between the horizontal planes passing through T2 and T10 vertebrae. The aortic cross and the azygos vein split the thoracic esophagus into two segments: a supraazygo-aortic segment and an infraazygo-aortic one;
- The diaphragmatic part (1 cm) is the esophageal part passing through the diaphragm muscle;
- The abdominal part (2-3 cm) is the segment of the esophagus that resides in the abdominal cavity and opens in the stomach.

CHAPTER II

ESOPHAGEAL CANCER

Esophageal cancer is the 8th most common cancer in the world, the 6th leading cause of death by cancer and one of the four cancers with the worst prognosis, next to liver, pancreatic and lung cancer. (5)

Although it is not the most frequent neoplastic pathology, representing about 1% of all cancers and 6% of all gastrointestinal cancers, it is a cancer with a high mortality rate, very similar to pancreatic cancer and 4 times higher than rectal cancer.

A variety of factors were responsible for the disease. In the United States, most cases of esophageal cancer are believed to be due to excessive alcohol consumption and / or a long history of smoking.

The relative risk increases with the amount of tobacco smoked and the quantity of alcohol consumed. Whiskey consumption seems to be associated with a higher incidence than the consumption of wine or beer. The occurrence of esophageal cancer was also associated with ingestion of other carcinogens, such as nitrite, smoked opiates and fungal toxins in pickled vegetables, and with lesions of the esophageal mucosa caused by some physical injuries such as exposure to very hot tea over a long period of time, ingestion of lye, radiation-induced injuries and chronic achalasia.

B.PERSONAL CONTRIBUTION

CHAPTER III

STUDY MOTIVATION. OBJECTIVES. MATERIAL AND METHODS

The steadily increasing incidence of esophageal cancer (8th in the world) both worldwide and in our country and the special problems of diagnosis, staging and treatment that the surgeon faces, fully justify the choice of this research theme for this thesis.

Based on the current status of the problem, that has been synthesized in the chapters of the general part, we conducted a clinical prospective and retrospective trial, using the experience of Surgical Clinic I Craiova, reflected in a number of 49 cases of esophageal cancer, admitted and treated in the clinic during the last 10 years (2005-2014).

We included in the study only true esophageal cancers and excluded eso-gastric junction cancers, given that they are now considered a distinct clinical and anatomical entity, well defined through etiology, clinical signs and standardized therapeutic algorithm.

CHAPTER IV

RESULTS

In the study we conducted esophageal cancer was ranked the fourth after colon cancer, rectal cancer and gastric cancer, accounting for 4.03% of all tumors of the digestive tract; it must be noted that there was an almost perfect tie between the incidence of esophageal cancer and that of esogastric junction cancer, recognized as a separate, well defined anatomic and clinical entity, considering that, according to the Siewert classification, esogastric junction cancer includes adenocarcinomas of the distal esophagus localized at 1-5 cm above the esogastric joint, that appear on specialized areas of intestinal metaplasia. There was a total of 4.9 new cases / year on average, with limits from 2 to 14 new cases / year, also noting the obvious tendency of growth during the last 5 years, with a peak in 2014 (12 new cases / year).

In our personal study, the incidence of esophageal cancer by age and sex generally respected the data reported in the literature.

Mean age of patients was 63 years, with margins of 44 and 83 years and the peak incidence in the sixth decade of life.

For the diagnosis we used a diagnostic algorithm that included clinical examination, biological, imaging and endoscopic investigations, an accurate diagnosis being established based on histopathological findings on biopsy fragments, collected during endoscopy or based on a complete morphological examination of excised parts.

All patients who underwent palliative procedures had a favorable immediate postoperative evolution, with no complications and/or deaths; upon discharge they were directed to oncology clinics for monitoring and specific treatment (chemotherapy and adjuvant radiotherapy). Unfortunately, we do not have data on their evolution and survival rate.

The postoperative evolution of patients that underwent radical operations was positive in 10 cases. There were eight immediate postoperative complications (2 general complications and 6 local complications) and 4 deaths.

Among the general complications there have been bilateral pleural effusions with acute respiratory failure in one case, remitted under conservative treatment, and pulmonary embolism, resulting in death in one other case.

CHAPTER V

DISCUSSIONS

Esophageal cancer is one of the most severe cancers of the digestive tract; being the 8th most common cancer in the world and the 6th leading cause of cancer death, along with liver cancer, pancreatic and lung cancer, it is the cancer with one of the worst prognosis.

The incidence of esophageal cancer in the literature, evaluated at 1% of all cancers and 6% of cancers of the digestive tract, increases along with age. In regions with a high incidence, the frequency of esophageal cancer increases progressively after the age of 25, with a peak in the 60-70 years age group, a fact as confirmed also by our study, that has recorded 59.1% of cases in patients over 60 years of age.

There is a clear predominance of esophageal cancer in men, that has been also confirmed by our study (sex ratio = 16/1), which can be partly explained by the higher number of drinkers and smokers among men. Recent studies, such as Yang et al. (2011) showed that risk factors alone cannot fully explain the higher incidence of esophageal cancer in men and they have considered the possible protective role of estrogen.

Although the area of origin of patients is not mentioned in the literature as a risk factor, we recorded a higher incidence of esophageal cancer in patients from rural areas compared to those in urban areas (1.57/1 in our study, compared to 1.3/1 in the literature). This finding is similar to the data in Nagel’s study in 2007, conducted on 52.000 people from 10 european countries, according to which incidence of esophageal cancer is higher poor regions and in populations with a lower educational level. [75]

The etiopathogeny of esophageal cancer is still unclear, but it involves several risk factors.

Chronic alcohol consumption (present in 69% of our cases) is considered the main risk factor, and the association of smoking (43%) increases the development of neoplasms. The relative risk in white men who consume too much alcohol and smoke is 35.4 times higher than in men from the same area that do not consume alcohol and do not smoke. In men of color the risk is about 149.5 times higher [25]. Alcohol alters the cellular DNA by decreasing the intracellular metabolic activity and thus altering the detoxification function while, at the same time, accelerating oxidation [26]. It is a solvent-specific lipid-soluble compound and it allows carcinogens in tobacco to cross the esophageal epithelium more easily [27]. The pathogenesis seems to be related to the inflammation of squamous epithelium leading to malignant dysplasia and in situ carcinoma [28].

Chronic inflammation is the substrate of intestinal metaplasia development, regardless of etiology. Chronic gastro esophageal reflux disease (16.3% in our study) causes inflammation and ulceration of the squamous epithelium, which, if it persists, causes intestinal metaplasia [29,30]. At first the squamous epithelium changes into a cardial type columnar epithelium comprised of mucinous columnar epithelium and mucous or mixed mucous-oxyntic glands. Persistent aggression and chronic inflammation transforms the mucinous columnar epithelium in the intestinal phenotype as a result of secondary metaplastic reaction [31, 31]. Most authors agree that the pathogenic sequence is as follows: reflux disease - intestinal metaplasia - dysplasia (incomplete, complete) - carcinoma in situ, followed by invasive carcinoma. Dysplasia is regarded as a precursor to invasive cancer, while severe dysplasia is commonly associated with adenocarcinoma [33].

In Barrett's esophagus (10% in our study), metaplasia is characterized by the replacement of normal squamous esophageal epithelium with a specialized columnar epithelium.

Initially it occurs at the transition zone and it extends proximally. Reflux is different in patients with Barrett's esophagus than in those with reflux esophagitis; it is both acid and bilious and it has diffuse quality (duodenal, gastric and esophageal) [13, 14]. The risk of Barrett's esophagus increases three times in those with 1-5 years old symptoms and 6.4 times in those with symptoms older than 10 years [15]. Progression towards cancer can be explained by the persistence acid reflux or bile in some patients with

Barrett's esophagus. Bile reflux continues in 20-34% of medically treated patients, while 10-50% of patients with fundoplication suffer a relapse several years after surgery.

In our study out of 8 patients histologically diagnosed with adenocarcinoma, 5 patients were known with Barrett's esophagus and in 3 other patients gastro esophageal reflux injuries were identified.

Esophageal cancer diagnosis is determined by an algorithm that includes clinical examination, biological, imaging and endoscopic investigations, an accurate diagnosis being established based on histopathological findings on biopsy fragments, collected during endoscopy or based on a complete morphological examination of excised parts.

The esophageal syndrome is the main element of clinical diagnosis; dysphagia is the most important symptom in the early detection of esophageal cancer, being easily noticed by patients. Unfortunately, dysphagia does not worry the patients (especially those in rural areas with a low educational level) enough to make them see a doctor, leading in many cases to a late diagnosis, in advanced stages (III and IV), despite an obvious symptomatology and accessible imaging and endoscopic investigations. Retrosternal pain of variable intensity is found in about 50% of cases, while other signs of the esophageal syndrome (sialorrhea and regurgitation) are rarely present, probably because the fast evolution to stenosis of esophageal cancer does not allow an important dilation of the esophagus above the stenosis, underpinning these signs. Significant weight loss, sometimes up to cachexia, signs of dehydration and neoplastic impregnation syndrome, the consequence of an intake deficit and the consumptive nature of the disease, usually accompany dysphagia, but are less useful for early diagnosis, being the prerogative of advanced phases.

There isn’t a specific biological syndrome, biological investigations being just usual investigations, not specific for the etiologic diagnosis, but useful for patient monitoring and pre, intra and postoperative rebalancing. Tumor markers (CA 19-9 and HER2), also not specific, are useful in assessing prognosis and in monitoring therapeutic response.

The diagnosis is based on imaging and endoscopic investigations, but their value is uneven.

The barium swallow, the investigation of choice until the introduction of digestive endoscopy, highlights the tumor, evaluates the degree of the obstruction and the state of the esophagus above the tumor. The limits of this method are related to the difficulty in identifying superficial cancers, a disadvantage largely eliminated by the double

contrast exploration, and to the impossibility of determining the benign or malignant nature of the tumor or the degree of local invasion; It is also contraindicated when there is a clinical suspicion of a eso-bronchial fistula.

The simple chest X-ray (performed in all patients) is a routine imagistic investigation that can identify the presence of lung metastases and tumoral adenopathy in pulmonary hilum.

The CT scan is the most used imagistic investigation for pre-therapeutic staging (as it allows the identification of local invasion and the presence of distant metastases) and for assessing the effectiveness of neoadjuvant therapy and detecting relapses.

The upper digestive endoscopy with biopsy and the upper echo endoscopy are the main morphological preoperative evaluation methods, enabling tumor topography, clinical type, obstruction degree and loco-regional invasion, while also taking a tissue fragment for histopathological examination. Information provided by echoendoscopy are more accurate in assessing local and regional staging than those offered by a CT scan, but the latter is superior in assessing systemic invasion.

The topographic distribution of tumors, revealed by imagistic and endoscopic investigations (lower third 51%, medium third 32% and upper third 16%) corresponds to the literature data, although for some authors (Internnullo 2008) [76] the predominance of tumors located in the lower third is much stronger (81%). The main macroscopic type of tumor, identified by endoscopic and imagistic investigations, was the protrusive one, followed by the stenosing type and the ulcerative type; all tumor types lead to a complete or partial obstruction of the esophageal lumen, clinically expressed by the dysphagia severity.

The final diagnosis is based on the findings of the histopathological examination of samples collected during biopsy and excised parts, the main histological type being the squamous one for cancers located in the upper and mediu third and adenocarcinoma for cancers located in the lower third, in the vicinity of the cardia.

Pre-therapeutic staging using the TNM system and the data provided by of morphological imaging and endoscopic investigations revealed that all the cases studied belonged to advanced stages: 31 (63.2%) stage III (IIIA 7 cases, IIIB 1 case and IIIC 23 cases) and 14 (28.5%) stage IV, the remaining 4 cases being unknown.

Treatment of esophageal cancer is a complex medical and surgical one, triple therapy (neoadjuvant chemotherapy and radiotherapy followed by surgery) being the most extensively studied algorithm in the last decade. The effectiveness of this

approach has been the subject of four trials [64, 65, 66, 67], the first and last of whom recorded a higher survival rate for triple therapy, while in the other two studies reported similar survival rates.

Tumor staging is the most important criteria for choosing the therapeutic algorithm. Unfortunately, both in our study and in many other studies in the literature, patients with esophageal cancer are diagnosed in advanced stages (63.2% stage III and 28.5% stage IV) despite the fact that the esophagus is one of the segments of the digestive tract most available for imaging and endoscopic investigations, which usually determine the diagnosis. The explanation lies, at least partly, in the peculiarities of the esophageal syndrome in cancer, namely that, unfortunately, dysphagia, which occurs quite early, does not worry most of the patients (especially those in rural areas, with a low educational level) enough to make them see a doctor, the retrosternal pain is usually missing at the onset, and other signs of the esophageal syndrome (regurgitation and sialorrhea) are rarely present, probably because the quick evolution towards stenosis of esophageal cancer does not allow a significant dilation of the esophagus above the stenosis, underpinning these signs.

Currently the UICC classification (Union for International Cancer Control), divides patients in two distinct therapeutic categories, each with different treatment indications:

- patients with local and regional invasion (T and N) in various evolving stages
- patients with systemic invasion (M1).

For patients with neoplastic systemic invasion there is no cure, and these, along with patients with locally advanced cancers where radical surgery is contraindicated, account for about 50% of cases and undergo exclusively surgical or endoscopic palliative treatment (19 cases în our survey). In these patients adjuvant chemotherapy and radiation therapy is nowadays the standard in nonsurgical treatment of locally advanced and systemic disease.

In patients with local and regional tumor invasion surgery remains the gold standard and, with the prognosis being deeply influenced by lymphatic invasion, there is a need for lymphadenectomy both for lowering the risk of relapse and for establishing the actual staging (pTNM). Tumor topography, circumferential invasion and local and regional extension are the criteria used in choosing the surgical approach, the extent of the resection and the way to restore transit. Esophagectomy with double approach -

thoracic and abdominal (Ivor-Lewis method) was the choice procedure used by us în 8 cases with tumors located in the medium third or the upper part of the lower third, the major disadvantage being a greater severity of a possible postoperative intrathoracic fistula at the anastomotic level. Esophagectomy with triple approach – cervical, thoracic and abdominal (Mac Keown method - right posterior and lateral thoracotomy, laparotomy and left lateral and cervical incision) is the choice procedure for cancers of the upper third (4 cases), while an exclusively abdominal approach (2 cases) is the choice option for abdominal esophagus cancers, extended more towards the head than the cardia. In order to restore the transit we used almost exclusively the stomach (13 cases out of 14 operated), due to its known advantages:

 sufficient length to reach the cervical region in most patients and the possibility to be used for an anastomosis with the pharynx [Akiyama et al. 1978];

 it requires a single anastomosis for the continuation of the digestive tract;

 the technical procedure is relatively;

 the adjacent caul is an important resource for anastomosis;

 there is no major septic risk due to the lack of a diverse bacterial flora particularly dangerous, as in the bowel.

Unfortunately, radical surgery with oncologic curative intent is encumbered by an important postoperative morbidity, the anastomotic fistula (6 cases) being the main local complication, and by a still high postoperative mortality (4 cases of 14 operated) and the rate of local relapse was 14.28%.

Several algorithms have been proposed for the multimodal therapy of esophageal cancer: neoadjuvant chemotherapy + surgery, neoadjuvant radiotherapy + surgery and neoadjuvant chemotherapy + radiotherapy + surgery.

Therapeutic options, both surgery and adjuvant therapy are the same for both main histopathological types of esophageal cancer, squamous cell carcinoma and adenocarcinoma.

CHAPTER VI

CONCLUSIONS

1 Esophageal cancer is one of the most severe cancers of the digestive tract; it is the 8th most common cancer in the world and the 6th leading cause of death by cancer.

2 The incidence of esophageal cancer, estimated in the literature to 1% of all cancers and 6% of cancers of the digestive tract (4.01% in our study) increases along with age, a fact confirmed by our study (59.1% of cases seen in patients over 60 years).

3 There is a clear predominance of esophageal cancer in men (sex ratio = 16/1 in our study), which is partly explained by the higher number of drinkers and smokers among men, the protective role of estrogen being also involved.

4 There is a higher incidence of esophageal cancer in patients from rural areas compared to those in urban areas (1.57/1 in our study, compared to 1.3/1 in the literature).

5 The esophageal syndrome is the main element of clinical diagnosis; dysphagia is the most important symptom in the early detection of esophageal cancer (87.7% in our study).

6 The diagnosis is based on imaging and endoscopic investigations, whose value is, however, uneven.

7 The barium swallow (25 cases = 51.02%) identified the esophageal stenosis in 14 (56.0%) cases, showed an incomplete picture in 9 (36.0%) cases and the existence eso-bronchial fistulas in 2 (8%) cases.

8 The chest X-ray - a routine imaging investigation carried out in all cases, showed the presence of lung metastases (4 cases = 8.16%) and tumor lymphadenopathy in the hilum (2 cases = 4.08%).

9 The CT scan (25 cases = 51%) - the most widely used imaging investigation for pre-therapeutic staging, for assessing the effectiveness of neoadjuvant therapy and for detecting relapses - allowed the identification of local and regional invasion (circumferential invasion of the esophagus in 6 cases, aortic and left pleural invasion in 1 case) and the presence of distant metastases in 18 cases.

10 The upper digestive endoscopy with biopsy (42 cases - 85.7%) and the upper echo endoscopy (12 cases - 25%) - the main methods for preoperative morphological evaluation - enable tumor topography, clinical type, obstruction degree and loco-regional invasion, while also taking a tissue fragment for histopathological examination.

11 The topographic distribution of tumors, revealed by imagistic and endoscopic investigations (lower third 51%, medium third 32% and upper third 16%) corresponds to the literature data, although for some authors the predominance of tumors located in the lower third is much stronger (81%).

12 The protrusive type was the main macroscopic type of tumor, identified by endoscopic and imagistic investigations, followed by the stenosing type (13 cases) and the ulcerative type (9 cases), leading to a partial (17 cases) or complete (24 cases) obstruction of the esophageal lumen.

13 Local and regional invasion, identified during upper echo endoscopy, affected the cardia in 3 cases, the aorta and the left pleura in 1 case each.

14 The final diagnosis is based on the findings of the histopathological examination of samples collected during biopsy (35 cases - 71.43%) and excised parts (14 cases - 28.57%), the main histological type being the squamous one for cancers located in the upper and medium third and adenocarcinoma for cancers located in the lower third, in the vicinity of the cardia.

15 Pre-therapeutic staging using the data provided by of morphological imaging and endoscopic investigations revealed that all the cases studied belonged to advanced stages: 31 (63.2%) stage III (IIIA 7 cases, IIIB 1 case and IIIC 23 cases) and 14 (28.5%) stage IV, the remaining 4 cases being unknown.

16 Treatment of esophageal cancer is a complex multimodal treatment, the choice of therapeutic methods and their sequencing in the therapeutic algorithm is based on the stage of the disease, age, general condition and biological balance of the patient.

17 Radical surgery (esophagectomy with lymphadenectomy) is the "gold standard" treatment for cancers at stage I and II and for resectable tumors in locally advanced stages; tumor topography, the degree of parietal invasion and regional extension are the criteria for choosing the type of approach, the type and extent of resection and the way to restore continuity of the digestive tract.

18 Esophagectomy with thoracic-abdominal double approach (Ivor Lewis method) was choice surgery (8 tumors in the medium third or the cranial portion of the lower

third); esophagectomy with Mac Keown triple approach (cervical, thoracic and abdominal) is the choice procedure for cancers of the upper third (4 cases), while an exclusively abdominal approach (2 cases) is the choice option for abdominal esophagus cancers.

19 A thoracic esogastric anastomosis is the main way to restore transit (13 of 14 cases that underwent radical surgery).

20 Radical surgery with oncological curative intent is encumbered by an important postoperative morbidity, the anastomotic fistula (6 cases) being the main local complication, and by a still high postoperative mortality (4 cases of 14 operated) and the rate of local relapse was 14.28%.

21 Palliative surgical or endoscopic treatment (19 cases) is reserved for patients with systemic neoplastic invasion and/or locally advanced cancers, which are contraindicated for radical surgery.

22 Adjuvant chemo and radiation therapy are nowadays the standard nonsurgical treatment of locally advanced and systemic disease.

CHAPTER VII

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