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Influence of the surgical technique on survival in the treatment of carcinomas of the cardia (Siewert Type II) - Right thoracoabdominal approach compared to transhiatal approach

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INTRODUCTION

Esophageal and gastric cancer are worldwide a serious health problem, which are very often lethal diseases with a case-fatality ratio of 84 and 75 percent respectively (Samm et al., 2017).

During the last decades many efforts have been made in order to better define the nature of adenocarcinoma located at the esophago-gastric junction (AEG). In fact this tumor has been handled both as a gastric tumor or an esophageal tumor, without managing to reach an univocal classification leading to a standard of care for those patients.

AEG definition and classification

According to the UICC-2010 classification system - used to stage the patients cohort analyzed in this study - AEG is defined as a tumor whose epicenter is within 5 cm of the esophago-gastric junction (EGJ) and extending into the esophagus, while tumors with epicenter within 5 cm of the esophago-gastric junction extending into the stomach are to be considered gastric tumors (Siegel et al., 2012).

A significant modification to this definition was introduced in the most recent UICC-2017 classification system (Brierley et al.): in fact tumors with their epicenters within 2 cm of the esophago-gastric junction (EGJ) and their extensions in to the esophagus should be classified using the esophageal scheme.

After many years of experience in the field of treatment of AEG, Siewert classified AEG into three different entities (Fig. 1):

- AEG type I: tumors with their epicenter within 1-5 cm above EGJ

- AEG type II: tumors with epicenter within 1 cm above and 2 cm below EGJ

- AEG type III: tumors with their epicenter 2 cm below EGJ

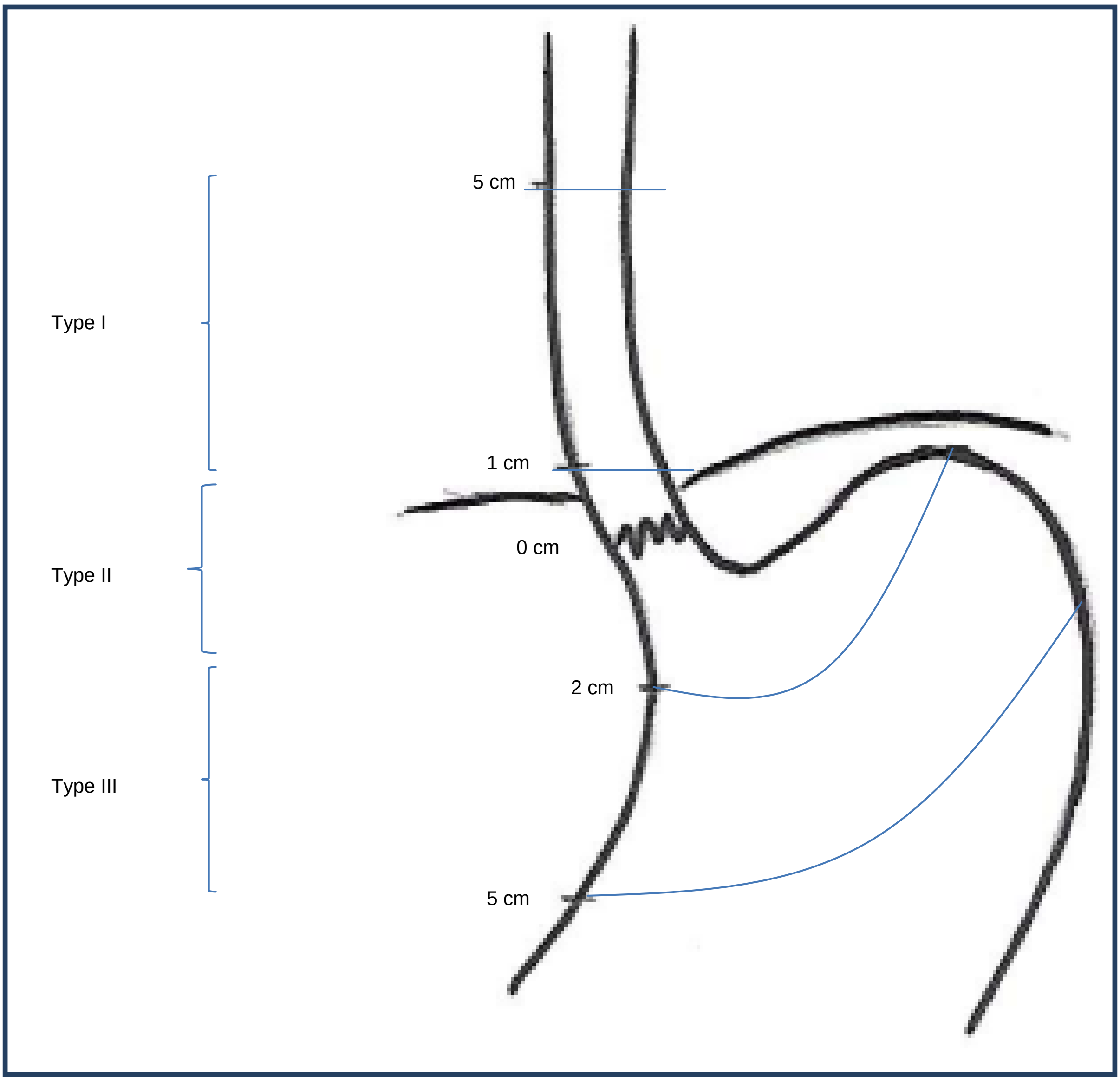

Fig. 1: Siewert Classification: the Z-line ist the passage between stratified squamous to columnar epithelium (0 cm)

Crucial to the definition of true cardia carcinoma is the anatomical definition of the cardia, which is the passage between the two-layered esophageal muscular wall and the three-layered stomach muscular wall. This passage can be intra-operatively detected as the passage between the tubular shaped esophagus, which does not present a serosa layer, and the stomach, which contrarily presents a serosa layer (Siewert et al.).

This can be endoscopically detected as the end of the rugal folds of the gastric mucosa (Stein et al., 2000).

The studies of Siewert´s group came to the conclusion that AEG I, or esophageal adenocarcinoma, should be treated as such, while AEG II and III, based on their biological behavior, should be classified as gastric cancer (Siewert et al., 1998, Siewert 2007).

Huang and Hasegawa (Huang et al., 2010, Hasegawa et al., 2012) as well came to the conclusion that the gastric cancer classification better fits to AEG II and III than esophageal tumors classification.

In contrast, Gertler et al concluded that neither the gastric nor the esophageal cancer classification properly suited AEG II/III (Gertler et al., 2011). Type II tumors in fact seem to have two distinct etiologies (esophageal adenocarcinoma originating from short or ultrashort Barrett´s esophagus and gastric adenocarcinoma caused by H.pylori infection and atrophic gastritis) (McColl et al., 2010, Derakjshan et al., 2008, Ren et al., 2009).

According to this position, literature suggests that, due to its different biology, AEG should be considered as an entity separate from gastric cancer as well.

Clinical features

Epidemiology

True cardia carcinomas are characterized by a higher frequency of differentiated types, greater depth of invasion, higher incidence of metastasis and poorer prognosis (McColl et al., 2010, Tajima et al., 2001).

The incidence of AEG is significantly increasing in the western countries, being at present the 2^{nd} most common cause of cancer-related death (Song et al., 2014).

Lot has been researched in understanding the carcinogenesis of this tumor and identifying its risk factors in order to do prevention and early diagnosis (McColl et al., 2010, Tajima et al., 2001).

Esophageal carcinoma (Müller et al., 2018/19)

Incidence:

Incidence of esophageal carcinoma is 8/100000/year, with a geographical difference which sees a higher incidence in Japan and England, maybe due to a higher consume of spicy food and tea. Male subjects seem to be more exposed (M/F 5/1) and the highest risk age is between 50 and 60 years.

Pathology:

The majority of esophageal carcinomas are adenocarcinomas (60-80%), especially in the distal segment and cardia, 20-40% are squamous-cell carcinomas, located predominantly in the upper esophagus and usually have a worse prognosis.

Undifferentiated carcinomas and melanomas can also be rarely found in the esophagus.

Due to the absence of a serosa layer, the local spread of these tumors is early and massive; the first route of spreading is through the periesophageal, mediastinal and perigastric lymph vessels for lower thoracic carcinomas, whilst the upper thoracic and cervical tumors spread through periesophageal and cervical lymph vessels.

Hematogenic metastases develop by migration through the gastric veins to the liver via the portal system (lower tumors), and to the lungs via the azygos vein and the upper cava vein from upper tumors.

Stomach carcinoma (Müller et al., 2018/19)

Incidence:

Incidence of stomach carcinoma is 19/100000 per year. Its incidence in Germany, like in other industrialized countries, is decreasing, maybe due to healthier alimentary habits. Male subjects seem to be slightly more exposed (M/F 1,5/1) and the highest risk age is above 60 years.

Pathology:

90% of these tumours are adenocarcinomas. They can be classified in papillar, tubular, mucinous, and signet ring cell differentiated and poorly cohesive type. The remaining 10% are squamous cell carcinomas, adenosquamous and undifferentiated.

The histological characteristics of stomach adenocarcinoma are often classified according to Lauren Classification, which differentiates between intestinal, diffuse and mixed type. The three entities have a different biological behavior, with repercussions on the therapeutic options.

- The intestinal type, present mostly as polipoid formed with a majority of glands and has a better prognosis (tubular, papillar and mucinous).
- The diffuse type presents an infiltrative growth into the mucosa and has a worse prognosis (signet ring cell type, poorly cohesive).
- Mixed type

The most frequent localization is antrum and pylorum (50-80%), the cardia and the smaller curvature are involved in 10-25% of the cases. 90% are solitary carcinomas, 10% of patients show multiple localizations.

The local spread of these tumors can involve the nearest organs as liver, pancreas and spleen, colon, diaphragm, peritoneum and mostly the great omentum. Lymphogenic metastases develop in the periesophageal, mediastinal and perigastric lymph nodes for cardia carcinomas, whilst antrum tumours infiltrate the perigastric lymph vessels along the bigger and smaller curves. Hematogenic metastases develop mostly in the liver.

Etiology and Risk Factors of AEG

Carcinogenesis of AEG, as for other gastrointestinal tumors, seems to be related to chronic inflammation. In fact inflammation represents a continuous damage of the tissue, stimulating the repair and re-growth systems.

Thus the importance in AEG carcinogenesis, diagnosis and cure, of a number of risk factors related to an increased inflammation of the cardia region.

These are gastro-esophageal reflux disease (GERD) (Zehetner et al., 2010, Lagergren et al., 1999), Barrett´s esophagus (BE) (Morrow et al., 2014), obesity (Lagergren et al., 1999), tobacco smoking (Lagergren et al., 2000), shorter dinner-to-bed time (Song et al., 2014) and H-pylori infection (Siveke et al., 2013).

- **GERD** and **Barrett´s esophagus**: BE is a change of the normal stratified squamous epithelium of the distal esophagus to metaplastic columnar epithelium of mucous-secreting goblet cells, caused by chronic GERD (Fitzgerald et al., 2013). Risk factor for progression form BE to AEG are esophagitis, long segment Barrett, dysplasia (Kastelein et al., 2014)
- It is proved that **obesity** is associated with an increased risk of colon cancer, postmenopausal breast cancer, endometrial cancer, renal cell cancer and adenocarcinoma of the esophagus (Boeing et al., 2013). Recent studies and meta-analyses showed a higher risk for AEG in obese subjects as well (Chen et al., 2013, Turati et al., 2012). The potential mechanisms throughout which obesity may have an influence on carcinogenesis in AEG are various. One is the increased intraabdominal pressure caused by overweight (Jung et al., 2013) promoting GERD and thus Barrett´s esophagus and therefore AEG (Wu et al., 2003). Another way obesity could have an influence on AEG development is through the induction of hyperinsulinemia. High levels of insulin-like growth factors, adipokine imbalance and estrogen might increase the cell proliferation and impair the apoptotic process (Lindblad et al., 2005, Mcmilian et al., 2006).

Furthermore obesity has been proved to evoke a proinflammatory state inducing high levels of proinflammatory cytokines.

- **Tobacco smoking**: current smoking status appeared to be associated to a moderately increased risk of both esophageal and gastric cancer, cardia adenocarcinoma and esophageal squamous-cell carcinoma.
  In a recent study (Cook et al., 2010) a strong association between cigarette smoking and esophagogastric junctional adenocarcinoma was demonstrated (OR = 2.18, 95% CI = 1.84 to 2.58). In addition, there was a strong dose–response association between pack-years of cigarette smoking and outcome ($P < .001$). Compared with current smokers, longer smoking cessation was associated with a decreased risk of all adenocarcinoma after adjusting for pack-years (<10 years of smoking cessation: OR = 0.82, 95% CI = 0.60 to 1.13; and ≥10 years of smoking cessation: OR = 0.71, 95% CI = 0.56 to 0.89). Sex-specific summary odds ratios were similar.
  Among ex-smokers the risk of gastric cardia adenocarcinoma was found higher as well (Lagergren et al., 2000).

- A study published in 2014 (Song et al., 2014) examinated the impact of **dinner-to-bed time** on incidence of AEG, suggesting that a shorter dinner-to-bed time increases the risk of AEG. Reversely post-dinner walk seems to decrease it. Some studies showed an increased incidence of GERD in subjects who go to sleep just after having dinner. An explanation of these results could be that the gastric distention after dinner could cause an increased transient relaxation of the lower esophageal sphincter (Dodds e t al., 1982). In several studies a night-time acid reflux was detected through 24-hours pH-metry (Dickman et al., 2007). This seems to be associated with more severe esophageal injuries, probably because of the long-lasting symptom characteristics (Lagergren et al., 1999). On the other side it is known that regular physical activity protects against AEG (Singh et al., 2013, Abioye et al., 2015) as much as against cancer of the colon, breast and endometrium (Colditz et al., 2006). This seems to be due to a lower incidence of obesity and its carcinogenetic mechanisms (described above), as much as to a very likely better health consciousness in the subjects having physical activity. Besides that, post-dinner walk seems to reduce GERD symptoms by increasing gastric emptying rate (Avidan et al., 2001).

- **H-pylori infection** is a spiral-shaped bacterium living in the mucus layer of the stomach. It secrates urease, an enzyme able to convert urea to ammonia, neutralizing the acidity of the stomach. Furthermore it can reduce the capacity of the local immune response to attack the bacterium (Polk et al., 2010, Busuttil et al., 2009). Although it is estimated that H. pylori is harbored in about two thirds of the population, with a higher incidence in developing countries and children, it does not cause illness in any of its hosts. Nevertheless it is accepted as a risk factor for peptic ulcer disease and for gastric cancer (mucosa-associated lymphoid tissue – MALT- and adenocarcinoma of the cardia). Its role in development of esophageal adenocarcinoma is more controversial and related to the fact that stomach colonization from H. pylori is eventually related to a reduced risk of adenocarcinoma.

Symptoms

The symptoms related to AEG are very unspecific and therefore in most of the cases the diagnosis is made when the disease is already in an advanced stage.

In fact, only 50% of the tumors are eligible for curative resections. For this reason screening with gastroscopy has a crucial role in early diagnosis.

The more common symptoms are:

- Weight lost due to reduced caloric intake as a result of abdominal pain, nausea and dysphagia (Wanebo et al., 1993).

- Gastrointestinal Bleeding (occult or overt) with consecutive anemia (Wanebo et al., 1993).
- Pseudoacalasia due to the infiltration of the Auerbach´s plexus as a result of the local extension near the EGJ (Kahrilas et al., 1987).

- A left supraclavicular adenopathy (Virchow´s node) or a periumbilical nodule (St. Mary Josephs´node) may be detected as a sign of nodal infiltration (Morgenstern 1979, Pieslor et al., 1986).

- Signs of tumor spread (Gilliland et al., 1992, Winne et al., 1965) may be ascites form peritoneal carcinosis, involvement of the ovaries (Krukenberg´s tumors), palpable lymphadenopathies left supraclavicular or axillar, and palpable liver tumors.

Diagnosis and staging

The diagnostic tools used in to detect and assess the stage of AEG are the following:

- Endoscopy
- Endosonography
- Barium swallow
- CT Scan and MRI
- PET-CT
- Laparoscopy

Endoscopy:

The gold standard for the diagnosis of AEG is conventional upper GI endoscopy (di Pietro et al.). In fact during this procedure it is possible not only to detect the lesion (Fig. 2), but also to take biopsies (Fig. 3) and to precisely describe the localization and extension. Correct assessment of AEG tumors includes the documentation of its dimension (tumor length, extent of circumferential involvement, degree of obstruction), the distance from teeth to the EGJ and the evidence of Barrett´s esophagus.

The necessity to increase the early diagnosis inevitably leads to the topic of screening programs: in a recent meta-analysis published in the UK (Graham et al., 1982) it is stated that screening should be recommended only for multiple risk factors, and that the threshold for screening should be lowered in the presence of positive family history.

The same study also indicates conventional upper GI endoscopy as the gold standard for screening of oesophageal malignancies. This is due to the very high accuracy, with a sensitivity between 92 and 96,6%, and a specificity between 84 and 94,6%.

Disadvantages of this examination are its costs, the need of sedation and possible complications (upper GI perforation and bleeding).

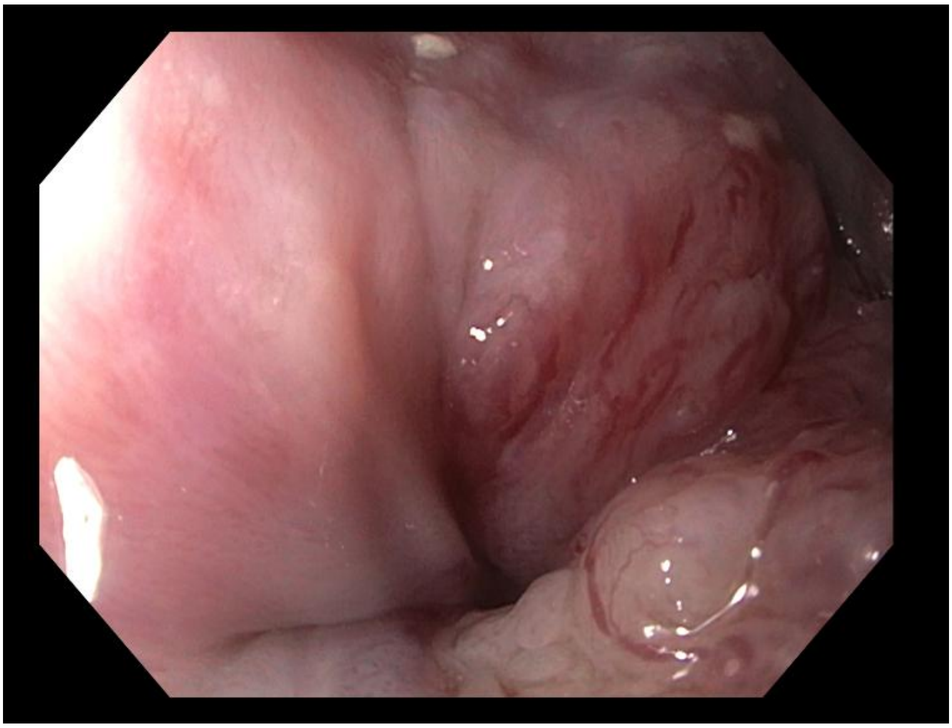

Fig. 2: endoscopic image of a cardia adenocarcinoma

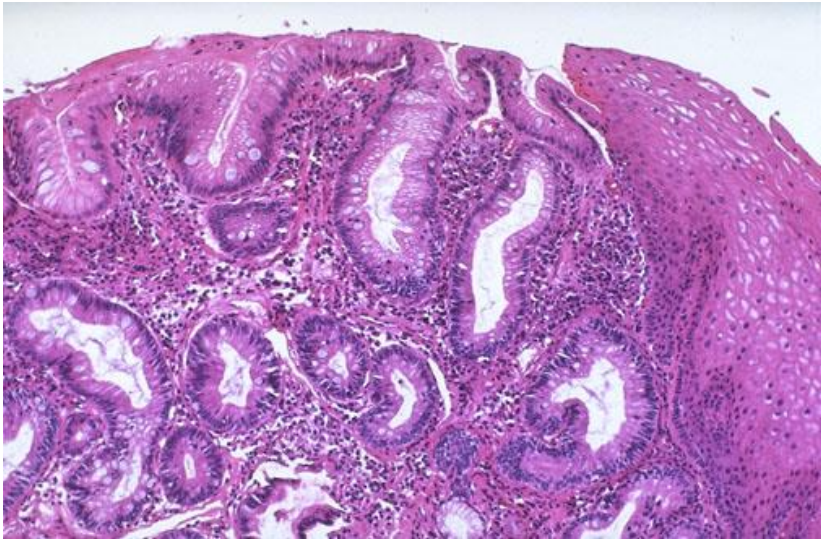

Fig. 3: histopathologic section of a cardia adenocarcinoma

Radiology:

Other less invasive examinations as barium swallow (Dooley et al., 1984) may as well detect AEG (Fig.4) but with a lower sensitivity and without the possibility of such a precise and complete description of the tumor. Furthermore the capacity to perform histology makes endoscopy the first choice examination both in screening and diagnosis of AEG.

Because of the presence of a better diagnostic option such as gastroscopy, barium swallow is rarely used nowdays.

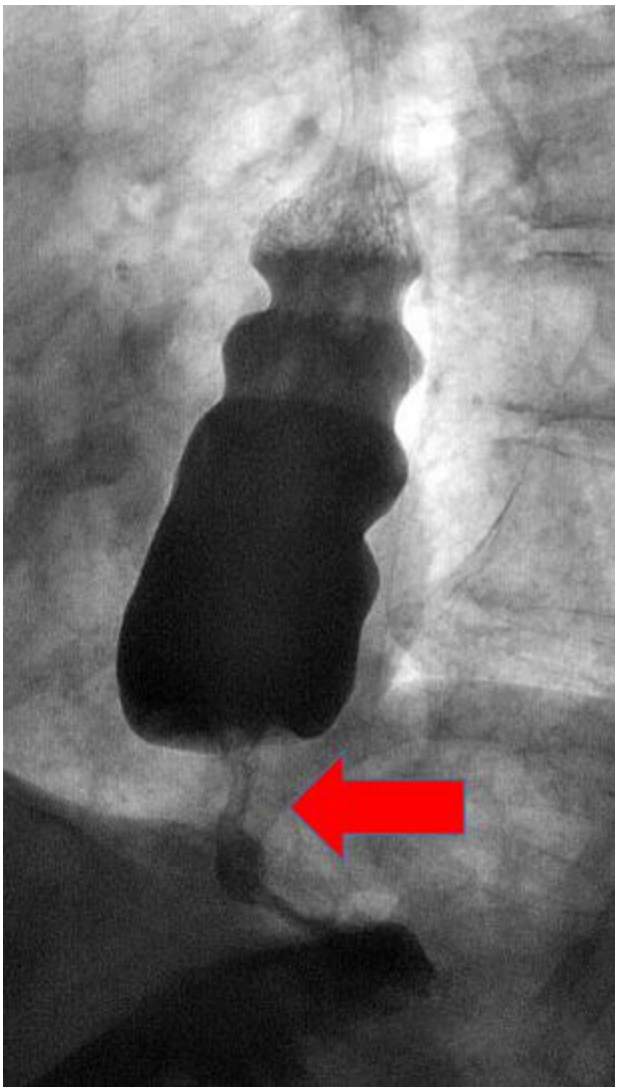

Fig. 4: barium swallow showing a stenosis of the cardia

Staging

After histological confirmation of AEG, it is necessary to perform an exact staging of the disease in order to assess the stage and therefore the proper treatment strategy.

The staging system for AEG is based on the local tumor extension measured as the depth of the wall invasion (T), the number of involved nodes (N) and the presence of metastasis (M).

In the Tab. 1 updated staging systems of esophagus and esofago-gatric junction carcinoma are described (Brierley).

Oesophagus 8th edition			
TNM definition			
Tis	Carcinoma in situ/high grade displasia		
T1a	lamina propria or muscularis mucosa		
T1b	Submucosa		
T2	muscularis propria		
T3	Adventitia		
T4a	pleura, pericardium, diaphragm		
T4b	aorta, vetebral body, trachea		
N0	no lymph nodes		
N1	1 to 2 regional lymph nodes		
N2	3 to 6 lymph nodes		
N3	7 or more lymph nodes		
M1	distant metastasis		
Grading			
Gx	Grade cannot be assessed—stage grouping as G1		
G1	Well differentiated		
G2	Moderately differentiated		
G3	Poorly differentiated		
G4	Undifferentiated		
Anatomic stage/prognostic groups			
I	T1	N0, N1	M0
II	T2	N0, N1	M0
	T3	N0	M0
IVA	T4a, b	N0, N1, N2	M0
IVA	Any T	N3	M0
IVB	Any T	Any N	M1

Tab. 1: Esophagus carcinoma including EGJ Staging – UICC 8

Endosonography (endoscopic ultrasound):

The gold standard in order to assess the T and N stage is endosonography (Barbour et al., 2012) of the upper GI tract.
Through the combination of endoscopy and ultrasonography (Fig. 5) it is possible to applicate the ultrasound probe on the very surface of the tumor, making it possible to describe the aspect of the layers of the hollow organ (T staging) as much as the morphological aspects of the local lymph nodes (N staging).

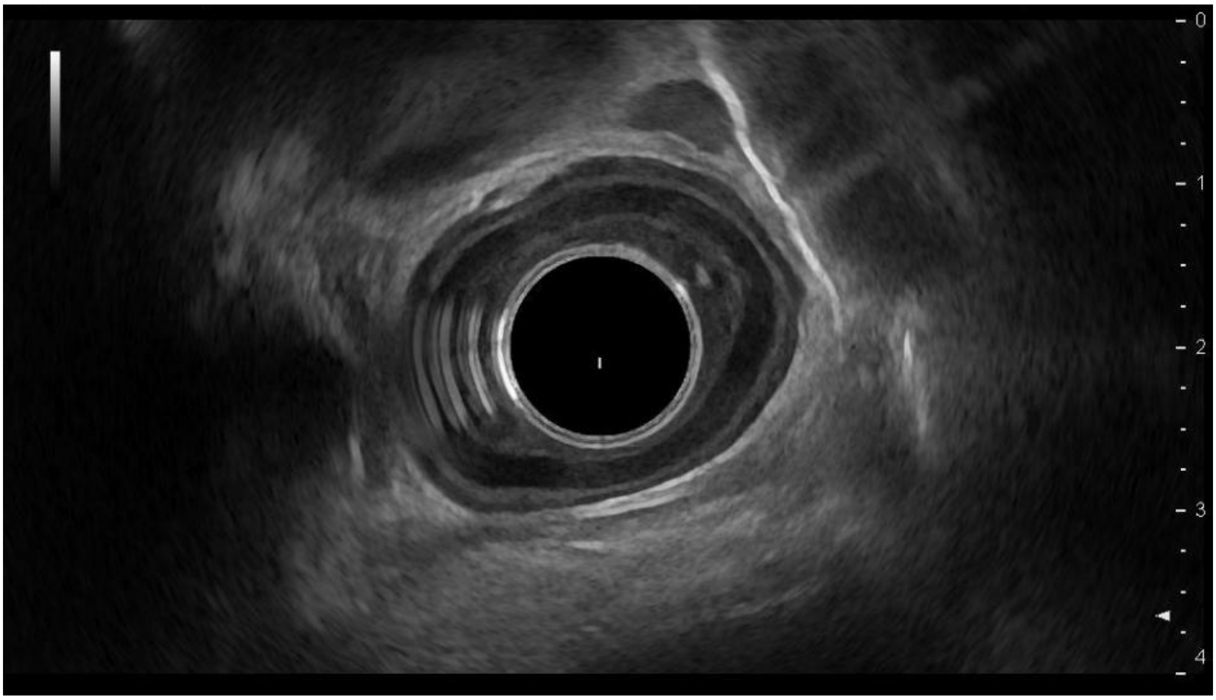

Fig. 5: Endosonographic image of a cardia tumor

This examination has an overall accuracy for T and N staging of 80 to 90 percent, being able to evaluate both perigastric and mediastinal lymph nodes (Barbour et al., 2012).

CT and MRI

CT scan (Fig. 6) of the thorax and the abdomen is a widely used staging examination, particularly with the aim of detecting liver and lung metastasis, as well as lymph nodes in the distance (intraabdominal, cervical or supraclavicular, etc.). Unfortunately the sensitivity of this examination is not particularly high.
MRI can also be used to assess the T and N stage of EJA.

A study recently published in Italy (Giganti et al., 2016), summarizes the accuracy of MR, CT and EUS as follows:

Preoperative Staging	MR	CT	EUS	MR vs CT	MR vs EUS	CT vs EUS
				p-value	p-value	p-value
T						
Sensitivity	67	83	100	0,56	0,16	0,32
Specificity	92	63	67	0,16	0,08	0,56
Accuracy	83	78	78	1	1	1
Positive predictive value	80	62	60	0,68	0,12	0,29
Negative predictive value	83	90	100	0,68	0,12	0,29
N						
Sensitivity	100	75	100	0,31	1	0,31
Specificity	57	57	36	1	0,08	0,08
Accuracy	66	61	50	1	0,25	0,61
Positive predictive value	40	33	31	0,29	1	0,29
Negative predictive value	100	89	100	0,29	1	0,29

Tab. 2: Performance characteristics of MR, multidetector CT and endosopic ultrasonography for local invasion (T) and nodal infiltration (N).

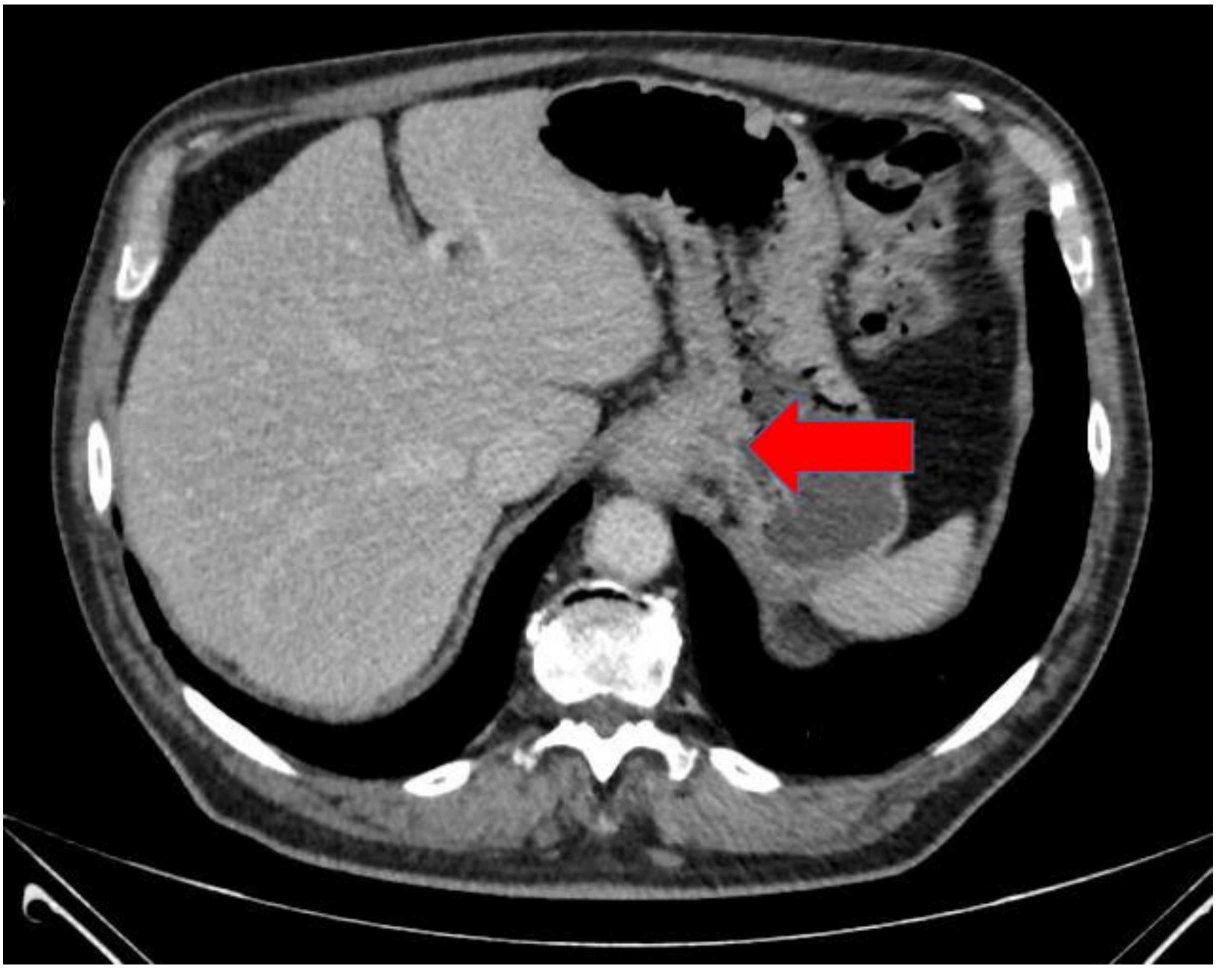

Fig. 6: CT image of a cardia carcinoma

PET-CT:

In order to achieve a better interpretation of pathological nodes or potential distant metastases detected with a CT scan, it is possible to perform Positron emission tomography–computed tomography (PET-CT) (Fig. 7), which can provide information on the metabolic activity of the target tissue (Erhunmwunsee et al., 2015). PET-CT is a nuclear medicine technique which combines, in a single gantry, a positron emission tomography (PET) scanner and a traditional CT scanner. It conjugates the capacity of CT to perform a rather precise slice imaging of the whole body, with the possibility to detect the level of metabolic activity through the injection of a contrast medium radiopharmaceuticals as fluorodeoxyglucose (FDG) and Fluroine-18, which will be concentrated in more metabolic active cells, such as tumor cells. (Townsend 2008)

A difficulty in the interpretation of these images is given from inflammation activity (like postoperative or infections for example), which can falsely be interpreted as tumor tissue.
Another limitation of this examination is due to the very high costs of transporting and stocking the contrast.

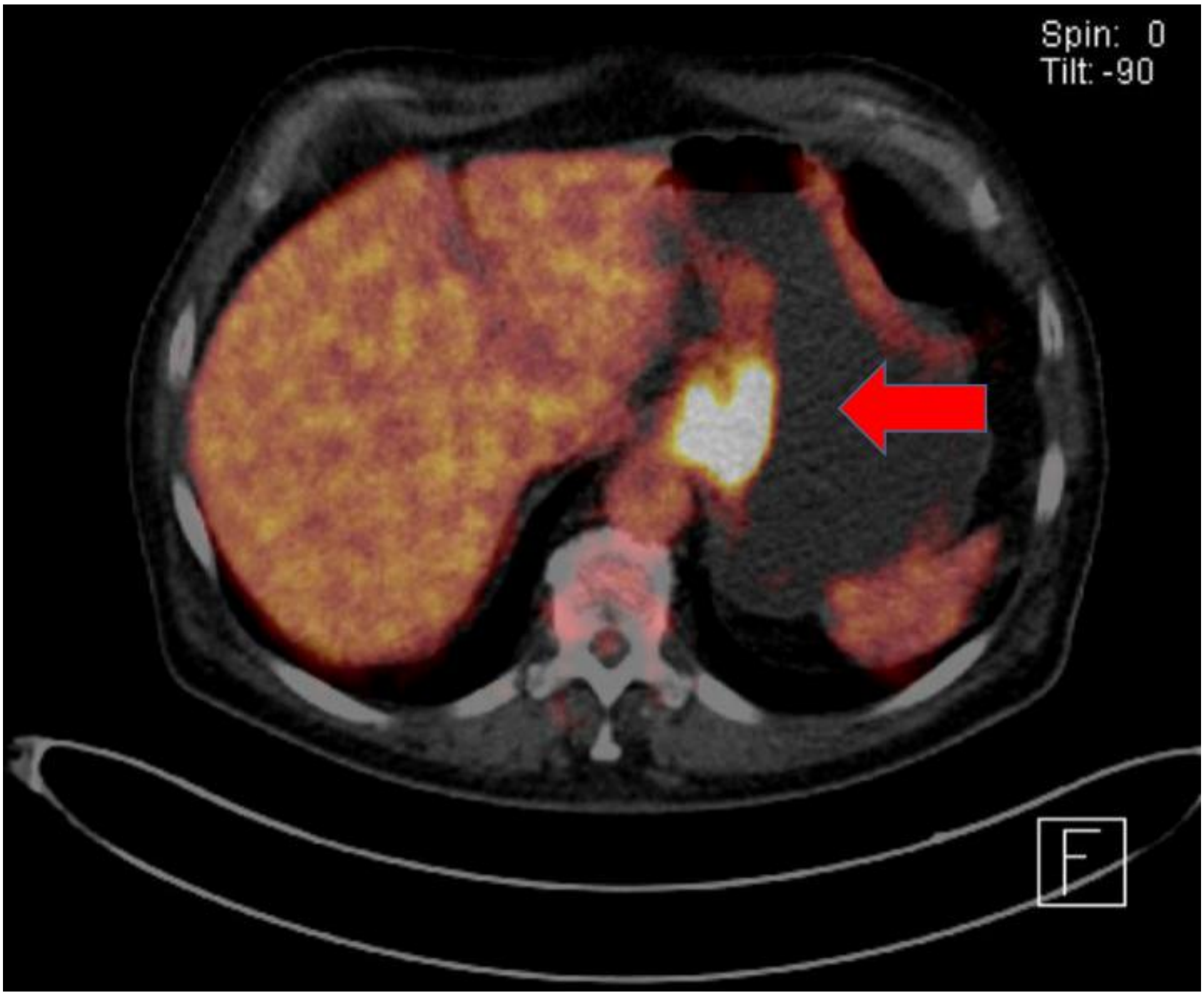

Fig. 7: PET/CT image of a cardia adenocarcinoma

Explorative laparoscopy:

To better assess the stage of locally advanced AEG, an explorative laparoscopy is recommended if a peritoneal carcinosis is suspected (Mortensen et al., 2012). In these cases a laparoscopy will allow to take direct vision of the liver, ovaries and peritoneal surface (Fig. 8a). During this procedure it is also possible to perform a histological or cytological sampling of the tissues.
The result of this examination has a crucial role in chosing neoadjuvant or palliative systemic treatment. In fact patient with a local or locally advanced tumor will go for a neoadjuvant treatment, while patients with histologically demonstrated metastatic spread are only for non-curative treatment options.

The elegibility to HiPEC is assessed through the peritoneal cancer index (PCI, in Fig 8b) . For this purpose, the peritoneal cavity is divided in 13 well-defined regions (see figure 8b). In each of the 13 regions, the size of the largest tumor nodule is measured. If no tumor is visualized, a score of “0” is given to that region. If the largest tumor nodule is smaller than 0.5 cm, the score is “1”. For tumors measuring between 0.5 cm and 5 cm, the score is “2”. For lesions larger than 5 cm, the score is “3”. If there is layering or a confluence of multiple small tumor nodules, the score is “3”. The PCI is calculated by adding the scores of all 13 regions together with a maximum score of 39 (13×3). (Gilly et al., 2006).

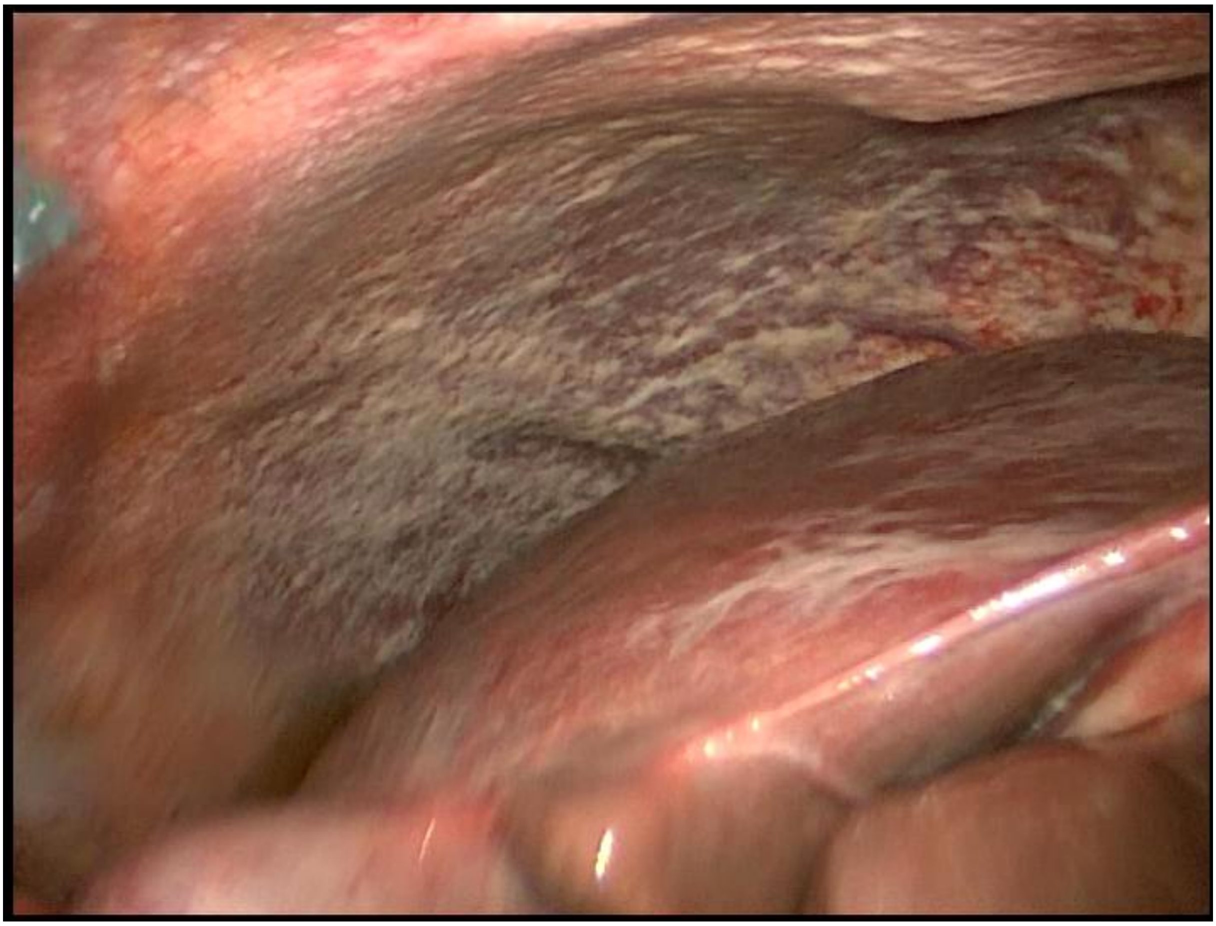

Fig. 8a: Peritoneal carcinosis detected through laparoscopy

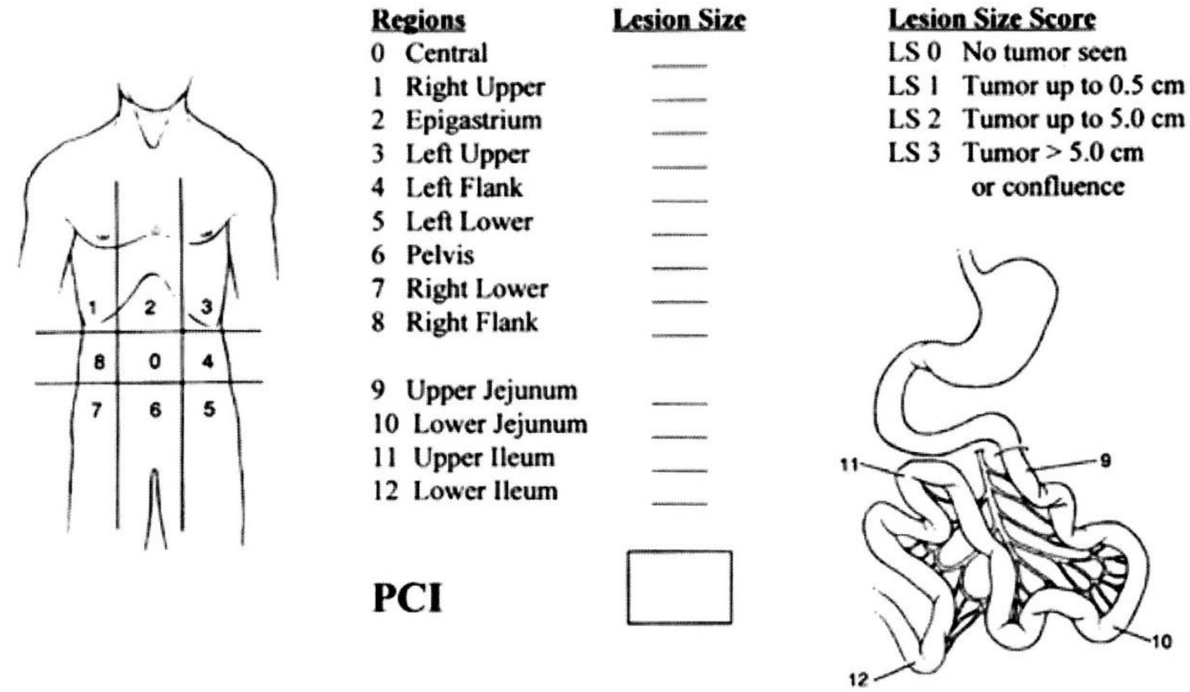

Fig. 8b: peritoneal cancer index

Treatment

Chemotherapy

Nowadays multimodality treatment, either consisting of perioperative platinum-based chemotherapy (CT) or neoadjuvant radiochemotherapy followed by surgery is the standard of care in Western centers for locally advanced tumors (Samm et al., 2017, Cunningham et al., van Hagen et al., 2013, Shapiro et al., 2015).

Recent studies (Samm et al., 2017, Siewert, 2006, Huang et al., 2011) demonstrated that histopathologic response to chemotherapy is an independent prognostic factor.

- MAGIC-trial

A landmark trial on this topic, the MAGIC trial (Cunningham et al.), showed a clear down-staging in patients with locally advanced AEG treated preoperatively with three cycles of epirubicin, cisplatin and 5-fluorouracil (ECF regimen) compared to non treated patients. Furthermore the postoperative complications and mortality were not higher in the chemotherapy group than in controls.

5-year survival rate was 36% for patients receiving perioperative chemotherapy, vs 23% in the control group.

A major weakness of the MAGIC trial is the fact that most of the patients underwent an inappropriate lymphadenectomy (only 43% of resected patients received a D2 lymphadenectomy), suggesting that the perioperative administration of chemotherapy might compensate the inadequate surgical treatment (Ychou et al., 2011).

- ACCORD-trial

Another study comparing a perioperative treatment to surgery demontrated that R0 resection rates in patients who underwent a preoperative regimen with cisplatin anf 5-fluorouracil were significantly higher than in the non-chemotherapy cohort (84% vs 73%). Also in this case the 5 year survival rate was higher in patients receiving perioperative systemic chemotherapy (38% vs. 24%). (Schumacher et al., 2010).

- EORTC-trial

Another confirmation of the benefit of a perioperative chemotherapy comes from Schumacher et al. (Schumacher et al., 2010).

After a neoadjuvant regimen with cisplatin, 5 fluorouracil and folinic acid (PLF) a higher rate of R0 resection was detected, as much as a downstaging of the tumor.

- FLOT

A recent work from Sprinfield et al. compared four different perioperative regimens, two duplets (cisplatin and 5 fluorouracil or oxaliplatin and 5 fluorouracil) and two triplets (epirubicin, platinum and 5 fluorouracol or taxane, platinum and 5 fluorouracil). The last one seemed to achieve a higher rate of complete regression. (Springfeld et al., 2015).

Another study published in 2016 (Al-Batran et al., 2016) reported findings from the phase 2 part of the phase 2/3 FLOT4 trial, comparing histopathological regression in patients treated with a docetaxel-based triplet chemotherapy versus an anthracycline-based triplet chemotherapy before surgical resection. This study suggests that FLOT4 is perioperative feasible to administer, and might represent a more effective option for patients with locally advanced, resectable gastric or gastro-eosophageal junction adenocarcinoma.

Radiochemotherapy:

Though the combination of perioperative chemotherapy combined with a preoperative administration of radiation is increasingly considered as the standard for esophageal and esophagogastric adenocarcinoma (Reynolds et al., 2017).

- CROSS-trial

The CROSS-trial compared the outcomes of patients undergoing chemoradiotherapy (paclitaxel, carboplatin and 41,4 Gy in 23 fractions) vs. surgery only, showing a 47% 5 years survival in the multimodal arm vs. 34% in surgery only group. The rate of R0 resection was also clearly higher in the systemically treated patients (92% vs. 69%).(Shapiro et al., 2015, Van Hagen et al., 2012, Stahl et al., 2009)

- POET-trial

The POET-trial compared the outcomes of two cohorts undergoing a perioperative regimen of cisplatin, leucovorin and FU vs. cysplatin, etoposide and a preoperative administration of 30 Gy radiation in 15 fractions. 3 year survival was 47,4% in the chemoradiotherapy arm vs. 27,7% in the chemotherapy group. Beside that the pathological complete response rate was 15,6% vs. 2% respectively) (Stahl et al., 2009).

Resection

Though the important impact of systemic treatment in the battle against AEG, the removal of the primary tumor-mass is still the mainstay of the multimodal treatment.

Being the surgical resection an aggressive procedure with severe impact on the quality of life of patients and with potentially severe complications, it is mandatory to always consider the possibility to achieve an R0 resection through the least possible invasive procedure. In case of early cancers (T1a and T1b SM1) endoscopic mucosectomy associated to a strict follow-up is a valid option (Osumi et al., 2016, Tokyo National Cancer Center).

Endoscopic mucosectomy:

The endoscopic resection of the mucosa is a minimally invasive procedure that allows to completely remove tumor when the latter is confined to the most superficial layer of the mucosa. This procedure can be considered curative only after the pathological assessment detects (Japanese gastric cancer treatment guidelines):

- A T1a tumor differentiated type adenocarcinoma, well-to-moderately differentiated with no ulceration
- A T1a tumor with a maximum diameter of >= 30 mm, differentiated type, with no ulceration
- A T1a tumor with a maximum diameter of >= 20 mm, poorly differentiated or signetringcell, no ulceration
- A T1b /SM1) with a maximum diameter of >= 30 mm, differentiated.

Tumors with more aggressive aspects (dimension, depth of invasion, grading or ulceration) will need further surgical resection to allow the assessment of N status and be curative in case of nodal involvment.

Surgical resection:

Though it is generally accepted that surgery is the mainstay of therapy for AEG, it is still matter of discussion which resection technique should be adopted as gold standard.

At present the two most frequently used approaches are esophageal resection with proximal gastrectomy and gastric-tube reconstruction via a right or left thoraco-abdominal approach (RTA/LTA) (Shapiro et al., 2015, Yamashita et al., 2011) or alternatively an extended gastrectomy through an abdominal-transhiatal approach (TH) (Yamashita et al., 2011, Barbour et al., 2007, Leers et al., 2009, Siewert et al., 2000, Sasako et al., 2006).

Esophageal resection with proximal gastrectomy and gastric-tube reconstruction via a right or left thoraco-abdominal approach (RTA/LTA)

A partial gastrectomy is performed through an abdominal access (laparotomy or laparoscopy) in order to prepare the gastric pull up. In this phase of the operation a perigastric lymphadenectomy is also performed. Afterwards esophagectomy and mediastinal lymphadenectomy are performed through a right thoracotomy. The operation is completed by pulling up the remain of the stomach which has been shaped as a tube along the greater curve and is connected to what is left of the esophagus high in the chest (at the level of the Azygos vein).

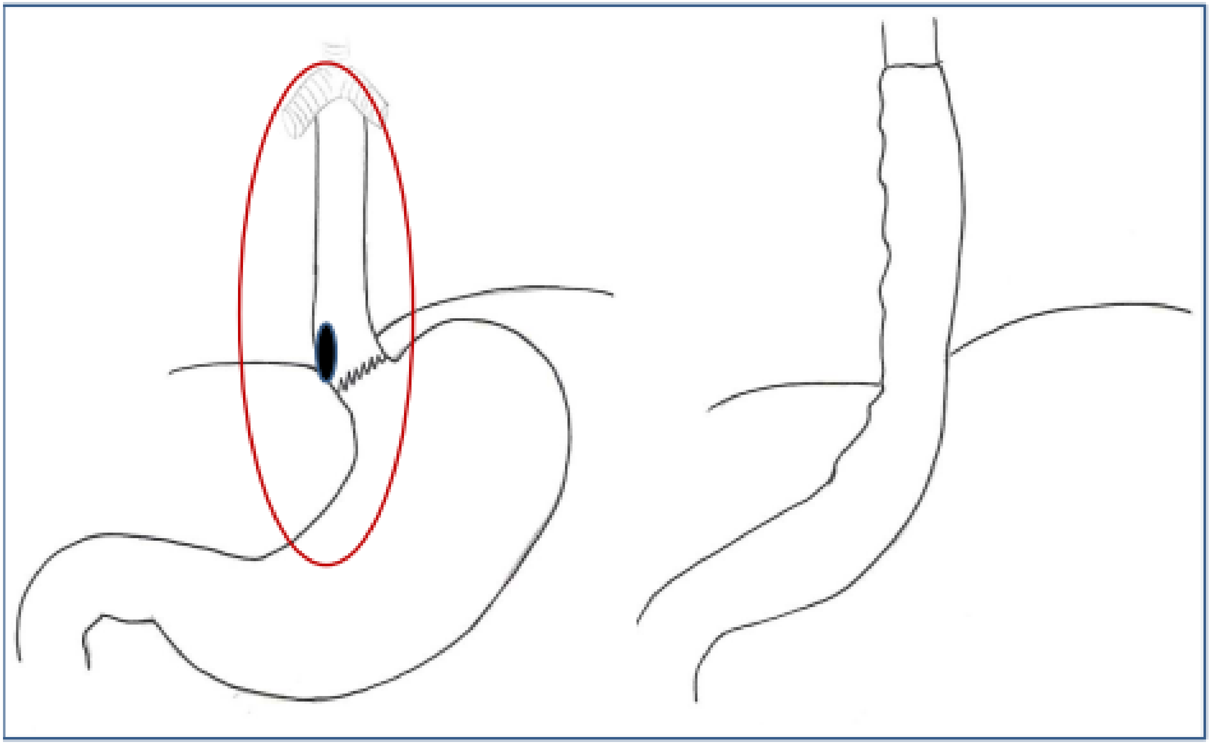

Fig. 9: Esophageal resection with proximal gastrectomy and gastric-tube reconstruction via a right or left thoraco-abdominal approach (RTA)

Extended gastrectomy through an abdominal-transhiatal approach (TH)

A total gastrectomy is performed through an open abdominal access (laparotomy), A D2 lymphadenectomy (a description of the lymphadenectomy will follow in the next paragraph) is also performed. In this case esophagectomy and lymphadenectomy in the lower mediastinum are performed through the hiatus. The operation is completed performing an Roux-Y anastomosis between the jejunum about 70 cm from duodenum, and the thoracic esophagus. The operation is completed by performing a suture between the first part of the jejunum about 50 cm after the esophago-jejunum anastomosis in order to ensure the proper flow of the bile and the pancreatic juice.

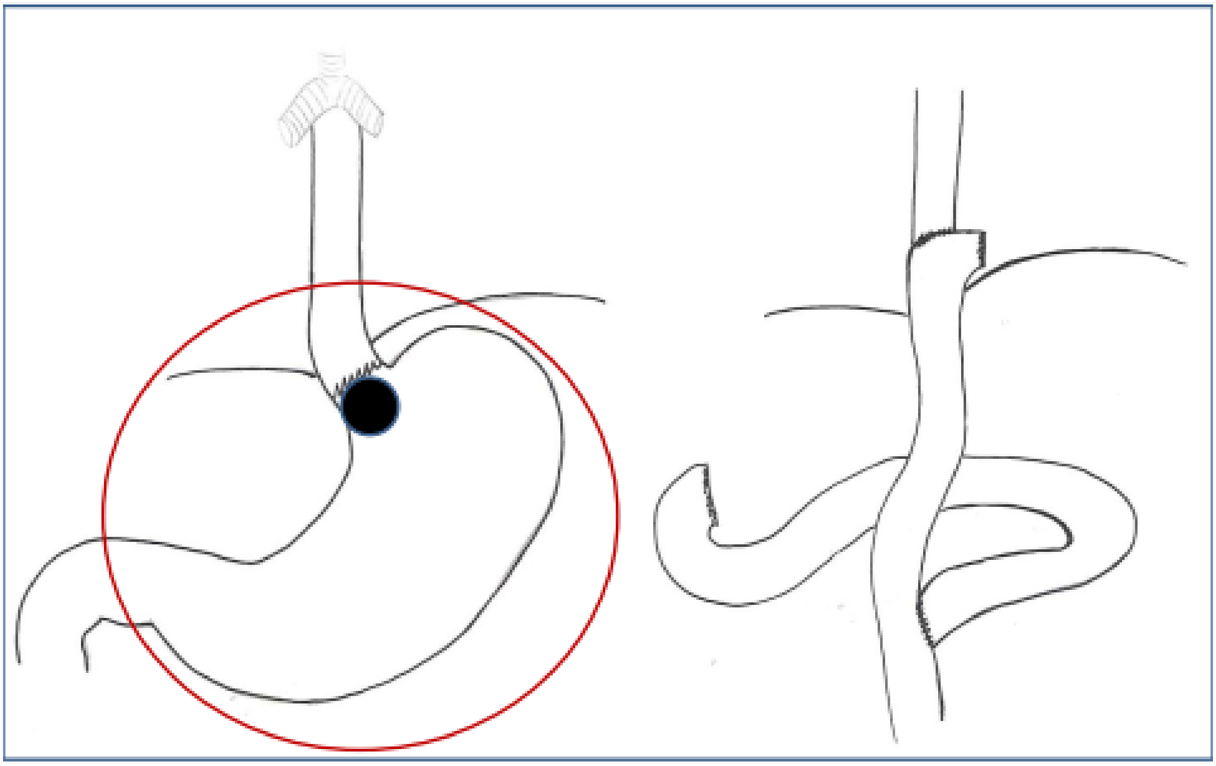

Fig. 10: Extended gastrectomy through an abdominal-transhiatal approach (TH)

Arguments in favor of the more invasive thoraco-abdominal approach are the possibility of achieving greater oral margins and more extended mediastinal lymph node dissection. Conversely TH is a less invasive procedure, additionally allowing for more extended intra-abdominal lymphadenectomy along the greater curvature which needs to be left unattended in RTA/LTA in order not to compromise the blood-supply of the gastric-tube. However, the anastomosis in TH is technically more challenging, due to the often high extension into the mediastinum. The effective role of these factors is still to be elucidated.

The role of lymph node dissection (Yamashita et al., 2011)

Despite an abundance of publications about lymphadenectomy in surgery of true cardia carcinomas, no gold standard has been established. At present it is usual to perform a D2 dissection when performing a gastrectomy (including therefore the stations 1 to 12 (Fig.11), and the lower mediastinal stations. When performing a thoracic approach the abdominal lymph nodes dissection will be less extensive, but the mediastinal lymphnodes up to the bronchial bifurcation will be removed.

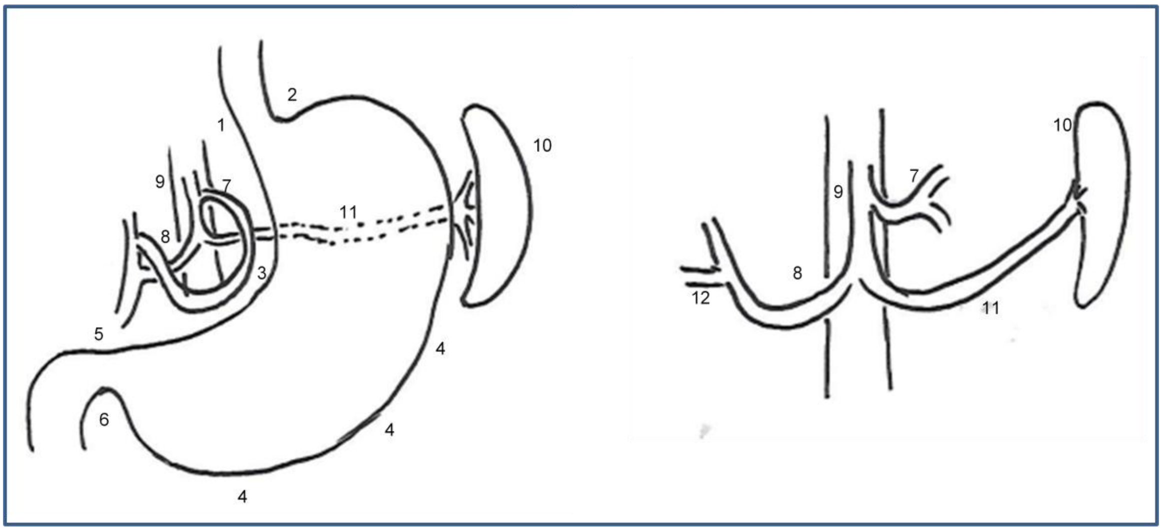

Fig. 11: Gastric lymphnodal stations:

1- Right cardiac
2- Left cardiac
3- Lesser curvature
4- Greater curvature
5- Suprapyloric
6- Infrapyloric
7- Left gastric artery
8- Common heparic artery
9- Celiac axis
10-Splenic hilus
11-Splenic artery
12-Hepatoduodena ligament

Minimally invasive approach

With the development of robotic surgical technology and equipment, minimal invasive resection for EJA has been widly used.

In a study recently published (Zang et al., 2018), it is observed that in case of esophagectomies, the mediastinal and abdominal lymphadenectomy can be conducted by thoracoscopy and laparoscopy respectively. After that a gastric tube is placed and the reconstruction is performed in the mediastinum. For TH, the whole procedure is accessed by laparoscopy and the lower mediastinum is accessed transhiatally. After lymphadenectomy the anastomosis can be performed laparoscopic-assisted or totally laparoscopic. As for Siewert type III, both circular and linear stapler can be used to perform reconstruction.

A study published in 2019 (Yoontaek e tal., 2019) compared the surgical and oncological outcome of 108 patients undergoing TH for true cardia adenocarcinoma (37 laparoscopic and 71 open), showing that the laparoscopic approach is feasible and safe, it gives advantages in terms of a better visualisation of the surgical field, of lesser postoeprative pain and blood loss, as much as a lower infection rate. On top oft hat it showed short- and longterm oncological result siminalr tot he open approach.

A recently pubished study (van den Berg et al., 2018) comparing the outcomes of combined laparoscopic-thoracoscopic approach for RTA with fully open surgery, showed that the minimally invasive approach is as safe as the open, presenting less blood loss without affecting the oncological accuracy.

It is likely to believe that the use of a minimally invasive approach in treatment of true cardia adenocarcinoma, is destined to increase in the clinical routine (Wang et al.).

AIM OF THE STUDY

Although the clinical research throughout the last decades focused on defining a gold standard for AEG treatment, it is still unclear which surgical procedure between RTA and TH should be preferred.

Aim of our analysis is to analyze the outcome of patients treated in our center in order to evaluate if any of the two surgical approaches is superior regarding oncological outcome, R0 resection rate and survival.

Objectives of our analysis are:

Oncological outcome

To define the difference in the rates of R0 resection achieved through the two different techniques, as much as the impact of the surgical approach on the lymph nodes dissection.

Perioperative morbidity and mortality

To define which surgical approach is related to a lower complication rate and better postoperative outcome.

Survival

To define if there is a statistical significant difference in postoperative survival after the two different resection techniques.

Recurrence

To investigate if the surgical approach has an impact on future recurrence and their location.

PATIENTS AND METHODS

Data Collection

Tumor- and patient-related data of all patients undergoing curative RTA or TH for Siewert type II AEG at the Klinikum Rechts der Isar, Munich, Germany, between 2000 and 2013 were extracted from a prospectively documented esophageal and gastric-cancer data base.

Inclusion criteria

All patients with histologically proven adenocarcinoma of the esophago-gastric junction (AEG II after Siewert endoscopic classification) and with a potentially resectable disease were enrolled.

Exclusion criteria

Patients with a secondary malignancy, systemic metastases (M1) or R2 resection were excluded from the analysis.

Staging

Patients were staged by CT of the thorax/abdomen/pelvis and esophago-gastro-duodenoscopy (EGD), including an endoscopic ultrasonography of the tumor (EUS) for assessment of the depth of invasion (uT).

- tumor length
- extent of circumferential involvement
- degree of obstruction
- distance from teeth
- evidence of Barrett´s esophagus.

Since the patients were recruited between 2000 and 2013, we used the 2010 UICC TNM staging system (Sobin et al., 2011).

Oesophagus 7th edition				
TNM definition				
Tis	Carcinoma in situ/high grad displasia			
T1a	lamina propria or muscularis mucosa			
T1b	Submucosa			
T2	muscularis propria			
T3	Adventitia			
T4a	pleura, pericardium, diaphragm			
T4b	aorta, vetebral body, trachea			
N0	no lymph nodes			
N1	1 to 2 regional lymph nodes			
N2	3 to 6 lymph nodes			
N3	more than 6 lymph nodes			
M1	distant metastasis			
Grading				
Gx	Grade cannot be assessed—stage grouping as G1			
G1	Well differentiated			
G2	Moderately differentiated			
G3	Poorly differentiated			
G4	Undifferentiated			
Anatomic stage/prognostic groups				
IA	T1	N0	M0	G1, G2, Gx
IB	T1	N0	M0	G3
	T2	N0	M0	G1, G2, Gx
IIA	T2	N0	M0	G3
IIB	T1,T2	N1	M0	Any G
	T3	N0	M0	Any G
IIIA	T1,T2	N2	M0	Any G
	T3	N1	M0	Any G
	T4a	N0	M0	Any G
IIIB	T3	N2	M0	Any G
IIIC	T4a	N1, N2	M0	Any G
	T4b	Any N	M0	Any G
	AnyT	N3	M0	Any G
IV	AnyT	Any N	M1	Any G

Tab. 3a: Esophagus carcinoma Staging (2010 UICC)

Stomach 7th edition			
TNM definition			
Tis	Carcinoma in situ/high grad displasia		
T1	lamina propria or muscularis mucosa		
T1b	Submucosa		
T2	muscularis propria		
T3	Adventitia		
T4a	visceral peritoneum		
T4b	adjacent structures		
N0	no lymph nodes		
N1	1 to 2 regional lymph nodes		
N2	3 to 6 lymph nodes		
N3a	7 to 15 lymph nodes		
N3b	more than 15		
M1	distant metastasis		
Anatomic stage/prognostic groups			
IA	T1	N0	M0
IB	T1, T2	N0	M0
IIA	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
IIB	T1	N3	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
IIIA	T2	N3	M0
	T3	N2	M0
	T4a	N1	M0
IIIB	T3	N3	M0
	T4a	N2	M0
	T4b	N1	M0
	T4b	N0	M0
IIIC	T4a	N3	M0
	T4b	N2, N3	M0
IV	AnyT	Any N	M1

Tab. 3b: Stomach carcinoma Staging (2010 UICC)

Treatment

All cases were discussed in a multidisciplinary tumor conference prior to the beginning of treatment and after the surgical procedure. Patients undergoing a perioperative systemic treatment were re-staged and re-discussed in tumor board.

Patients with locally advanced tumors (cT2 cN+ cM0, cT3/4 cN_{any}cM0) underwent neoadjuvant or perioperative chemotherapy using platinum-based regimens. Four weeks after the end of the chemotherapy protocol the surgical procedure was scheduled.

The two standard techniques used were esophageal resection with proximal gastrectomy and gastric-tube reconstruction via a right thoraco-abdominal approach (RTA) and total gastrectomy through an open abdominal access (laparotomy) with a D2 lymphadenectomy as described before.

Leading factors in the choice between the two surgical procedures were the localization of the tumor and its extension in mediastinum.

Beside tumor charachteristics, the patient conditions and the preference of the surgeons were crucial in the surgical strategy.

The assessment of the tumor charachteristics were performed through an endoscopy of the upper GI with ultrasonography.

Additionally to the standard preoperative investigations as blood work, ECG, imaging of the lungs, the assessment of the perioperative risk (with particular attention to the possibility of standing a 2-3 hours long on-lung ventilation regimen) was based on the ASA classification and a measurement of the lung function, including a spirometry and an emogas analysis.

Pathological assessment

All specimens were examined in our pathologic institute. The pathological assessment was performed per standard guidelines and based on the 2010 UICC TNM staging system (Sobin et al., 2011).

In patients undergoing preoperative chemo- or radiochemotherapy the tumor regression was assessed per Becker et al (Becker et al., 2003).

Lymph nodes were sent altogether with the main specimen and separated from the pathologist. The R status was assessed based on both the resection margins and the deepest layers of resection. An intraoperative pathologic examination of frozen sections of the resection margin was performed in order to avoid R1 resections.

Follow Up

All patients received a follow-up in our multidisciplinary out-patient clinic (tumor therapy center) according to the german guide-lines (Tab. 4)

	Phisical	Blood work	Thorax X-Ray	CT	Abdome Uktrasound	Gastroscopy
3 Months	X	X	X		X	
6 Months	X	X		X		X
9 Months	X	X	X		X	
12 Months	X	X		X		X
18 Months	X	X	X		X	
24 Months	X	X		X		X
36 Months	X	X	X	X	X	X
48 Monts	X	X	X	X	X	X
60 Months	X	X	X	X	X	X

Tab. 4: Follow up schedule applied.

In the presence of recurrence the case would be multidisciplinary evaluated and eventually a systemic or surgical treatment scheduled.

The follow-up was performed in our center for at least 5 years postoperatively; afterward the patients were discharged into the care of their general practitioner.

Statistical Analysis

Survival Analysis

Differences in 30d mortality were investigated using the χ^2-test. Survival analysis was performed using the Kaplan-Meier method for estimating survival probabilities and the log rank test for comparisons between patient groups. Median survival and hazard ratios were calculated and multivariate analysis of predictors was performed using a Cox proportional hazards model. p-values lesser than 0,05 were considered as statistically significant.

Variables with a $p<0.1$ in univariable Cox regression analysis were entered into the multivariable model.

Propensity score matching

To correct for the sampling bias in the choice of the surgical procedure, we performed propensity score matching of prognostic variables and variables that could influence the choice of the procedure. Hereby 1:1 matching with a caliper of 0.2 using the nearest-neighbour method as matching algorithm and logistic regression as estimation algorithm was employed (81).
The statistical analysis was performed using SPSS Statistics V. 23 (IBM Corp, Ehningen, Germany) with a R plugin and R version 2.1.3 (R Core Team (2015). R: A language and environment forstatistical computing. R Foundation for Statistical Computing,Vienna, Austria.URL http://www.R-project.org/). SPSS was fitted with a custom dialog for propensity score matching (Propensit score matching in SPSS).

The present study underwent the evaluation of our ethical commission and received a positive vote.

RESULTS

Baseline characteristics (Tab. 4)

270 patients were eligible for the study; 228 were male and 42 female; 91 (33.7%) underwent RTA and 179 (66.3%) were treated by TH, average age was 58.8±10.3 and 63.3±11 years respectively. Males received remarkably more often an RTA than females (35.96% vs. 18.42%). Neoadjuvant chemotherapy was administered in 191 cases, 83 (91.2%) patients undergoing RTA and in 108 (60.3%) patients undergoing TH (p=0.001). An R0 resection was achieved in 69 (75.8%) and 139 patients (77.7%), respectively (p=0.735). An extraluminal extension of the resection to adjacent organs/structures was necessary in 11 (12.1%) patients undergoing RTA and 68 (38%) undergoing TH (p< 0.001). The mean esophageal extension of the tumor was 4.8 cm and 2.7 cm in the RTA vs. TH group (p=0.001). No significant difference in the number of resected lymph nodes was detected (RTA vs. TH: 27.9 vs. 26.4; p=0.244).

Parameter		RTA	%	TH	%	P
pts.		91	*33.7*	179	*66.3*	
age (mean±SEM)		58.8±10.3		63.6±11.0		***0.001*** *
Sex	Male	82	*90.1*	146	*81.6*	*0.067* §
	Female	9	*9.9*	33	*18.4*	
ASA	1	73	*80.2*	107	*59.8*	***0.003*** §
	2	12	*13.2*	52	*29.1*	
	3	6	*6.6*	20	*11.2*	
neoadj. CTx	No	8	*8.8*	71	*39.7*	***<0.001*** §
	Yes	83	*91.2*	108	*60.3*	
UICC 2010	0	6	*6.6*	5	*2.8*	*0.114* §
	I	14	*15.4*	51	*28.5*	
	II	29	*31.9*	55	*30.7*	
	III	34	*37.4*	55	*30.7*	
	IV	8	*8.8*	13	*7.3*	
R-status	0	69	*75.8*	139	*77.7*	*0.735* §
	1	22	*24.2*	40	*22.3*	
R-status oral margin	0	87	*96.7*	166	*92.7*	*0.277* +
	1	1	*1.1*	7	*3.9*	
	X	2	*2.2*	6	*3.4*	
Grading	1	1	*1.1*	2	*1.1*	*0.358* +
	2	20	*22.0*	55	*30.7*	
	3	62	*68.1*	115	*64.2*	
	4	6	*6.6*	5	*4.1*	
	X	2	*2.2*	2	*1.1*	
extralum. ext.	No	80	*87.9*	111	*62*	***<0.001*** §
	Yes	11	*12.1*	68	*38*	
esophageal ext. [cm] mean (min-max)		4.8 (0-11)		2.7 (0-8)		***<0.001*** #
resected LN mean (min-max)		27.9 (10-63)		26.4 (5-71)		*0.244* #

* T-test, § X^2-test, # Mann-Whitney U-test, + Monte-Carlo significance

Tab. 5: Baseline characteristics: 270 patients with AEGII were surgically resected. Of these, 91 patients (33.7 %) received right thoraco-abdominal resections (RTA) and 179 patients (66.3%) underwent transhiatal abdominal resection (TH)

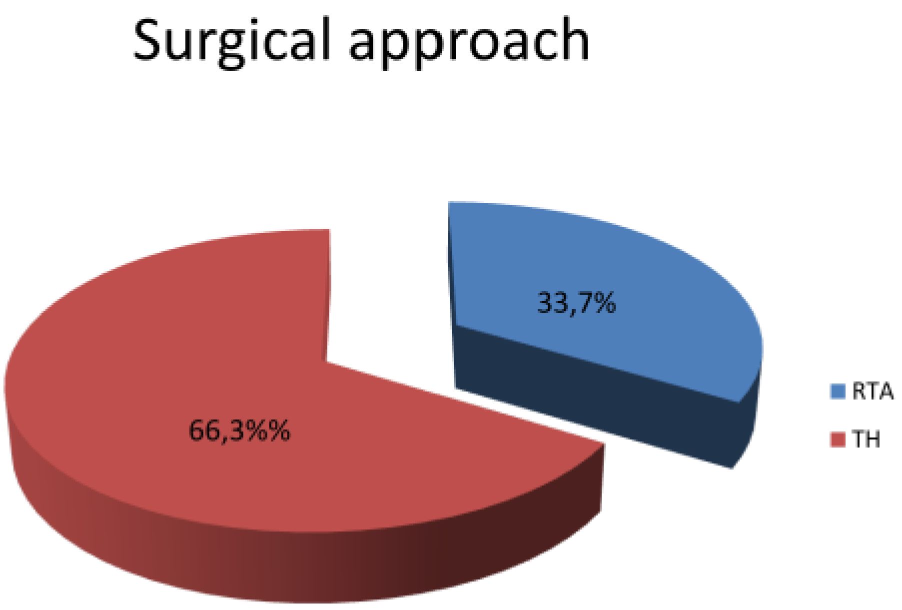

Fig. 12: 91 RTA were performed and 179 TH

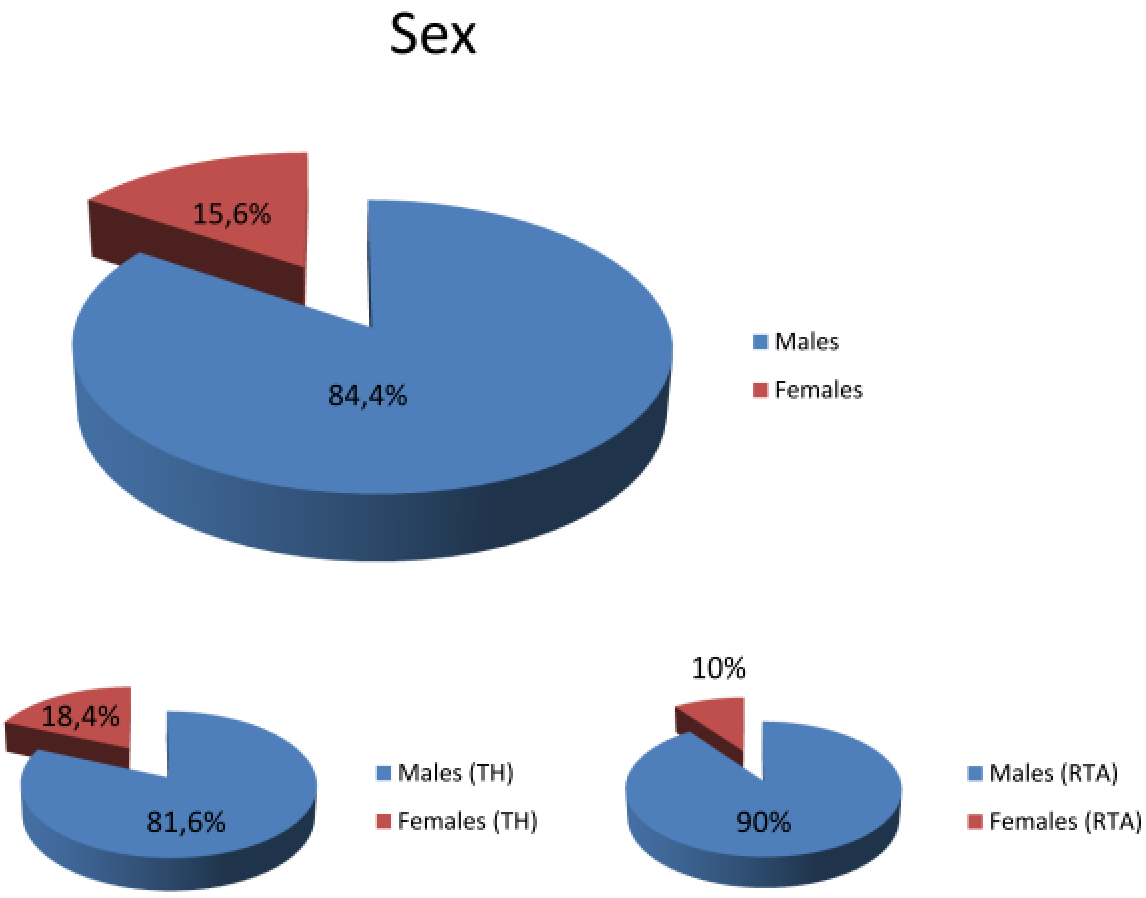

Fig. 13: In the investigated cohort (270 patients) 228 subjects were male and 42 were female.

Males received remarkably more often an RTA than females (35.96% vs. 18.42%).

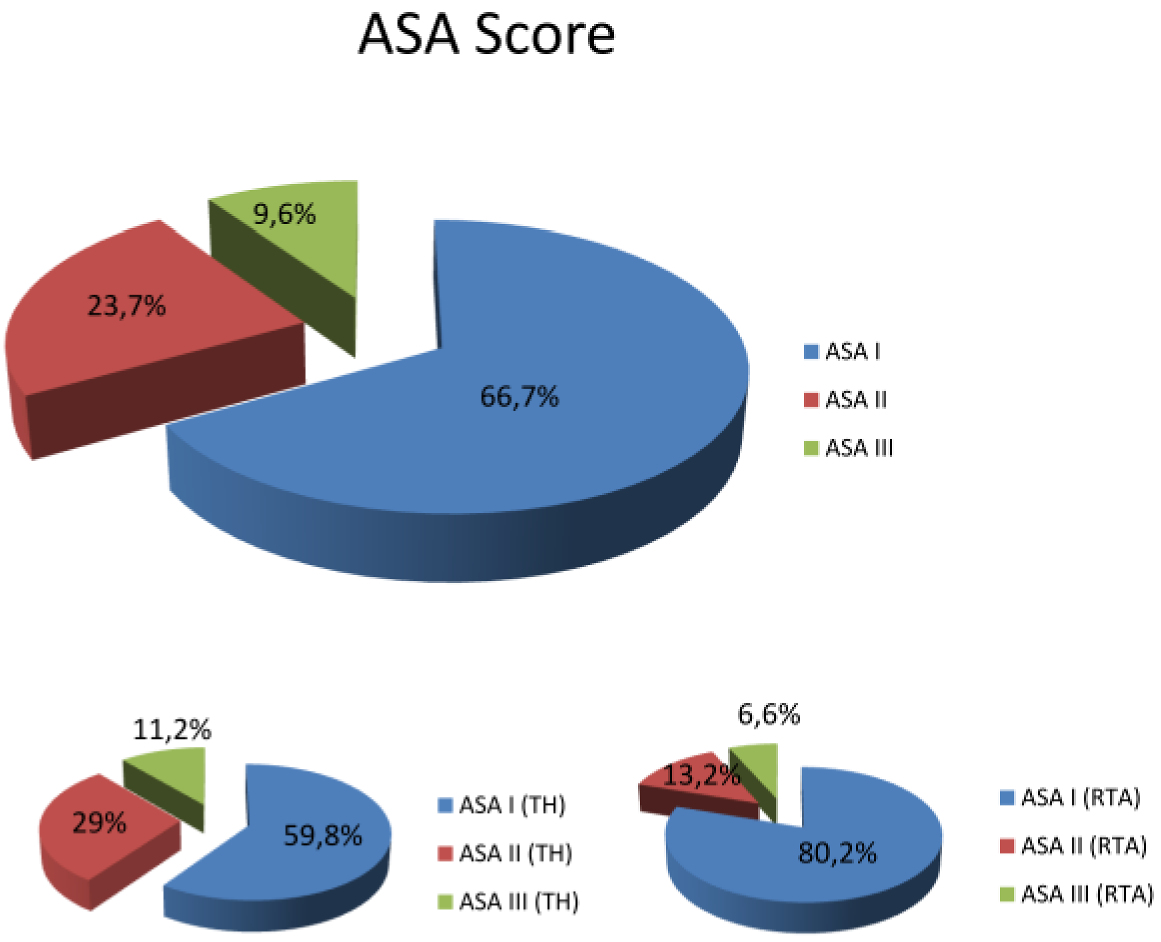

Fig. 14: Demography of ASA Score in our patients cohort

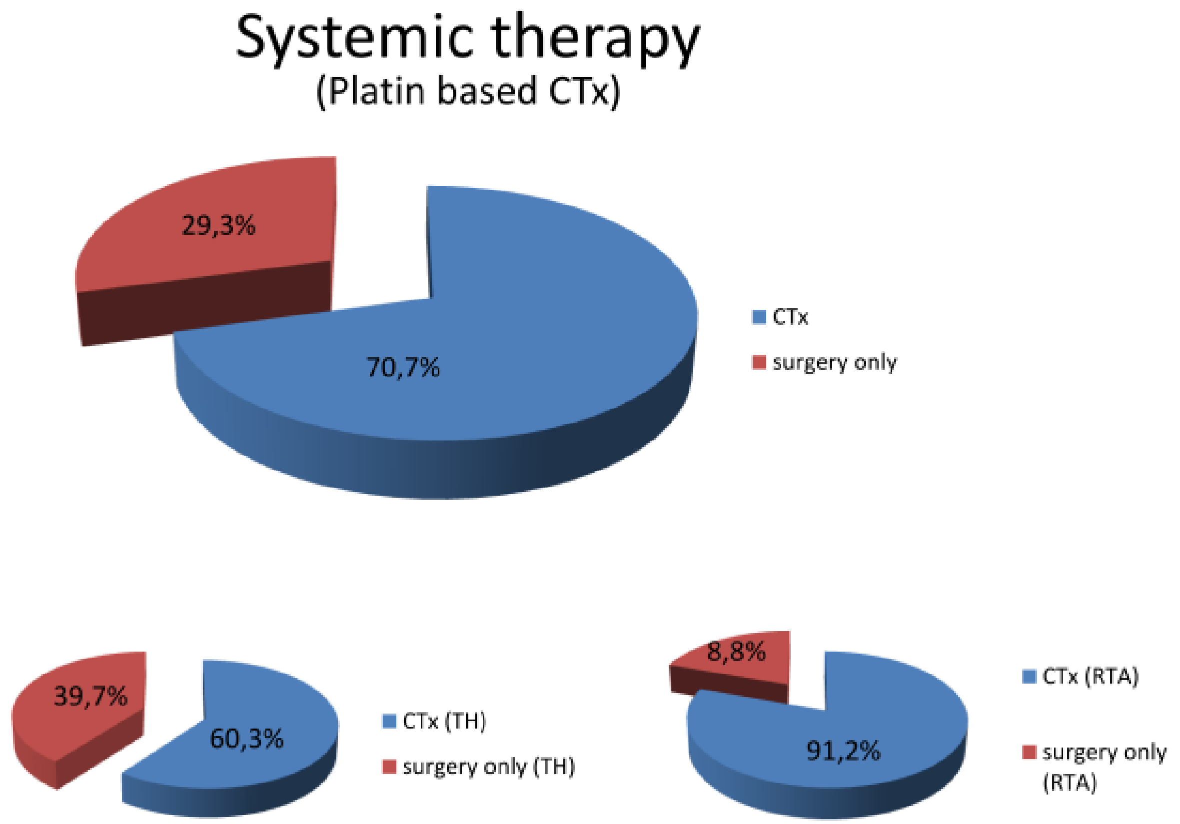

Fig. 15: Neoadjuvant chemotherapy was administered in 191 cases, 83 (91.2%) patients undergoing RTA and in 108 (60.3%) patients undergoing TH (p=0.001).

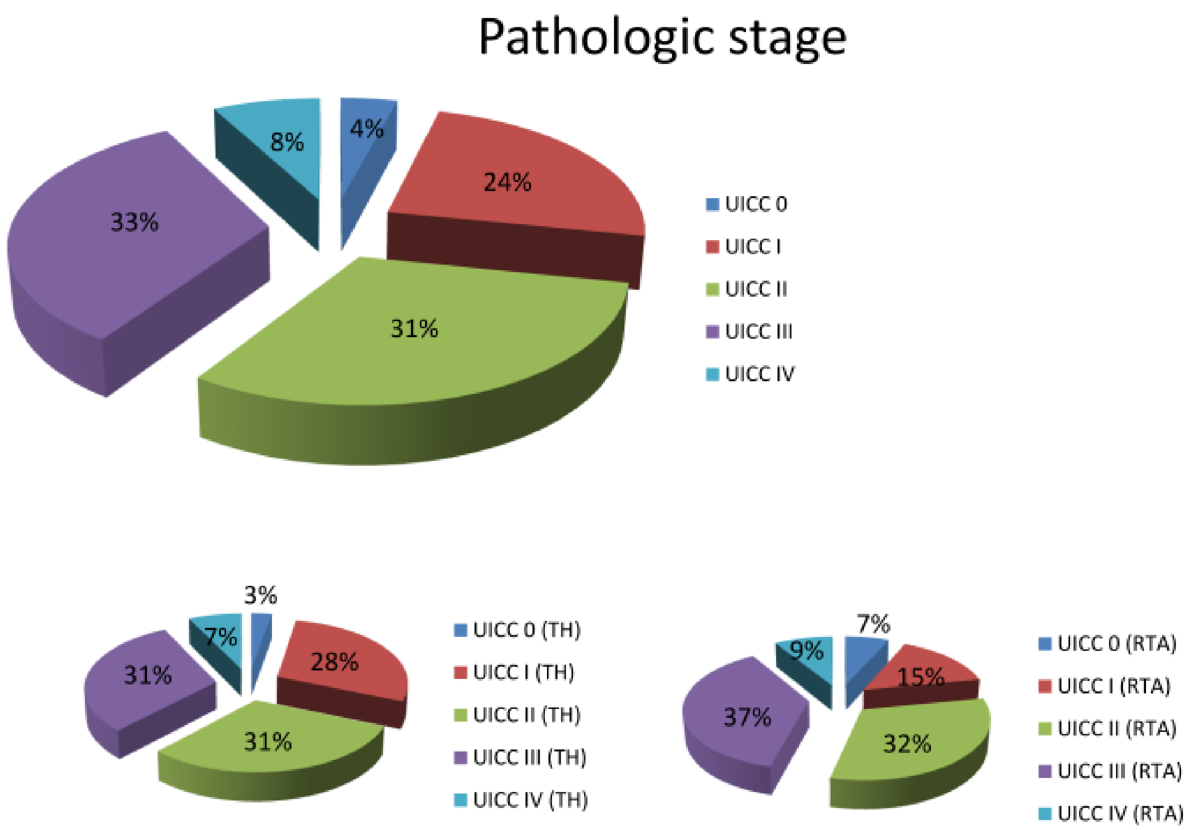

Fig. 16: Most of our patients presented a stage II tumor, the staging was slightly worse in the cohort undergoing TH

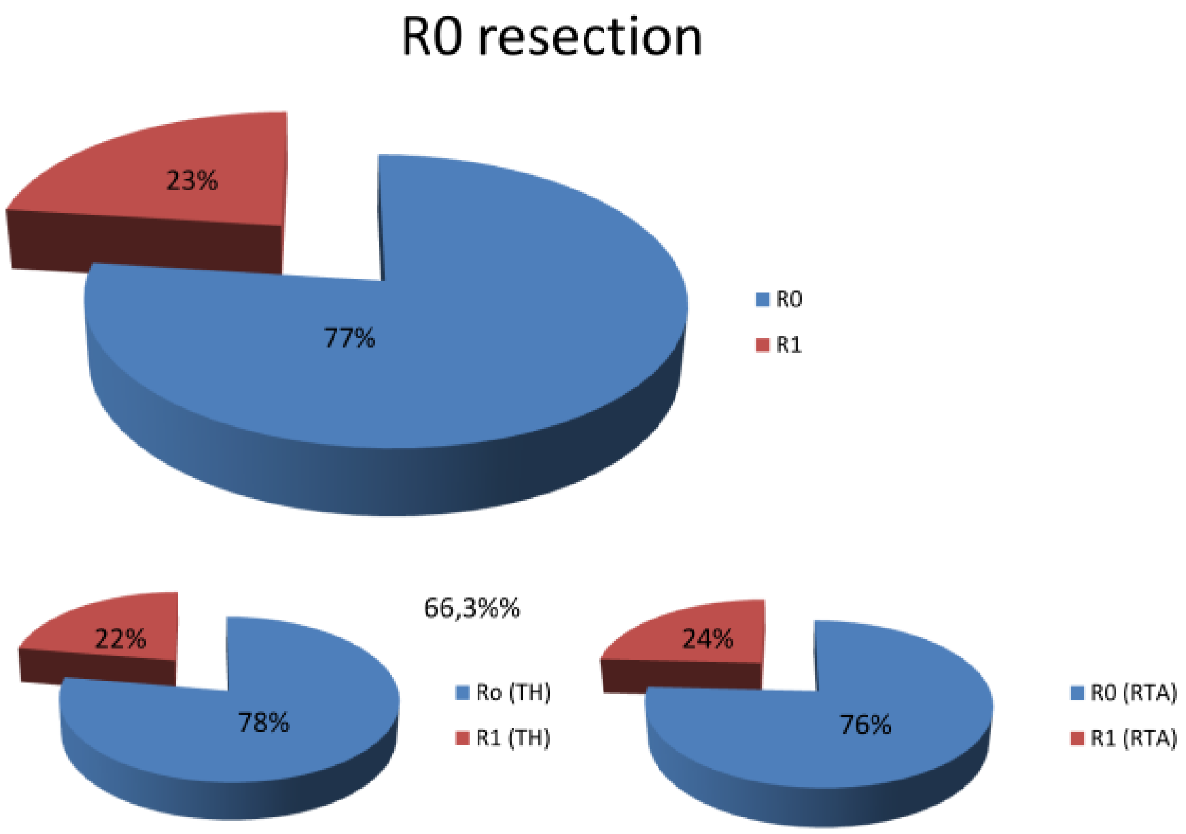

Fig. 17: the achievement of an R0 resection was relatively low, mostly due to the infiltration of the esophageal wall.

Morbidity and mortality (Tab. 6)

The RTA group showed a higher complication rate (34.1% vs. 24.6%; *p*=0.006), mostly due to anastomotic leaks (4.4% vs. 2.8%) and wound infections (12.1% vs. 1.7%).

This, however, did not translate into a higher 30 day mortality rate, which was 1/91(1.1%) in the RTA group and 8/179(4.5%) in the TH group (*p*=0.134).

parameter		**RTA**	*%*	**TH**	*%*	*p*
pts.		91	*33.7*	179	*66.3*	
30d mortality	No	90	*98.9*	171	*95.5*	*0.134*#
	Yes	1	*1.1*	8	*4.5*	
complications	None	60	*65.9*	135	*75.4*	***0.006***+
	anast. Leak	4	*4.4*	5	*2.8*	
	wound inf.	11	*12.1*	3	*1.7*	
	intraabd. abscess/peritonitis	1	*1.1*	8	*4.5*	
	other postoperative	8	*8.8*	15	*8.4*	
	Medical	7	*7.7*	13	*7.3*	

§ X^2-test, # Fisher's exact test, + Monte-Carlo significance

Tab. 6: Clinical outcomes: 30-day mortality and postoperative complications

Recurrence (Tab. 7)

The RTA group presented a higher recurrence rate (33%), which was mostly systemic. Recurrence in the TH group was observed in 23.5% of cases, which occurred mostly locally (*p*=0.025).

parameter		RTA	%	TH	%	*p*
pts.		91	*33.7*	179	*66.3*	
recurrence	None	61	*67.0*	137	*76.5*	***0.025***[§]
	R1/progression	4	*4.4*	13	*7.3*	
	local	3	*3.3*	11	*6.1*	
	LYM	7	*7.7*	5	*2.8*	
	HEP	4	*4.4*	2	*1.1*	
	PER	2	*2.2*	5	*2.8*	
	OTH	3	*3.3*	3	*1.1*	
	Multiple	7	*7.7*	3	*1.1*	

[§] Monte-Carlo significance

Tab. 7: Recurrence: Localizations

Survival

As shown in the following graphics, patients undergoing TH showed a statistically insignificant better outcome in terms of overall-survival (OS) (*p*=0.448). Median OS was 34.4±6.2 months for patients undergoing RTA and 48.6±10.7 months for the TH group (Fig. 18).

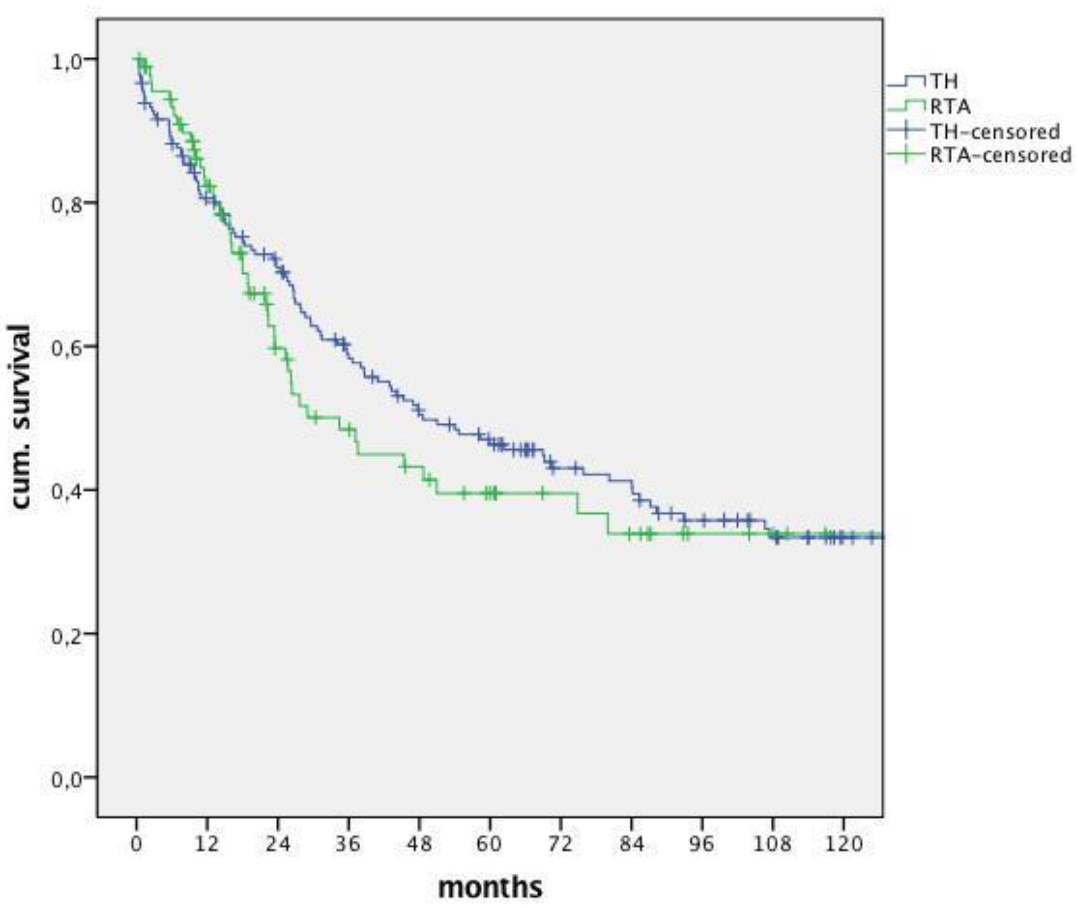

Fig. 18: Overall Survival (Median OS: RTA: 34.4±6.2 months; TH: 48.6±10.7 months), p=0.448

Disease free survival (DFS) was longer in the TH group, marginally not reaching significance-level (Median DFS for RTA vs. TH: 22.0±3.6 months vs. 43.0±7.2 months, *p*=0.085) (Fig. 19).

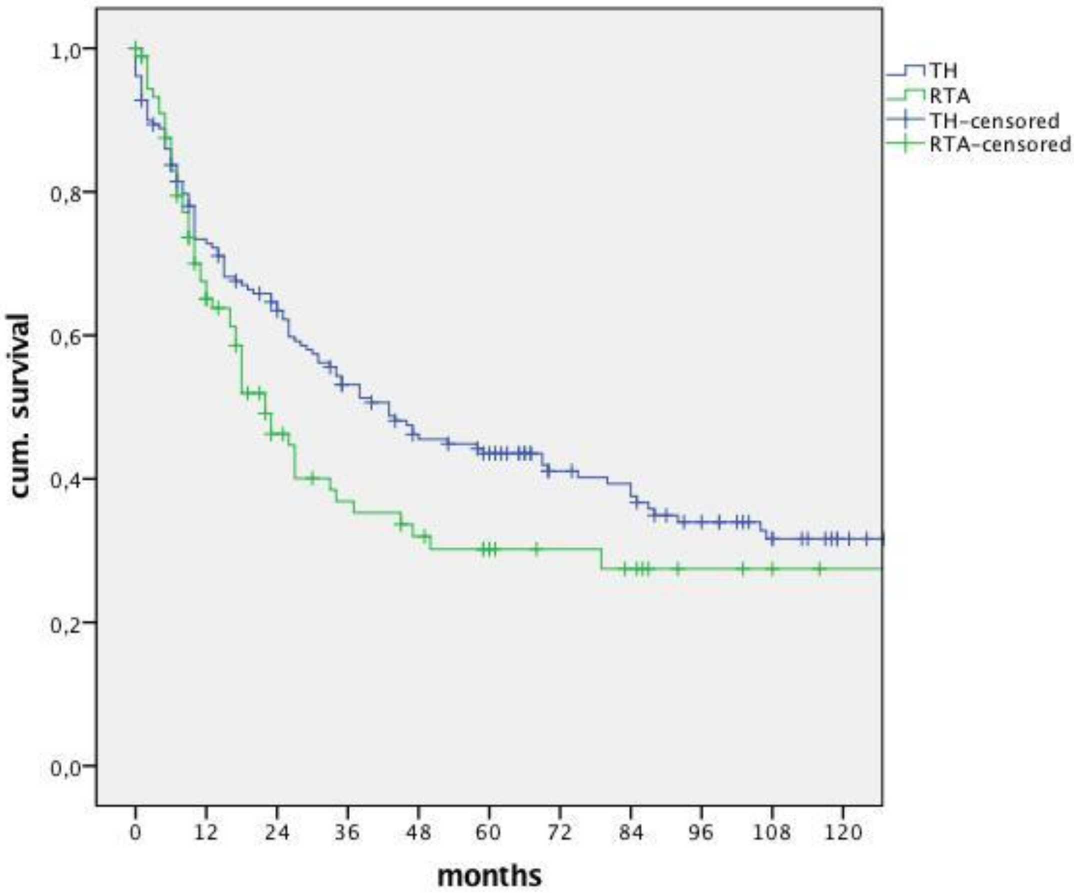

Fig. 19 Disease free survival (Median DFS: RTA: 22.0±3.6 months; TH: 43.0±7.2 months), p=0.085

Conversely the outcomes in terms of OS in patients with a tumor extending higher than 3 cm into the thoracic esophagus was better when treated by RTA than with TH. This difference, however, again did not reach significance-level (esophageal extension ≤3cm: median OS RTA vs. TH: 58,3±16,6 months vs. 25,7±3,4 months, *p*=0.064; esophageal extension >3cm: median OS RTA vs. TH: 35,9±9,4 months vs. 37,5±11,9 months, *p*=0.592) (Fig. 20a and b).

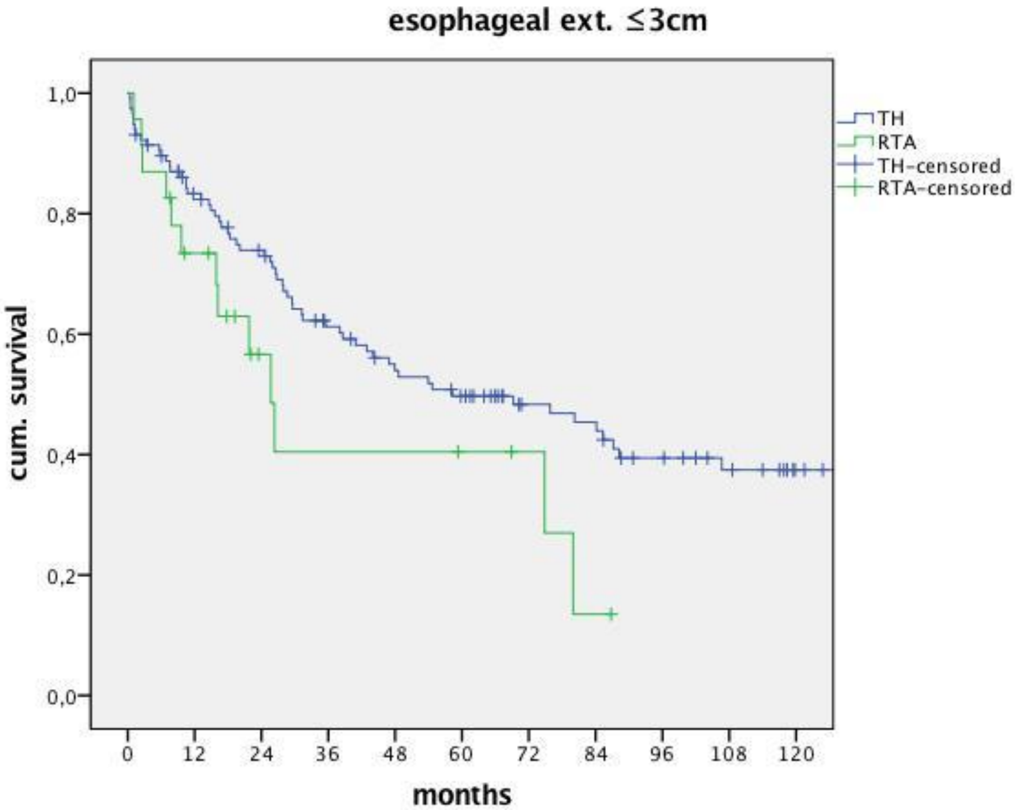

Fig. 20a: Esophageal extension <3cm: median OS RTA vs. TH: 58.3±16.6 months vs. 25.7±3.4 months, *p*=0.064

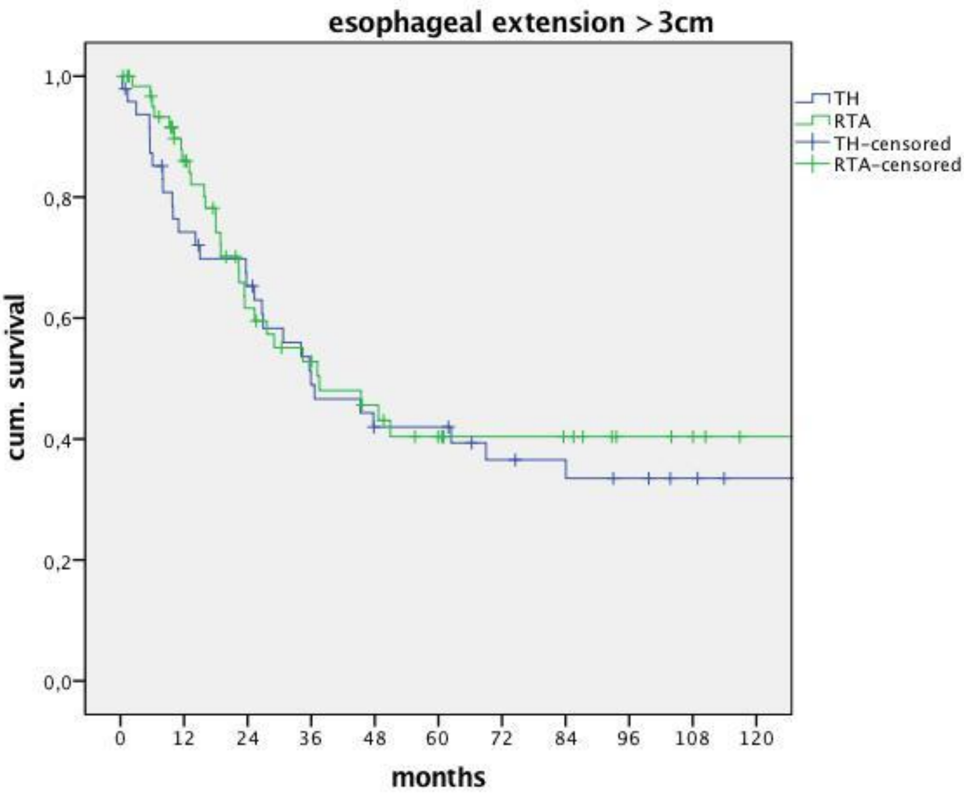

Fig 20b: esophageal extension >3cm: median OS RTA vs. TH: 35.9±9.4 months vs. 37.5±1.9 months, p=0.592

Prognostic factors (Tab. 9 and Fig. 21-23)

Age (p=0.047), ASA score (p=0.025), R-status (p<0.001) and UICC stage (p<0.001) were prognostic factors in univariable Cox regression analysis, while grading marginally failed to reach significance-level (p=0.057).

Parameter		RTA	%	TH	%	P
pts.		59	*50*	59	*50*	
age (mean±SEM)		59.0±1.4		60.8±1.6		*0.552**
Sex	Male	53	*89.8*	48	*81.4*	*0.190*§
	Female	6	*10.2*	11	*18.6*	
ASA	1	48	*81.4*	44	*74.6*	*0.132*§
	2	5	*8.5*	12	*20.3*	
	3	6	*10.2*	23	*5.1*	
neoadj. CTx	No	7	*11.9*	4	*6.8*	*0.342*§
	Yes	52	*88.1*	55	*93.2*	
UICC 2010	0	4	*6.8*	2	*3.4*	*0.814*§
	I	12	*20.3*	14	*23.7*	
	II	16	*27.1*	19	*32.2*	
	III	23	*39.0*	19	*32.2*	
	IV	4	*6.8*	5	*8.5*	
R-status	0	46	*78*	43	*72.9*	*0.521*§
	1	13	*22*	16	*27.1*	
Grading	1	1	*1.7*	0	*0*	*0.705*+
	2	17	*28.8*	19	*32.2*	
	3	37	*62.7*	35	*59.3*	
	4	2	*3.4*	4	*6.8*	
	X	2	*3.4*	1	*1.7*	
extralum. ext.	No	49	*83.1*	47	*79.7*	*0.636*§
	Yes	10	*16.9*	12	*20.3*	
esophageal ext. [cm] mean (min-max)		3.97 (0-11)		3.780 (0-8)		*0.983*#
resected LN mean (min-max)		28.2 (10-63)		26.79 (5-56)		*0.634*#

*T-test, §X^2-test, #Mann-Whitney U-test, +Monte-Carlo significance

Tab. 8. Baseline characteristics after propensity score matching: 118 patients with AEGII were matched (59 from each cohort). 105 patients undergoing TH were unmatched, 27 undergoing RTA were unmatched. No patient was discarded.

After these factors were entered into the multivariable Cox model, age, ASA-class and higher UICC stage were identified as independent negative prognostic factors for OS.

		Hazard Ratio	95% CI		Significance p-value
			lower	Upper	
Age	(yrs.)	1.020	1.005	1.036	0,017
ASA	I				0,021
	II	0.555	0.367	0.840	
	III	0.835	0.466	1.494	
UICC	0				<0,001
	I	3.334	0.447	24.855	
	II	7.283	1.000	53.043	
	III	15.471	2.141	111.777	
	IV	60.513	7.936	461.438	

Tab. 9: Independent prognostic factors (multivariable Cox analysis): Age, ASA and UICC stag

After propensity score matching (PSM) for ASA, age, UICC stage, R-status, grading, extent of esophageal involvement, neoadjuvant chemotherapy and postoperative complications there was no difference in OS (RTA: 37.5±13.6 months TH: 35.7±6.5 months , p=0.669) and DFS (RTA: 27.0±7.9 months TH: 24.0±6.5 months , p=0.535).

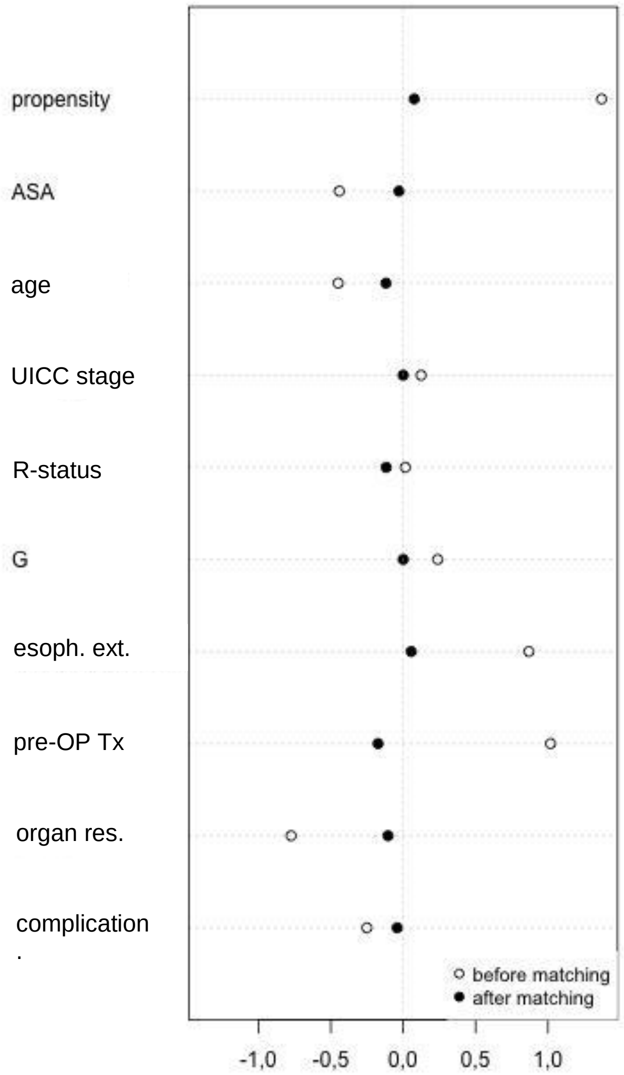

Fig. 21a: Propensity score matching to control for prognostic confounders: age>60 years, higher ECOG status, higher UICC stage and R2 resection were identified as independent negative prognostic factors for overall survival.

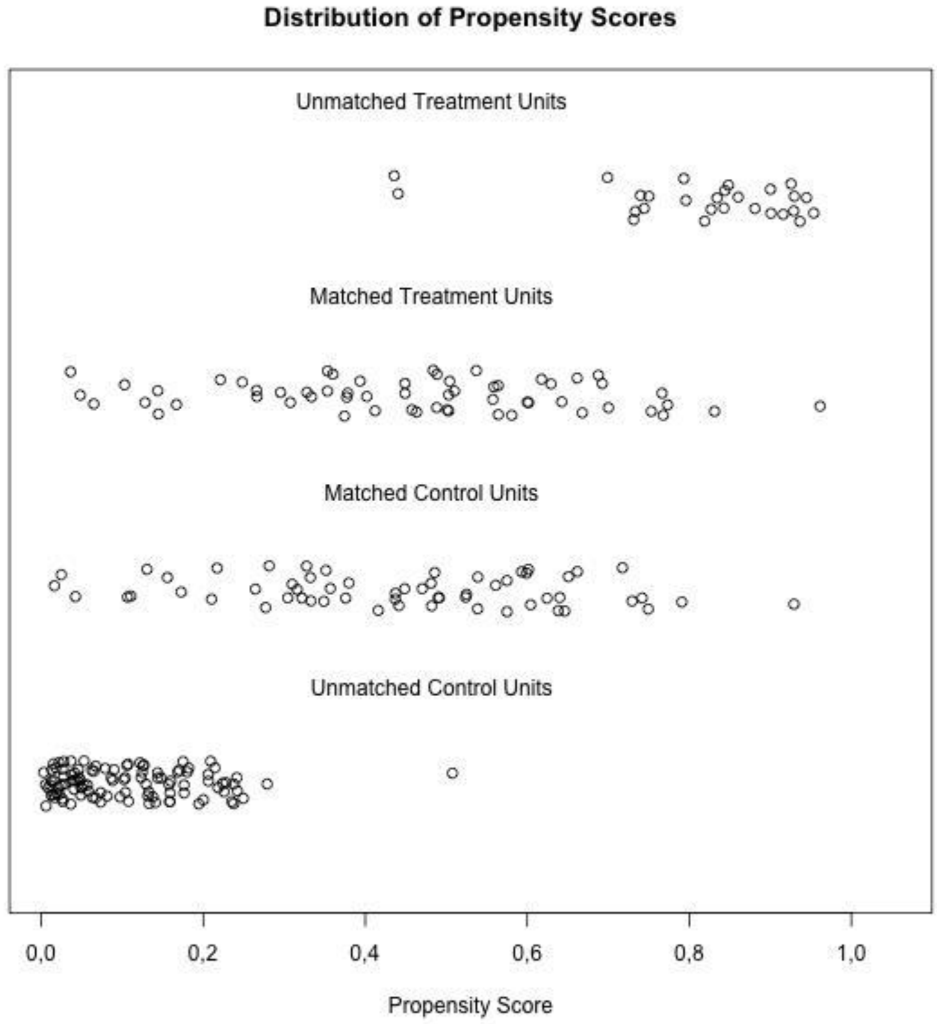

Fig. 21b: Distribution of propensity scores before and after matching

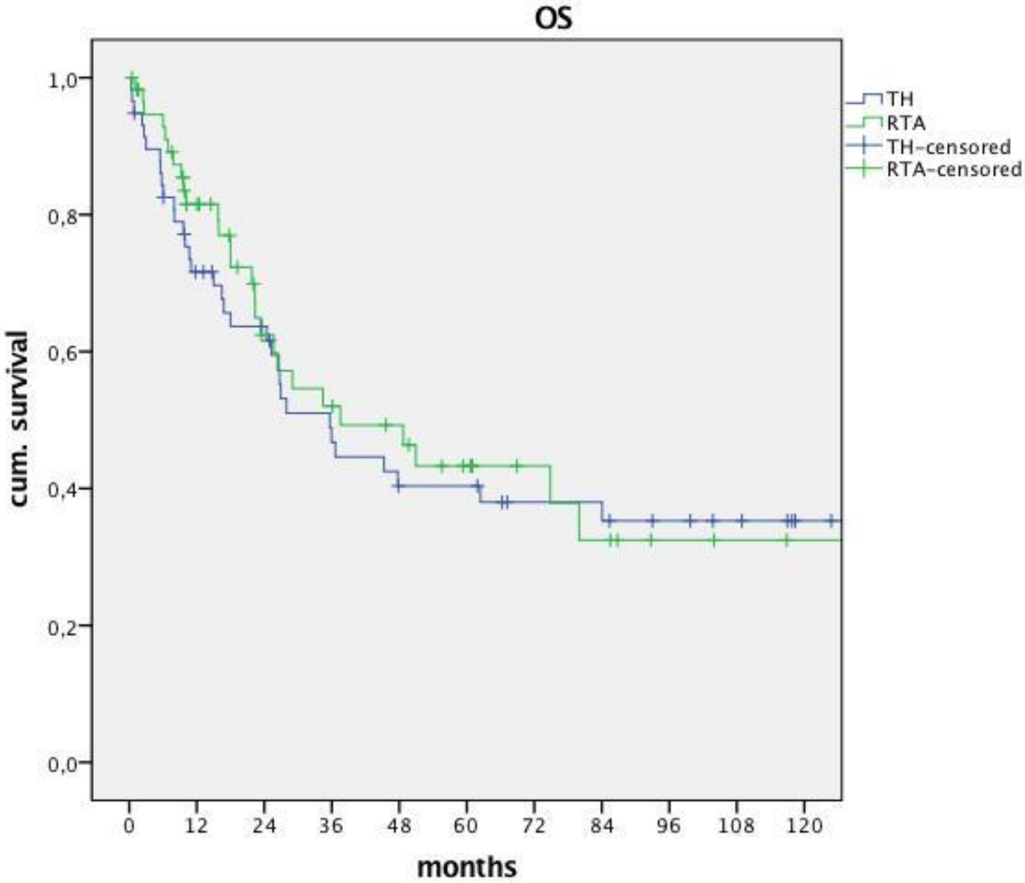

Fig. 22: OS – matched patients (n=62 vs.62). Median OS: RTA: 37.5±13.6 months; TH: 35.7±6.5 months, p=0.669

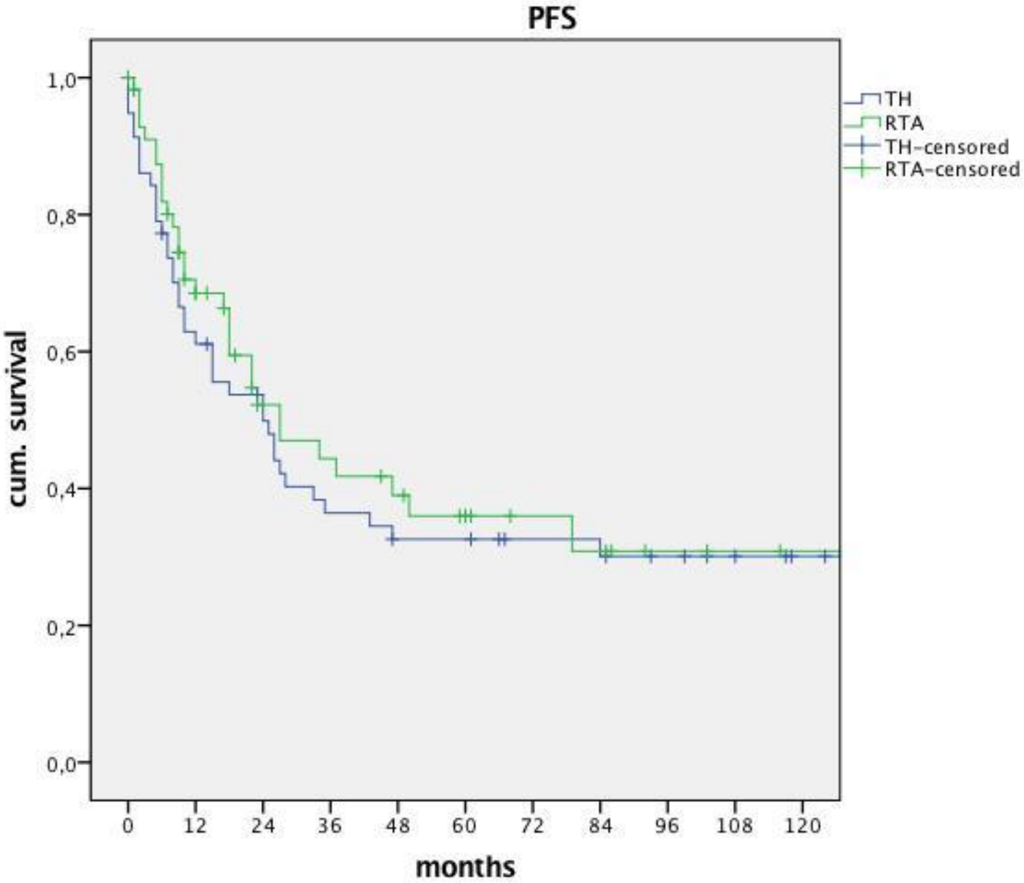

Fig. 23: DFS after matching DFS – matched patients (n=62 vs.62). Median DFS: RTA: 27.0±7.9 months; TH: 24.0±6.5 months, p=0.535.

DISCUSSION

In order to establish if there is a difference in oncological accuracy between the two techniques we compared the results of the two cohorts in terms of survival, recurrence and extension of the intrathoracic resection and of the lymph node dissection.

Survival

Based on our results, it appears that both surgical techniques are comparable from an oncologic point of view, both yielding satisfactory surgical outcomes in a high volume center.

Regarding differences in the extent of lymph node dissection, this study could not detect a statistically significant difference in outcome (neither OS nor DFS) between RTA and TH.

Conversely, OS in patients with a tumor extending higher than 3 cm into the thoracic esophagus was better when treated by RTA than with TH.

It has to be stated that this result might be influenced by a selection bias. In fact it is possible that the choice of performing a RTH rather than TH could be influenced by a better physical condition of the respective patient.

A study including AEG I, II and III (Hosoda et al., 2015) obtained results similar to this analysis, without significant difference between RTA and TH. Main predictors for poor survival were (y)pT3-4 and N3 stage stages, R1 or R2 and the absence of splenectomy. Thoracotomy could also be identified as a negative prognostic factor.

Kurokawa et al compared the 10 years follow-up data of 85 patients undergoing LTA vs. 82 undergoing TH for EJA type II and III in a multicentre prospective randomized phase 3 trial in 2015 (Kurokawa et al., 2015). The results showed no advantage in terms of OS or recurrence rate for LTA. Morbidity and mortality were, however, significantly worse after LTA. The same conclusion was reached by Carboni et al (Carboni et al., 2008).

Conversely (Omloo et al., 2007) Omloo et al. compared the two surgical approaches on 220 patients with EJA I and II and revealed a survival benefit after performing RTH but only for EJA I.

The low rate of R0 resections achieved in our study has to be noticed (75,8% and 77,7% respectively in RTA and in TH groups). This could be explained through the quite advanced stage of the disease in our cohort of patients and the fact that margin-positivity predominantly occurred in the third dimension, where radicality is limited at the aorta and no frozen sections can be obtained during surgery. In fact the R0 rate at the oral margin exceeded 90% in both groups (96,7% and 92,7% respectively in RTA and TH groups).

Recurrence

The RTA group presented a higher recurrence rate (33%), which was mostly systemic. Recurrence in the TH group was observed in 23.5% of cases, which occurred mostly locally (p=0.025).
This finding contradicts the common belief that the more invasive RTA is justified by the achievement of better oncological results. Nevertheless we cannot even state that TH guarantees better oncological results, since and UICC stage was slightly worse in the RTA cohort.

A recently published meta-analysis (Heger et al., 2017) evalued eight studies comparing the surgical and oncological outcomes of cardia adenocarcinoma patients undergoing trans-thoracic resection vs. transhiatal resection. In this study no results on recurrence rate were disclosed therefore we can hardly compare our results.

Intrathoracic extension

One of the paramount questions for the choice of the operative procedure in EJA is whether it is technically possible to obtain a safe oral margin by performing a TH and if there is an intrathoracic extension beyond which the probability to achieve an R0 resection is lower? The studies of Mine et al. (87) proposed a cutoff of 2 cm for esophageal invasion. Kurokawa et al., reached the same conclusion in a multicentre prospective randomized phase III trial (Kurokawa et al., 2015). Another study shows that a reasonable cut-off for the RTA vs TH could be an intra-thoracic extension greater than 3 cm, both in terms of survival and R0 resection achievement (mine et al., 2013). Sasako et al. evaluated the OS and the comorbidity of left thoraco-abdominal resection (LTA) vs. TH as resection for AEG II and III in an RCT on 302 patients, showing that LTA cannot be justified to treat EJA II and III if the length of esophageal invasion is 3 cm or less (Sasako et al., 2006). In fact in order to oncologically completely remove these tumors the esophageal resection should be extended very high into the thorax, a procedure which could be more safely and completely performed through a right thoracotomy.

The findings of our analysis are in line with these results. As a matter of fact, according to our findings, patients with an intra-thoracic extension of the tumor of more than 3 cm don´t seem to have a survival benefit from TH compared to RTA, as shown in Figure 3.

Lymph Node Dissection

Our results showed no significant difference in the number of resected lymph nodes (LN). This could be explained by the fact that LN-dissection in the D2-compartment was routinely performed in both groups.
However, it remains elusive if there were considerate differences in lower mediastinum node dissection, as there is no date on this specific issue. This is explicated by the fact that an "en-bloc" resection is considered mandatory and therefore the lymph nodes were left attached to the specimen without separate examination neither by the surgeon nor by the pathologist.

Nevertheless the clinical therapeutic and diagnostic role of the exact extent of lymphadenectomy in EJA is still to be clarified.

A study by Okholm et al stated that the dissection of local lymph nodes offers a significant therapeutic benefit, because the most frequent infiltrated lymph nodes (LN) are located in the nearest regional LN stations; furthermore the survival decreases as the metastasis become more distant (Okholm et al., 2014).
Another study by Yamashita et al (Yamashita et al., 2011) suggested that a clear anatomic distinction of EJA could provide insight on the appropriate extent of the lymphadenectomy. Nevertheless, the paracardial and the lesser curvature LNs must be dissected in order to achieve a proper staging and cure. The same conclusion was reached by Hasegawa et al (Hasegawa et al., 2013), stating that the involvement of further LN-stations implicates the existence of micro-metastasis beyond the limitations of the surgical field, which could be more safely controlled by systemic CTx.
Goto et al (Goto et al., 2014) detected a higher N-stage in Siewert type II rather than type III, probably due to more advanced pT-stages. These results underline the importance of -abdominal lymphadenectomy, especially of the lower perigastric LN. The actual impact of lower mediastinal lymphadenectomy could not be properly investigated in this analysis.
The minimally required number of LNs to be dissected is still considered elusive. A retrospective, exploratory study by Sisic et al (Sisic et al., 2013) evaluated the number of metastatic LNs comparing the oncological outcome in 316 EJA I and II

patients. Their results showed a high prognostic relevance of the number of dissected LNs. RTA ensures a better lymphadenectomy of the lower mediastinum, but no resection of the LNs at the greater stomach curvature and the pylorus. Conversely the standard lymphadenectomy in TH is a D2 lymphadenectomy including the LN stations #19, #20, #110 and #111 (Hosokawa et al., 2014), which allows for an improved intraabdominal lymphadenectomy, but cannot be similarly radical in the mediastinum.

Many efforts have been made in order to assess a priority in the way lymphadenectomy during resection of EJA should be performed.

In 2011 Yamashita et al. (Yamashita et al., 2011) published a study comparing the extent and location of nodal dissection to assess the survival benefit of extensive lymphadenectomy. A low incidence of LN-metastasis at the greater curvature was detected, and the index of estimated survival benefit from the dissection of stations #4d, #4sb and #6 in AEG II tumors was zero.

Hosokawa et al. reviewed the recurrence pattern of EJA after radical resection (Hosokawa et al., 2014). The most frequent routes of tumor cell dissemination in EJA II was hematogenous (lymphatic in EJA I and disseminative in EJA III). Multivariate analysis revealed that mediastinal LN-metastases were an independent prognostic indicator of poor rence-free survival. The recurrence rate in patients with mediastinal LN-metastases at the time of surgery was 100%. These data seem to suggest that mediastinal lymph node dissection may be effective for local control, but may not significantly improve prognosis.

As these data were not available for this analysis, it has to be stated that this is a major limitiation. Due to the heterogeneous data in the literature, further study on the role of optimal lymph node dissection for true EJA are required.

Morbility and mortality

In our study the RTA group showed a higher complication rate (34.1% vs. 24.6%; *p*=0.006), mostly due to anastomotic leaks (4.4% vs. 2.8%) and wound infections (12.1% vs. 1.7%). This was expected, because of the higher invasiveness of the transthoracic approach. However the higher complication rate did not influence the 30 day mortality rate, which was 1/91(1.1%) in the RTA group and 8/179(4.5%) in the TH group (*p*=0.134).

This data are comparable with the meta-analysis performed by Heger et al. (Heger et al., 2019) which showed a significantly lower rate of postoperative morbidity at comparable oncological and surgical outcomes and postoperative short-term mortality.

Propensity score matching

One of the main aims of our study was to achieve the best possible comparability in the two patients' cohorts in order to better define the actual impact of the surgical technique on the oncological and surgical outcome. PSM is a statistical method applied to reduce possible selection-bias in observational/non-randomized studies, which was initially proposed by Rubin and Rosenbaum in 1983, ruling out confounders in non-randomized studies. Ruling out the differences among the patients analyzed here propensity score (PS) matching analysis was applied as statistical method to eradicate the differences in baseline characteristics between the two treatment groups.

It is widely accepted that the best study model is a completely randomized experiment (Pattanayak et al., 2011, Heinze et al., 2011), where the assignment to treatment is blind and not at all influenced by the characteristics of patients. Only in this way the balance on background measurements such as age, sex and medical histoly can be achieved.

This kind of study is for obvious reasons (logistics, economics and above all, ethics) not always applicable. In these cases an observational study will be performed, leading to a bias in the assignment of the treatment. For example if a procedure is very risky, most likely elderly patients as much as patients with higher perioperative risk will more often receive the control procedure, i.e. the control group will have a much higher incidence of elderly or ill subjects.

To help balance this bias, patients will be subclassified based on their characteristics (covariates).

The propensity score is defined as the propability that a subject will receive a specific treatment based on the observed covariates (Austin et al., 2009). In an observational study patients are grouped based on their similar characteristics and the propensity score may differ from group to group, but it will be the same within the patients belonging to the same group.

By comparing patients with similar estimated propensity scores, an observational study can resemble a randomized experiment (Pattanayak et al., 2011).

There are three types of statistical analyses based on the propensity score (96):

- Propensity score matching
- Stratification on the propensity score

- Covariate adjustment using the propensity score.

We, as many other researchers, preferred the PSM method because it seems to be able to eliminate a greater degree of treatment selection bias, it can compare baseline characteristics between treated subjects and controls, moreover it does not require the specification of the outcomes model and it allows for estimation of risk differences and relative risk.
On the other side PSM presents as a limitation the reduction in sample size due to omission of unmatched subjects.

There are more possible algorithms:

- Greedy matching: subjects in the treatment cohort will be matched with the next control subject in the same PS even if it would be a better match to a subsequently considered treated subject.
- Optimal matching: pairs of treated and control subjects are formed so as to minimize the differences within pairs.
- 5→1 matching: a greedy matching is applied in several phases in which treated-cohort pairs will be matched on the first 5 digits of PS, then on the first four digits, and so long until they will be matched on the first digit.

After PSM, the baseline characteristics of our cohort were well balanced (Fig. 4a). In multivariate Cox analysis the impact of the surgical technique and the extent of lymphadenectomy were not as pronounced as the more “classical” factors as age, ASA and tumor stage. Conclusively, survival analysis after PSM revealed, that there were no differences in OS when the patient cohorts were balanced for possible confounders.

Limitations

Single center retrospective analysis:

The analysis was done in a single center cohort and possible selection bias seem to be present and not controlled by PSM.

Although PSM is well accepted as method to eradicate selection bias (Kim et al., 2916), there are some unmeasured factors, such as for example the biological /genetical differences and the influence of the surgeon's expertise on outcome.

Lymph node harvesting technique:

As previously discussed we performed the lymph nodes harvesting „en bloc“, id est without separating the nodes from the organ. This technique, established in the west world since UICC 1999 does not allow the assessement oft he station to which the lymph nodes belong.

CONCLUSION

The present analysis could not detect a statistically significant difference between RTA and TH from the oncologic point of view; unexpectedly RTA was not associated with higher morbidity and mortality.

Conclusively RTA for Siewert Type II EJA should be preferred whenever the oral tumor margin cannot be safely reached via a transhiatal approach. Hereby an esophageal extension of the tumor >3cm seems to be a reasonable cutoff.

This cutoff should be further tested and proved; in this regard a prospective, randomized, controlled, multiscentric trial is scheduled.

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