Eso-gastric junction adenocarcinomas. Etiology, pathogenesis and therapeutic options

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Although it is known under various names (eso-cardial cancer, eso-gastric cancer or eso-cardio-tuberorosity cancer), it wasn’t until the International Congress in Munich in April 1997 that eso-gastric junction adenocarcinoma became an entity on its own, as suggested by Siewert, Stein and Feith. It entails all tumors within 5 cm both proximally and distally from the anatomical region known as cardia, that show wall infiltration and lymphatic dissemination towards the mediastinum as well as the abdomen.

Siewert differentiated 3 anatomical entities of the eso-gastric tumors:

- adenocarcinomas affecting the distal esophagus, situated at 1-5 cm above the eso-gastric junction (EGA type I),
- the real adenocarcinomas of the cardia, situated within 1 cm proximally and 2 cm distally of the eso-gastric junction (EGA type II) and
- subcardial gastric tumors, situated at 2-5 cm below the cardia and which infiltrate the eso-gastric junction, the distal esophagus or both (EGA type III).

However, in 2000, the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) adjusted the Siewert classification by changing some of the criteria. Thus, eso-gastric tumors extending beyond the eso-gastric junction are considered to be eso-gastric adenocarcinomas, regardless of the greater tumor volume, the tumors situated entirely above the eso-gastric junction are regarded as esophageal cancers and those located entirely under the eso-gastric junction are considered to be proximal or gastric body cancers, according to their size.

My tackling this particular subject in cancer surgery is related to a number of factors, including the constant increase in incidences of esophageal cancer (the seventh most frequent cancer worldwide) and eso-gastric cancer, the diagnostic, staging and treatment challenges, as well as the high mortality rates, eso-gastric cancers having a 5-year survival rate of 16-32%.

To support these reasons I conducted a mixed (prospective and retrospective), multicenter clinical study, over a period of 5 years (2005-2010), enlisting 60 cases of eso-gastric cancer patients from Surgery Departments in two major hospitals: the County Clinical Hospital in Craiova and the Clinical Emergency Hospital in Bucharest.
The inclusion criteria concur with Siewert and WHO’s definition of eso-gastric cancers. The objectives set for this study are:

- to evaluate the incidence and population groups at risk for developing this disease,
- to identify the risk factors as well as etiological and pathophysiological aspects involved in triggering the disease,
- to establish a clinical and paraclinical diagnostic protocol, as well as pretreatment staging criteria,
- to establish a tumor staging-related therapeutic approach and to compare my results against the ones already published.

General features

**Definition:** although known under various names (eso-cardial cancer, eso-gastric cancer or eso-cardio-tuberorosity cancer), the eso-gastric adenocarcinomas have become a clinical entity with alarmingly high incidence and mortality rates in our country as well as worldwide. This category includes three anatomical entities: distal esophagus tumors, true cardial tumors and proximal stomach tumors, all having in common wall infiltration and lymphatic dissemination towards the mediastinum as well as the abdomen\(^1\)\(^,\)\(^2\).

In order to perform a radical surgical intervention, a clear definition and classification of eso-gastric junction tumors were needed. This happened in April 1997, at the International Congress in Munich, where it was agreed to accept the proposition forwarded by Siewrt, Stein and Feith to define all tumors, situated within 5 cm proximal and distal to the cardia as eso-gastric tumors.

**Incidence:** it varies greatly in terms of region, ethnicity and histological types of tumors, which reflects the combined effects of environmental factors and genetic background upon carcinogenesis\(^3\).

In most countries, including Romania, the incidence is rather small, of 5/100000 cases, but it reaches endemic proportions in some Asian populations (China, Japan), in Iran, on Caspian Sea’s shoreline, or in Transkei province, in Africa. In most western
countries (USA, Canada, Western Europe) the prevalence of adenocarcinomas is high, whilst that of squamous carcinomas is decreasing. It has been noticed that environmental factors influencing peoples’ life style has led to a change in the squamous carcinoma and adenocarcinoma proportion, with a significant incidence increase of the adenocarcinomas affecting the distal esophagus and the cardia, which are also known as eso-gastric junction cancers.

**Etiology:** environmental factors, such as life style, geographic and regional variations, act as triggers of carcinogenesis. The genetic susceptibility and the familial predisposition are considered to play a smaller part. \(^{[5]}\)

Other risk factors have been identified, such as alcohol, tobacco, a diet lacking vitamins A and C, riboflavin, oligo elements, constant exposure to common food carcinogenic substances (nitrosamines and their precursors). \(^{[6]}\)

The major triggers for eso-gastric junction adenocarcinomas are reflux disease, Barett esophagus and obesity. \(^{[7]}\)

**Pathogenesis:** the chronic inflammation, regardless of its etiology induces intestinal metaplasia. Gastric reflux disease triggers an inflammation and ulceration of the squamous epithelium, and if persistent, intestinal metaplasia occurs. \(^{[8]}\)

The epithelial dysplasia is regarded as a precursor of an invasive cancer, while high-graded dysplasia is frequently associated with adenocarcinoma. \(^{[9]}\)

**Diagnosis:** the clinical manifestations of eso-gastric cancer are the milestone of the diagnostic protocol, which will later dictate further investigations.

Over 50% of superficial cancers are discovered accidentally, while an upper endoscopy is conducted. However, over 90% of patients complain of swallowing problems: heartburn, foreign body-like sensation or even transient food clogging of the esophagus.

Dysphagia exists in up to 80-90% of patients with locally advanced cancer, thus reaching an incurable stage.

**Imaging**
The chest x-ray, with its front and side incidences, is a routine examination, which may yield signs such as: pulmonary hilum invasion, a deviated/ compressed trachea, infectious broncho-pulmonary complications, pulmonary and or bone secondaries, malignant pleural/ pericardial effusions (diagnosed via fine-needle aspiration of pleural/pericardial fluid, with biochemical and cytological readings), as well as other pre-existent, associated, cardio-pulmonary conditions.

A barium swallow is significant in certain stages of the disease. When a superficial cancer is suspected, although unable to confirm the malignant nature of the tumor, a double-contrast swallow may be helpful in detecting most superficial lesions. Sometimes, the mere presence of a large tumor is the hallmark for the diagnosis.

The CT scan is probably the most useful imagistic investigation for diagnosing eso-gastric cancers, for pretreatment staging, as well as for evaluating the effects of adjuvant therapy and identifying any potential metastases.

The MRI scan has its limitations, similar accuracy as CT scans, but at higher costs. It doesn’t really provide better information regarding aortic invasion, mediastinum lymph node invasion or surgical staging.

Upper GI endoscopy with lesion biopsy is the standard diagnostic tool for eso-gastric cancers. The macroscopic aspect varies in accordance with the lesion’s developmental stage. Conventional upper GI endoscopy is limited by the interpretation difficulties of minimal mucosal changes; unfortunately, these limitations occur with high-resolution upper GI endoscopy as well. The diagnostic effectiveness of upper endoscopy has increased after implementing tissue staining (such as toluidine blue 1-2%, Lugol's solution 1-2%). Although tissue staining is not really specific for cancers, chromoendoscopy allows biopsy sampling from the distinctly colored pathological mucosa. [10]

Abdominal ultrasound is limited to identifying liver (including tumors with the same tomographic isodensity as the rest of the liver) and abdominal lymph node metastases. Mediastinum ultrasound is useful in identifying some cervical and upper mediastinum metastases.
**Bronchoscopy** is indicated in central and superior thoracic tumors in order to exclude tracheal or left bronchial invasion or to confirm the presence of an eso-tracheal-bronhial fistula.

**Bone scintigraphy** is not a screening tool for patients with occult metastases and is indicated only if bone pain is present or elevated levels of alkaline phosphatase are identified.

**Positron emission tomography (PET scan)** quantifies the regional tissue radioactivity, reflecting the metabolic processes, the blood flow and the state of tissue receptors. However, it is rather difficult to interpret these results because of limited spatial resolution.

**The optical coherence tomography (OCT scan)** typically employs near-infrared light and has a resolution of 10 microns, producing real-time slices of the gastro-intestinal tract, which corroborated with particular light-dispersion properties shown by Barrett esophagus mucosa create a suitable diagnostic tool in identifying intestinal metaplasia and high-grade dysplasia in patients with Barrett esophagus.

**Biochemical markers.** Malignant tumor proliferation is associated with a high cellular glucose uptake rate (particularly glycolysis), which represents a biochemical marker of cellular transformation.¹¹

F-FDG-6-phosphate is a radiopharmaceutical used in PET scans for identifying metastatic neoplastic lesions. FDG-PET scan reflects the metabolic activity at cellular level, allowing staging diagnosis and adequate therapy, as well as assessing therapeutic efficiency and early metastatic identification. It locates neoplastic deposits in normal-sized lymph nodes.¹²

**The minimal invasive surgery** (thoracoscopy or laparoscopy) is indicated in patients with advanced cancer, which are potential candidates for open esophagectomy for staging and biopsy purposes.¹³

Esophageal cancer staging is important for setting the therapeutic protocol and its outcome. The most useful classification is the TNM classification, which includes location, tumor size and its report with the esophageal wall, lymph node invasion and metastases. According to the TNM classification, eso-gastric junction adenocarcinomas include the following: the adenocarcinoma affecting a Barrett esophagus is considered
to be esophageal cancer and those involving the cardia and the subcardial region are considered to be gastric cancers. However, these tumors are regarded as esogastric junction cancers because of their clinical and histological characteristics, not to mention their bleak prognosis when diagnosed in advanced stages.

**Treatment:** esophageal cancer is one of the most aggressive solid tumors, with a global 5 year-survival rate of 10%. The 5 year survival rate for one of the treated, superficial cancers reaches 92-93%, but the 25 year-survival rate is about 45%.

Surgery and medication therapy need to be considered for pre-cancerous states as well (Barrett esophagus).

Antacid therapy with proton pump inhibitors alleviates or even cures reflux disease by increasing the intragastric pH and normalizing the esophageal pH.

Prophylactic surgery for Barrett esophagus-born adenocarcinomas is dedicated to mechanical defects and up to 85-93% of patients are cured. Antireflux surgery is another, more effective treatment for low-grade dysplasia compared to drug therapy, because it allows a proper control of both acid, bile and pancreatic reflux.

Surgical treatment: in up to 20% of patients the tumor cannot be resected because of metastases or because of the precarious medical state of the patient at the time of diagnosis.

The resected piece must include the thoracic and abdominal esophagus along with the small gastric curvature for type I cancers and for types II and III it must include 4-6 cm of esophagus above the tumor, the entire stomach, the greater omentum and the spleen.

The Siewert classification is useful for choosing the adequate surgical treatment. In type I eso-gastric adenocarcinomas it is indicated to perform a subtotal esophagectomy (because of the possible esophageal submucosal infiltration) along with the small gastric curvature resection. For types II and III it is necessary to perform an extended total gastrectomy through an abdominal-transhiatal approach or through a combined abdomino-thoracic approach.

Adjuvant therapy may be useful when radiation and chemotherapy are combined with Ro resections for an improved long-term outcome in patients with eso-gastric cancers.
**Prognosis:** the postop mortality rate for type I cancers is 5% compared to 1.4% for types II and III.\[24\]

The most important prognostic element is the presence of lymph node metastasis. The 5 year survival rate after esophagectomy for small tumors without lymph node metastasis is 100%, compared to 43% when lymph node metastasis exist or 0-20% when vascular infiltration exists in addition to lymph node metastasis.\[25\]

**Part II**

Based on the current trend of this disease, already discussed in the previous chapter, I have conducted a mixed (prospective and retrospective), multicenter clinical study, over a period of 5 years (2005-2010), enlisting 60 cases of eso-gastric cancer patients from Surgery Departments in two major hospitals: the County Clinical Hospital in Craiova and the Clinical Emergency Hospital in Bucharest.

The inclusion criteria concur with Siewert and WHO’s definition of eso-gastric cancers, all tumors of the gastric fornix or those of the gastric body extending to the cardia and abdominal esophagus have been excluded. Results: in our study, the incidence of eso-gastric junction cancers bore two distinctive aspects:

- the overall increasing incidence of this type of cancer, which is similar to the most recent reports, the peak of this increase having been noticed between 2009 and 2010.
- As a borderline condition, the incidence of eso-gastric junction cancers account for 14.2% of all gastric cancers and for 76.3% of all esophageal cancers, which makes is the main topographic type of esophageal cancer.

Males are prone to develop this disease, and male/female ratio is 3/1, with a variable geographical range of 1.5/1 and 8/1.

Based on the corroborated information from imagistic investigations (barium swallow, upper GI endoscopy, CT, eco-endoscopy) we were able to employ the TNM classification for esophageal or gastric cancer staging. We discovered that similar proportions from both groups (n=12 from Craiova group and n=11 from Bucharest group), totalizing nearly 50% (n=23, 40.35%) of all patients presented stage IV tumors.
at the time of diagnosis. The remaining patients, all of which underwent surgery (radical or palliative) had stage IIA cancers (3 cases, 5.26%), stage IIB (11 cases, 19.24%), stage IIIA (17 cases, 29.8%) and stage IIIB (3 cases, 5.26%).

The preferred surgical treatment for our eso-gastric cancer patients was eso-gastric resection completed with mediastinal and abdominal lymphadenectomy. As such, the first therapeutical decision was to surgically evaluate the resection option based on the pretreatment staging criteria.

The types of surgical interventions performed include superior eso-gastrectomy and total gastrectomy. We had 39 radical operations in 60 patients.

The resected fragments (39 cases) were all included in a vast histological study, designed to pinpoint the histological subtype of adenocarcinoma, the cellular differentiation grade, the stromal types and their differentiation grades and the possible association with other etiologies.

The postoperative morbidity rate was 38.4% (n=15), with 4 cases (23.5%) within the Craiova group and 11 cases (50%) within the Bucharest group. The anastomotic fistula was the main complication, affecting 7 cases (17.9%) in the Craiova group and 5 cases (22.72%) in the Bucharest group.

The postoperative mortality rate was 17.94% (7 deaths), with the main causes of death attributed to MSOF triggered by the unfavorable evolution of 5 out of 7 fistula cases and to pulmonary complications (bronchopneumonia in 1 case and pulmonary embolism in 1 case).

We analyzed the postoperative outcome results by the means of specific statistical methods in order to establish some predictive factors influencing the postoperative evolution of eso-gastric patients. As independent variables we considered the age, the genre, the type of resection and the type of surgical approach performed. We established that the genre and the type of resection do not influence significantly the survival rate, whilst the surgical approach has a major impact upon survival.
Bibliography:


Curriculum vitae

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1996 - 2002 The University of Medicine and Pharmacy, Craiova
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