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Postoperative outcome and overall survival after surgery for esophageal cancer; a retrospective, single- center experience of 320 patients encompassing 14 years

Doctor thesis at the medical faculty

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Abstract:

Introduction: Surgery is considered the only curative treatment for resectable esophageal carcinoma with improving results over the last decades. Aim of the present retrospective, single- center analysis was to identify potential factors influencing postoperative morbidity and survival in patients with esophageal carcinoma subjected to surgical therapy

Patients and Methods: Patients who underwent surgery for esophageal cancer at the University Clinic of Saarland between 01.01.2001 and 31.12.2014 were included. Primary end points were postoperative morbidity and overall survival (OS) after esophagectomy. Patient- and tumor- related properties, operative and postoperative data were included in the analysis. Statistical analysis was performed using χ^2 test and binary logistic regression in case of categorical variables and Mann-Whitney U test in case of non- parametric, not normally distributed continuous variables. The distribution of continuous variables was tested with Kolmogorov- Smirnov test. Statistical significance was set at $p \leq 0.05$. Survival data were recorded by the Cancer Registry of Saarland or the house doctors, respectively. A 6 months' follow- up was routinely performed including endoscopy. Log rank test and Cox- regression were performed for survival analysis. Statistical analysis was conducted in IBM SPSS Statistics V22.0.

Results: 320 patients with esophageal cancer were treated in the University Clinic of Saarland from 01.01.2001 and 31.12.2014. Men/ women ratio was 268:52 (83.8%:16.2%), median age of patients at time of operation was 63 years (28- 88 years). More than half of the patients (n=179) were subjected to abdomino- thoracic esophageal resection (TAE) with intrathoracic anastomosis *(*55.9%). Transhiatal esophagectomy (THE) with intraabdominal anastomosis was performed in 59 patients (18.4 %), abdomino- thoracic esophageal resection with cervical anastomosis in 52 patients (16.3 %), and transhiatal esophagectomy with cervical anastomosis in 30 patients (9.4 %), respectively. In 222 patients (69.4 %) a hand- sewn, double- row, end- to- end anastomosis was performed, whereas 98 patients received a stapled, end- to- side anastomosis (30.6 %). Median overall survival was 17 months (0, 146.5 months). The 1-, 3- and 5 –year survival rates were 65.2%, 41.7%, and 30.7%, respectively. The 30-, 60- and 90- day mortality rate was 5.9% (19/320), 9.4% (37/320), and 12.8% (41/320), respectively.

12.5% (40/320) of patients had a minor postoperative complication (Clavien- Dindo grade I- II). 26.9% (86/320) of patients experienced a major postoperative complication (Clavien- Dindo grade III-IV), thus requiring surgical, endoscopic or radiological intervention or management in Intensive Care Unit (ICU). 12.8% (41/320) of patients had a lethal postoperative complication (Clavien- Dindo grade V). In 47.8% (153/320) of patients, the postoperative course was uneventful.

Advanced tumor stage, SC histological subtype and presence of major or lethal postoperative complications Clavien- Dindo grade III- V were significant, independent factors for worse OS ($p<$ 0.001, OR= 0.239, $p=$ 0.028, OR= 1.506, and $p=$ 0.005, OR= 0.582, respectively).

Female gender, anastomotic leak and respiratory complications were significant, independent factors for higher rate of major and lethal postoperative complications (Clavien- Dindo III- V) after resection for esophageal cancer in the multivariate regression analysis with $p=$ 0.002, OR= 0.417, $p<$ 0.001, OR= 0.028, and $p<$ 0.001, OR= 0.121 respectively.

Anastomotic leak was significantly related with presence of COPD ($p=$ 0.026, OR= 2.109, 95% CI= 1.096- 4.061. Neoadjuvant therapy, surgical experience, type of surgery and type of anastomosis did not significantly influence the rate of anastomotic leak ($p=$ 0.853, OR= 0.942, $p=$ 0.274, OR= 1.264, $p=$ 0.893, OR= 1.023, and $p=$ 0.471, OR= 0.772, respectively).

Intrathoracic stapler anastomosis as part of an abdomino-thoracic esophageal resection rendered better postoperative results (n=176), in terms of anastomotic leak and stricture, in comparison to hand- sewn anastomosis (8% vs. 14.3%, p= 0.22, 6% vs. 13.5%, p= 0.10, respectively), however not reaching statistical significance. In addition, 90- day mortality was significantly lower in the stapler anastomosis group (2% vs. 13.5%, $p=$ 0.02 respectively), due to the higher rate of reoperations in the hand- sewn anastomosis group (8% vs. 34.1%, p= 0.001).

Conclusions:

Esophageal surgery for cancer is associated with a high risk for major surgical complication. Advanced tumor stage, histological subtype (squamous cell carcinoma), and major or lethal postoperative complications Clavien- Dindo grade III- V were significant, independent factors for worse OS after resection for esophageal cancer. In conclusion, any efforts improving surgical performance are mandatory, since continuous improvements in this field will result in a better patient outcome.

1. Introduction:

1.1 Epidemiology.

The squamous- cell esophageal carcinoma is worldwide the most frequent histological type of esophageal tumor. The incidence varies in different geographical areas. Areas with high incidence rates of esophageal cancer are Iran, central China and South Africa with 200 new patients every year per 100.000 inhabitants. In the western countries however, esophageal adenocarcinoma is more frequently diagnosed than squamous- cell esophageal carcinoma.

The incidence of esophageal cancer in Germany is about 4-5/ 100.000 residents in males, and 0.5- 1/ 100.000 in female patients. Esophageal cancer was diagnosed in approximately 1.050 women and 3.900 men in Germany according to the “Robert Koch” institute in the year 2000 (I). The median age of patients with esophageal cancer is 65 years. 70 % of patients with esophageal carcinoma are diagnosed with advanced tumor stages (UICC III and IV) [1].

In Western countries, more than 80% of squamous-cell esophageal cancer (SCC) is associated with tobacco and alcohol consumption. Various predisposing factors for SCC were suggested in the past of which the most important are: Plummer- Vinson syndrome, celiac disease, sclerodermia, pernicious anemia, esophageal diverticuli, intoxication with acid and previous radiotherapy in the neck or the thorax [1]. On the other hand, obesity, chronic reflux disease and intestinal (Barrett) metaplasy were identified to be risk factors for AEG [1].

The adenocarcinomas of esophagus within 5 cm up and down the cardia are called adenocarcinomas of the gastroesophageal junction (AEG) according to international consensus.

The 5-year overall survival of patients with esophageal cancer remains poor, reaching 5% in some reports [1]. An increase of 5- year survival was however reported in Germany from 10% in 1980 to 20% in 2010, presumably due to the evolution of new therapeutic modalities (I).

1.2 TNM, UICC-, AEG- classification.

The human esophagus has a mucosa consisting of a squamous epithelium without keratin, a smooth lamina propria, and a muscularis mucosae. Esophageal carcinoma is divided in squamous- cell carcinoma, adenocarcinoma and adenocarcinoma of the gastroesophageal junction (AEG). Adenocarcinoma of the esophagus may be related to acid reflux, resembling a disorder of the lower esophagus known as Barrett esophagus [B1]. The most recent TNM and UICC classification in its seventh edition dates from January 2010 and is presented in tables 1- 4 [I]. The changes in the actual TNM, UICC classification compared to previous staging systems are: the exact number of the infiltrated/ tumorous lymph nodes is recorded due to its prognostic value. N1 means 1-2 lymph node metastases, N2 means 3-6 lymph node metastases and N3 more than 6 lymph node metastases. The pathological specimen should include >6 lymph nodes (LN). Positive infraclavicular LN or positive LN of the celiac trunk are no longer considered distant metastases (M1, stage IV disease). Squamous- cell carcinoma, adenocarcinoma and adenocarcinoma of the esophageal junction (AEG) are all classified as esophageal carcinoma. The argumentation in favor of the new classification is based on the similar prognosis of AEG and esophageal carcinoma, which is worse compared to gastric carcinoma of other locations.

The **Siewert classification system** is used for adenocarcinoma located at the gastro-esophageal junction. The junctional adenocarcinoma is divided into 3 subtypes [2, 3] (figure 1). The division is based upon the localization of the tumor center in relation to the cardia. The term cardia refers to the transition zone between the two- layer muscle of the esophageal and the three- layer muscle of the gastric wall. Cardia can precisely be identified only in the pathological specimen because the esophagus is not covered with serosa. The transition zone between squamous and cylindric esophageal epithel (Z-line) cannot be used to classify AEG, because the Z-line is subjected to changes in reflux disease (Barrett metaplasy). The transitional zone from esophagus to stomach can precisely be identified by endoscopy, where the proximal margin of gastric plication is the main point of orientation [2].

The 3 subtypes of AEG are:

- AEG I: The tumor center is localized until 5 cm orally from cardia.
- AEG II: The tumor center is localized directly in the cardia.
- AEG III: The tumor center is localized below the cardia.

The AEGs are divided according to Siewert et al. in 3 types [2] : the AEG of type I is the distant esophageal adenocarcinoma arising from Barrett mucosa with contact to the Z- line. The AEG of type II is the carcinoma of the gastric cardia and the AEG of type III is the subcardial carcinoma, localized in the stomach but still being in contact with the Z- line. This classification has gained broad acceptance, because the type of surgery depends on the localization of the tumor with respect to the gastroesophageal junction. The various surgical procedures for esophageal cancer are thoroughly described below.

Table 1. Primary tumor (T)[a,b]

Tx	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Tis	High-grade dysplasia.
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa.
T1a	Tumor invades lamina propria or muscularis mucosae.
T1b	Tumor invades submucosa.
T2	Tumor invades muscularis propria.
T3	Tumor invades adventitia.
T4	Tumor invades adjacent structures.
T4a	Resectable tumor invading pleura, pericardium, or diaphragm.
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.

[a](1) At least maximal dimension of the tumor must be recorded, and (2) multiple tumors require the T(m) suffix.

[b] High-grade dysplasia includes all noninvasive neoplastic epithelia formerly called carcinoma in situ, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.

Table 2. Regional lymph nodes (N)[a]

Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastases in 1–2 regional lymph nodes.
N2	Metastases in 3–6 regional lymph nodes.
N3	Metastases in ≥7 regional lymph nodes

[a] Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastasis.

Table 3. Distant metastasis (M)

M0	No distant metastasis.
M1	Distant metastasis.

Table 4. Histologic grade (G)

Gx	Grade cannot be assessed—stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated—stage grouping as G3 squamous

UICC Classification

Stage	T	N	M	Grade
0	Tis (HGD)	N0	M0	1, X
IA	T1	N0	M0	1-2, X
IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any

	Any	N3	M0	Any
IV	Any	Any	M1	Any

Restrictions of the new TNM, UICC- staging system. The new staging system for esophageal cancer is mainly based on retrospective data from the Japanese committee for registration of esophageal cancer. It is therefore most applicable to patients with squamous cell carcinomas of the upper third and middle third of the esophagus in contrary to the increasingly common distal esophageal and gastroesophageal junction adenocarcinomas in Western countries [4].

The lymph node involvement was revised in the new classification system; in particular, the previous characterization of involved abdominal lymph nodes as M1 disease was revised in the new classification system. Positive infraclavicular lymph nodes or positive lymph nodes of the celiac trunk are no longer classified as distant organ metastases (M1, stage IV disease). This change in the classification system indicates that tumorous infiltrated abdominal lymph nodes do not worsen the prognosis in contrast to remote organ metastases [5]. This alteration in the new staging system led to more liberally indicating surgical treatment, as regional lymph node involvement and/or positive lymph nodes of the celiac trunk should not be considered irresectable. Complete resection of the primary tumor (R0 resection) and lymphadenectomy of tumor- involved lymph nodes should therefore be performed.

In the new TNM-system the adenocarcinoma of the esophagogastric junction (AEG) is classified similar to the esophageal carcinoma. The reason was the similar prognosis of AEG and esophageal carcinoma, which is worse than that of gastric carcinoma in other sites [6][4]. The TNM- Classification has both prognostic and therapeutic value.

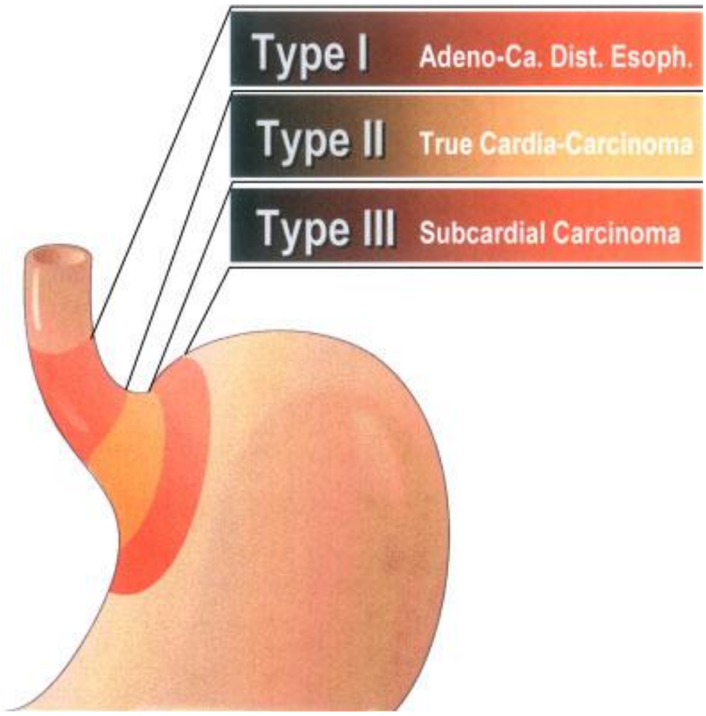


Figure 1: Topographic-anatomic classification of adenocarcinomas of the esophago–gastric junction (AEG) based on their relationship to the endoscopic gastric cardia.[3].

1.3 Diagnostic work- up. The preoperative diagnostic work- up includes an esophagogastroduodenoscopy with biopsy sampling, an endosonography and computed tomography (CT). The endoscopy plays a key role in diagnosing esophageal cancer; it provides preoperative information about the localization of the tumor and the tumor identity with the acquisition of specimen for histopathologic examination. In patients with dysphagia due to inoperable esophageal cancer or tumor recurrence, the enteral feeding of the patient can be enabled by percutaneous endoscopic gastrostomy (PEG). A PEG can also be used in patients who are no candidates for surgery because of cachexia to enhance the nutritial status before surgical treatment.

In patients with positive lymph nodes, neoadjuvant treatment could be considered prior to surgery. The preoperative T- and N- stages are estimated with endosonography (EUS). Detection of tumor infiltration of lymph nodes in the preoperative endosonography may determine the therapeutic strategy. Endoscopic ultrasound (EUS) can detect lesions of esophageal cancer and accurately determine the T stage. In a recent meta-analysis of EUS in esophageal cancer, sensitivity and specificity of EUS on esophageal cancer were 81.6% and 99.4% in T1, 81.4% and 96.3% in T2, 91.4% and 94.4% in T3, and 92.4% and 97.4% in T4, respectively [7]. The opportunity of endoscopic submucosal dissection requires presurgical detection of early cancer lesions without lymph node metastases [8].

Preoperative computed tomography (CT) is performed to detect remote organ metastases (M-stage) and to describe local infiltration of T4 tumors. [9].

Some studies support the use of PET-CT to detect distant organ metastases [10-14]. However, the value of 18F- FDG- PET- CT (fluorine-18 fluoro-2-deoxy-D-glucose-positron emission tomography combined with computed tomography) in the preoperative diagnostic work- up for esophageal cancer is currently under investigation. For example, the pre SANO trial investigates, whether FDG- PET- CT may accurately detect residual disease after neoadjuvant radiochemotherapy [15]. In fact, FDG- PET was not used in our institution for preoperative diagnostic work- up, whereas preoperative evaluation of pulmonary and cardiologic function was frequently performed in order to estimate the patient´s perioperative risk.

1.4 Therapeutic strategies. The therapy of esophageal cancer is interdisciplinary and depends on tumor stage and patient’s co- morbidities. Endoscopic therapy can be performed in patients with very early tumor stages (uT1a) and without lymph node involvement, whereas neoadjuvant treatment followed by surgical resection is usually performed in patients with advanced tumor stages (≥T3 and /or any N+) in the absence of distant organ metastases. The therapeutic plan is individually set for every patient within an interdisciplinary tumor board, in which surgeons, gastroenterologists, and radiotherapists take part.

1.4.1 Surgery for esophageal cancer.

Various surgical procedures were used for esophageal cancer patients during the reported period, of which a brief history and description are presented in the following.

S. Meltzer and J. Auer introduced the use of general anesthesia with positive- pressure ventilation under tracheal intubation in 1909 in the United States of America (USA) [16]. This advance has allowed F. Torek to perform the first successful transthoracic esophageal resection for cancer with left thoracotomy under general anesthesia in the USA [17]. Continuity of the gastrointestinal tract was provided by an external "rubber tube" that was put between the cervical esophagostomy and the gastrostomy. The patient has survived 13 years and was able to swallow liquid food. Direct reconstruction of the gastrointestinal tract after an esophagectomy with esophago -gastrostomy was performed in the mid- 1930s for the first time.

The main surgical procedures performed in our department were: transhiatal esophagectomy (THE), Ivor- Lewis abdomino-thoracic esophagectomy with intrathoracic anastomosis, and Mc Kewon abdomino-thoracic esophagectomy with cervical anastomosis.

Transhiatal esophagectomy (THE). The British surgeon G. G. Turner carried out the first successful transhiatal esophagectomy for cancer in 1933[18]. The continuity of the alimentary tract was reestabilished in a second operation using an antethoracic skin tube. In the following years, transhiatal esophagectomy without thoracotomy (THE) was performed only sporadically, usually as part of laryngopharyngoesophagectomy for pharyngeal or cervical esophageal carcinoma. The stomach was used to restore continuity of the alimentary tract. Kirk used this surgical procedure for palliation of unresectable esophageal carcinoma in 5 patients. Orringer “rediscovered” this technique for esophageal cancer in 1976. He supported THE because of avoidance of (1) combined thoracic and abdominal incisions in patients with esophageal obstruction and (2) a mediastinal anastomosis with its potential for mediastinitis due to leakage. In 2007, Orringer et al. retrospectively published the surgical results of THE in 2000 patients from 1976 until 2006 [18].

In the original procedure performed by Orringer in 1976, the esophagus was mobilized using two incisions, an upper abdominal incision and a second incision on the left side of the neck.

After removal of the esophagus, the remaining short segment of esophagus was attached to the stomach by means of a cervical esophagogastric anastomosis. An obvious advantage of the transhiatal esophagectomy is, that no opening of the thorax is required [18].

The transhiatal esophagectomy was also performed in our institution. In this surgical procedure, the hiatus esophagei is opened and the distal esophagus is mobilized. The surgeon can estimate at this point, if the tumor is resectable without opening the thoracic cavity. In the transhiatal esophagectomy, the stomach may be used for interposition, the so called gastric tube, otherwise total gastrectomy with resection of the distal esophagus is performed. In the preparation of the stomach, the A. and V. gastroepiploica dextra are identified and then resected. In the middle of the major curvature, the A. gastroepiploica sinistra can be separated. Preparation of the major gastric curvature is followed by the preparation of the minor gastric curvature. The left gastric artery is dissected. Lymphadenectomy is standardized. D2 dissections (N2 level) add the removal of nodes along the left gastric artery (station 7), common hepatic artery (station 8), celiac trunk (station 9), splenic hilus, and splenic artery (station 10 and 11). The lymph nodes of the lower mediastinum are also removed. In the reconstruction phase, esophagojejunostomy is performed [2]. Anastomosis was mainly hand-sewn from 2001 until 2012 in our institution and changed towards a stapler anastomosis.

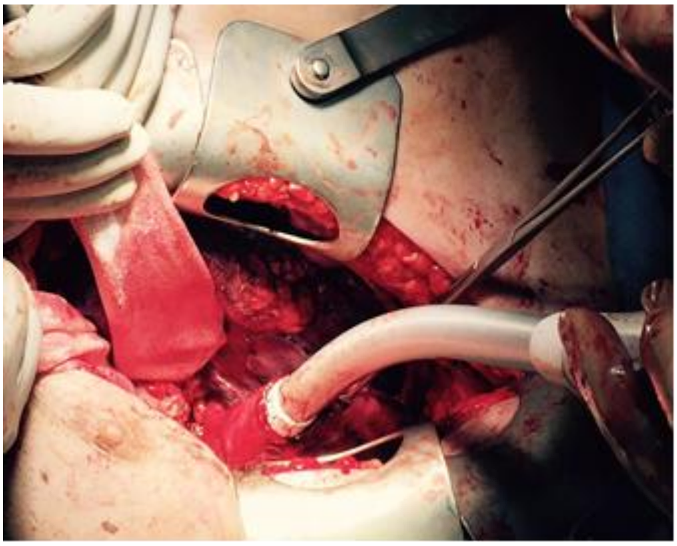
Abdomino- thoracic esophagectomy. After the first experience with esophagectomy, the proximal and distal remnants after resection were brought out subcutaneously and connected by external plastic tubes, skin tubes, or flaps. In 1933, Ohsawa reported the use of the stomach for orthotopic reconstruction of the resected esophagus. This technique was used in 18 patients in Japan [19]. Ohsawa performed a combined left thoracoabdominal incision for carcinomata of the lower third of esophagus.

Ivor Lewis described the right thoracoabdominal esophageal resection and reconstruction in 1946. He compared his technique to the left- sided approach and reported improved access to the 2 upper thirds of esophagus through the right- sided approach, the exposure of the whole esophagus after ligation of the azygos vein and the protection of the contralateral pleural cavity covered by the descending thoracic aorta [20]. The surgical procedure consists of a median laparotomy, where the stomach is mobilized for the preparation of the gastric tube.

The esophagus is then resected in the level of azygos vein through a right thoracotomy incision along the fifth intercostal space, and an intrathoracic esophagogastric anastomosis is performed. The anastomosis is performed with the circular stapler in end-to-side technique, the stapler is inserted over the open end of the gastric tube (“Krückstock”). The stapled anastomosis was sometimes oversewn with single 4-0 PDS stitches in our department.

The gastric conduits were routinely performed according to Kirschner/ Akiyama [21]; in three patients (3/179, 1.7%) a fundus rotation gastroplasty was performed to achieve longer gastric tubes and better blood supply [22]. In the conventional Kirschner- Akiyama gastric tube, the „neo- esophageal“ blood supply relies mainly on the right gastroepiploic vessels. The rationale of fundus rotation gastroplasty is the preservation of most of the arterial arcade along the minor curvature of the stomach [22]. In the experimental setting it has been demonstrated that the fundus rotation gastroplasty tube is longer and better perfused than the conventional gastric tube [23, 24].


(A)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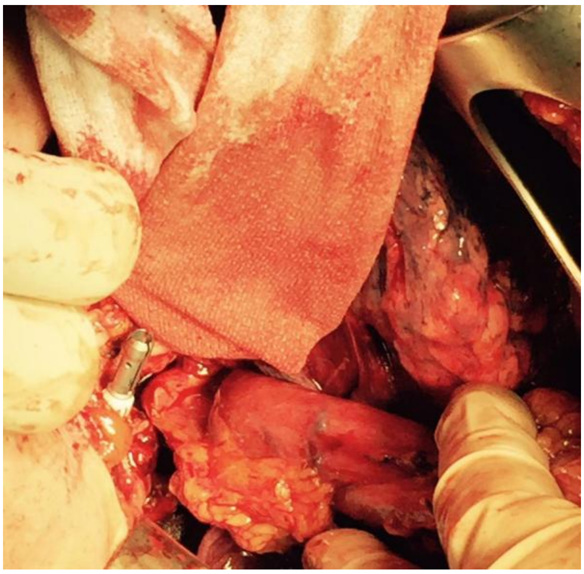
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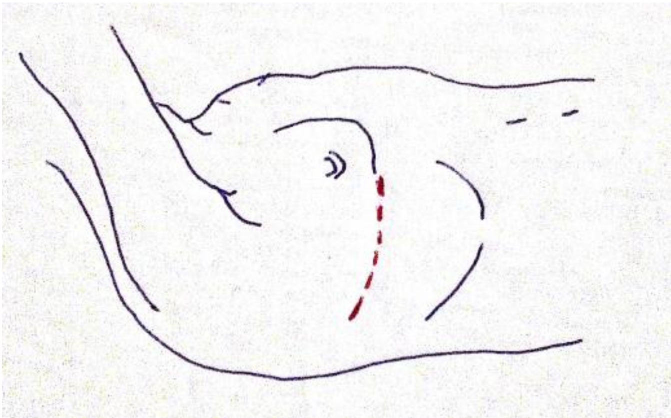

Figure 2. Ivor-Lewis abdomino- thoracic esophagectomy: In the abdominal part of the procedure, a D2 lymphadenectomy is performed and a gastric tube is prepared. In the thoracic part, the esophagus is dissected in the level of azygos vein. An esophagogastric anastomosis is performed. Formation of the gastric tube (A). One part of the circular stapler is inserted into the gastric tube (B), the other part is passed up though the esophagus and through the staple line (C). The two parts are then connected (DST Series™ EEA™ 25 mm single use stapler, Covidien, New Haven, CT, USA***)*** above the azygos vein (Copyright University Clinic of Saarland).

Mc Kewon 3- field esophagectomy. The three- field esophagectomy was described by Mc Kewon in 1976 [25]. In this type of surgery, a right posterolateral thoracotomy is performed at first, the esophagus is mobilized from the hiatus to the apex of the right chest. The abdominal part is analogous to the Ivor Lewis procedure. In the cervical part of the procedure, the anterior border of the left sternocleidomastoid muscle (SCM) is incised. After dividing the subcutaneous tissue and the platysma, the SCM and the carotid artery are retracted laterally, the larynx and trachea are retracted medially. In this surgical step an injury of the left recurrent laryngeal nerve should be avoided. As a next step, the omohyoid muscle, the inferior thyroid artery and the middle thyroid vein are divided. The esophagus is then bluntly dissected, posteriorly to expose the prevertrebal fascia. After completion of the mobilization, the esophagus is dissected away from the trachea, then clamped and transected in the neck with a scalpel. The gastric tube is retrosternally mobilized to the neck and a two- layer, hand- sewn esophagogastrostomy is performed [25].

The argument in favor of this more extensive surgical operation is, that lymph node metastasis in esophageal cancer occurs in early stages, involving in case of thoracic esophageal cancer the bilateral paratracheal lymph nodes, the paracardiac nodes, cervical lymph nodes and lymph nodes along the left gastric artery. Akiyama et al. reported good postoperative results with the Mc Kewon 3- field esophagectomy [26].

In patients with a history of previous gastrectomy, interposition of parts of the colon is necessary to reconstruct the gastrointestinal continuity, as described in the literature [27]. The ascending and transverse colon were used as interposed grafts. A colonoscopy to exclude malignancy was preoperatively performed in these patients.

All of the above mentioned surgical procedures were performed over a 14- year period in our department.

Classification of abdominal lymphadenectomy. The Japanese research society for the study of gastric cancer published a manual in 1963, standardizing lymphadenectomy and pathologic evaluations for gastric cancer. These guidelines recognized 16 lymph node stations (JGCA: Japanese classification of gastric carcinoma-2nd Engl.ed.)[28].

16 nodal stations are characterized in relation to the localization and extent of the primary tumor (N0-N4). The extent of lymphadenectomy is classified accordingly to the level of lymph node stations (D1-D4). In D1 dissections, only the perigastric nodes directly attached along the minor and major curvature of the stomach are removed (stations 1-6, N1 level). An incomplete N1 dissection is refered to as D0 lymphadenectomy. In D2 dissections (N2 level), the lymph nodes along the left gastric artery (station 7), the common hepatic artery (station 8), the celiac trunk (station 9), the splenic hilus, and the splenic artery (stations 10 and 11) are additionally removed. D3 dissections include the additional dissection of lymph nodes (LN) at stations 12, 13 and 14, along the hepatoduodenal ligament and the root of the mesenteric artery (N3 level). Finally, D4 resections include the LN stations 15 and 16 in the paraaortic and the paracolic region (N4 level). It is thought that the incidence of LN metastasis to any of the above described lymph nodal stations is higher, if the primary tumor is localized nearby. For tumors in antrum, tumor infiltrating the right paracardiac lymph nodes are staged as N2, while tumor infiltrating the left paracardiac lymph nodes are staged as N3. For tumors of cardia, the 5th and 6th lymph nodal stations belong to N2 level [28].

Summary of regional lymph nodes

No. 1 Right paracardial lymph nodes (LN)

No. 2 Left paracardial LN

No. 3 LN along the minor curvature

No. 4sa LN along the short gastric vessels

No. 4sb LN along the left gastroepiploic vessels

No. 4d LN along the right gastroepiploic vessels

No. 5 Suprapyloric LN

No. 6 Infrapyloric LN

No. 7 LN along the left gastric artery

No. 8a LN along the common hepatic artery (anterosuperior group)

No. 8p LN along the common hepatic artery (posterior group)

No. 9 LN around the celiac trunk

No. 10 LN at the splenic hilus

No. 11p LN along the proximal splenic artery

No. 11d LN along the distal splenic artery

No. 12a LN in the hepatoduodenal ligament (along the hepatic artery)

No. 12b LN in the hepatoduodenal ligament (along the bile duct)

No. 12p LN in the hepatoduodenal ligament (behind the portal vein)

No. 13 LN on the posterior surface of the pancreatic head

No. 14v LN along the superior mesenteric vein

No. 14a LN along the superior mesenteric artery

No. 15 LN along the middle colic vessels

No. 16a1 LN in the aorta

No. 16a2 LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)

No. 16b1 LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)

No. 16b2 LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)

No. 17 LN on the anterior surface of the pancreatic head

Apart from standard D2 lymphadenectomy, the lymph nodes of the lower mediastinum were routinely resected during transhiatal esophagectomy in our institution.

1.4.2 Clavien- Dindo classification of surgical complications.

Clavien et al. introduced a classification system for surgical complications using the example of cholecystectomy in 1992 [29, 30]. This system facilitates the assessment of the severity of postoperative complications. It is based on the required treatment, and due to its applicability, it was also used in other fields of surgery [31] to describe the severity of surgical complications. We used the Clavien- Dindo classification in our study to classify the severity of postoperative complications.

Table 5. The Clavien- Dindo Classification of surgical complications [30]

Grades: Definition
I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological intervention. Allowed therapeutic regimens are drugs like antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III: Requiring surgical, endoscopic or radiological intervention (**IIIa:** intervention under general anesthesia, **IIIb:** intervention under general anesthesia).
IV: Life- threatening complication including CNS complications† requiring IC/ ICU- management (**IVa:** single organ dysfunction, including dialysis, **IVb:** multiorgan dysfunction).
V: Death of patient.
Suffix \`d\`: If the patients suffers from a complication at the time of discharge, the suffix \`d\` (for \`disability\`) is added to the respective grade of complication. This label indicates the need for a follow- up to fully evaluate the complication.
† brain haemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks (TIA), IC: Intensive care, ICU: Intensive care unit.

1.4.3. Neoadjuvant therapy. The aim of neoadjuvant therapy regimens is to reduce local tumor infiltration, to prevent micrometastases, to increase the chance for R0 surgical resection, and consequently to increase long- term survival. A combined, neoadjuvant radiochemotherapy was carried out for squamous- cell and neoadjuvant chemotherapy without radiation for adenocarcinoma of the esophagus, depending on tumor stage in our institution. The surgical resection followed at about 4 weeks after the end of the neoadjuvant therapy. Until 2012 we used the PLF- scheme, based on cisplatin, folic acid, 5- fluoruracil (5-FU) and simultaneous radiation [45 Gy (1,5 per day)] in cases of squamous- cell esophageal carcinoma. Since 11/2012, we have performed the neoadjuvant radiochemotherapy regimen as proposed by the dutch CROSS trial for both tumor entities (adenocarcinoma and squamous- cell carcinoma), consisting in weekly administration of carboplatin und paclitaxel for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions) followed by surgery. This scheme has been reported to be associated with low perioperative mortality (4%), high rates of pathological complete responders (up to 49% in squamous- cell esophageal carcinoma) and acceptable adverse-event rates [32].

1.5 Aims and scope.

In the present study, we aimed to evaluate the results of the surgical therapy for esophageal cancer in our department in a time period from 2001- 2014. Primary end points were postoperative morbidity and overall survival after esophagectomy for esophageal cancer. Herein, we tried to identify risk factors for worse postoperative outcome and patients' overall survival.

In addition, special emphasis was given upon the impact of the type of anastomotic technique for gastrointestinal reconstruction (intrathoracic stapler versus hand- sewn esophagogastric anastomosis) after esophagectomy for cancer. A further focus was given on the impact of histological subtype (esophageal adenocarcinoma vs. squamous- cell carcinoma) on response to neoadjuvant therapy, disease free interval and overall survival.

2. Patients and methods:

Patients who underwent surgery for esophageal cancer at the University Clinic of Saarland between 01.01.2001 and 31.12.2014 were included in this study. The perioperative data of the patients are routinely registered in a prospective electronic database: however, all records were reviewed again before performing the statistical analysis. The endoscopic and pathological findings were revised to follow the current TNM classification system and to ensure the correct classification of AEG tumors. The following data were included in the analysis:

I. Patient characteristics:

- Age at the time of surgery (in years).
- Sex.
- Comorbidities limited to coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), obesity (BMI exceeding 30 kg/m^2).

II. Tumor characteristics:

-Tumor histology (squamous- cell carcinoma, adenocarcinoma, other histologies were excluded).

-Tumor localization according to the current UICC classification system.

- Preoperative neoadjuvant therapy (NAT).
- T-/N-/M- stage pre- and postoperatively.

-"Response" to neoadjuvant therapy, divided in "partial response" if a less aggressive tumor stage was diagnosed in the postoperative histopathologic specimen, in comparison to preoperative EUS staging, and "complete "response" to neoadjuvant therapy, if T0N0 was postoperatively diagnosed.

III. Operative data:

-Duration of the surgical procedure (in minutes).

-Blood loss (in ml).

-Number of dissected lymph nodes.

-Surgical experience: chief surgeons, senior surgeons who performed more than 20 esophagectomies, surgeons who performed less than 20 esophagectomies.

-Type of surgery: transhiatal esophagectomy with mediastinal anastomosis, transhiatal esophagectomy with cervical anastomosis, abdomino- thoracic esophageal resection with intrathoracic anastomosis, abdomino- thoracic esophageal resection with cervical anastomosis.

-Type of anastomosis (hand-sewn, stapler anastomosis).

IV. Postoperative data:

-Minor postoperative complications Clavien- Dindo grade I -II.

-Major postoperative complications Clavien- Dindo grade III –IV.

-Reoperation.

-Respiratory complications.

-Anastomotic leakage, defined as disruption of the anastomosis that led to extravasation of intraluminal content.

-30-, 60- and 90- days´ mortality.

-Duration of the hospital stay (in days).

-Anastomotic stricture and palsy of N. recurrens in the 6 months` follow- up. Anastomotic stricture was defined as dysphagia in the 6 months´ endoscopic control requiring intervention (endoscopic dilatation).

-Tumorprogress and disease free interval (DFI).

V. Overall survival data (OS):

-Survival (in months).

Perioperative management: During surgery, single- shot antibiotics ceftriaxon 2 g i.v. (clindamycin 600 mg i.v. in case of penicillin allergy) and metronidazol 500 mg i.v. were administrated. A nasogastric tube was positioned intraoperatively beneath the anastomosis and remained in situ for 5 days postoperatively, if not prematurely removed. The patient received parenteral feeding during these 5 days. If the anastomosis was patent in the postoperative radiographic control at the fifth postoperative day, the nasogastric tube was removed and enteral feeding with liquids was started. Postoperative chest X- rays were performed before and after removing the intraoperatively placed chest tubes, or whenever required during ICU stay.

Two easy- flow drainage tubes were intraoperatively placed into the abdomen (one in the hiatus esophagei, one under the liver, the gallbladder was routinely intraoperatively removed) and two intrapleural drains, if the thorax was intraoperatively opened (one basolateral, one cranial from the esophagogastric anastomosis). A third one was placed into the left pleural cavity, if left- sided pleura was opened intraoperatively.

All patients were initially admitted to the intensive care unit (ICU), at least for one postoperative day. The laryngeal tubus was immediately removed, if possible. Peridural catheter was used for analgesia if not contraindicated, and continuous positive airway pressure (CPAP) mask therapy was initially performed to prevent pulmonal atelectasis. Depending on the clinical course, patients were transferred to the intermediate care ward for the next 2- 4 days and then to the peripheral surgical wards. Parenteral feeding started at the first postoperative day to meet caloric requirements. Patients were postoperatively discussed in the tumorboard for the need of adjuvant therapy. The postoperative 6- months´ follow- up was routinely performed either by the primary care physician or in our hospital.

Severity of postoperative morbidity: In order to assess the severity as well as the clinical impact of perioperative morbidity, the Clavien- Dindo classification was used [30]. The overall postoperative morbidity during patient's first hospital stay was classified into minor (Clavien- Dindo grade I- II) or major complications (Clavien- Dindo grade III- IV). The group of minor postoperative morbidity consisted of complications treated conservatively. The group of major postoperative morbidity consisted of complications requiring surgical, endoscopic or radiological intervention (Clavien- Dindo grade IV), life- threatening complications requiring ICU management (grade IV) or lethal complications (grade V). All of the patients received parenteral feeding for 5 days. For this reason, the administration of parenteral feeding was not assessed as a Clavien- Dindo grade I complication. N. recurrens palsy was classified as Clavien- Dindo grade IIId complication. Mortality during the first hospital stay was stratified, and 30-, 60- and 90- days´ mortality were separately assessed.

Tumor management: Endosonography (EUS) was preoperatively performed as well as 6 months postoperatively during routine follow- up. In the preoperative work- up, a computed tomography (CT) was performed to detect any organ metastases. Neoadjuvant chemotherapy combined with radiation in case of SCC was preoperatively performed, if uT3 or N+ or both/higher tumor stage was diagnosed in preoperative endosonography [33]. The surgical resection followed 4- 6 weeks after the end of the neoadjuvant therapy. Until 2012, the PLF-scheme based on cisplatin, folic acid, 5- FU and simultaneous radiation [45 Gy (1,5 per day)] in cases of squamous- cell esophageal carcinoma was used. Since 2012, neoadjuvant chemoradiation regimen as proposed by the dutch CROSS trial, consisting in weekly administration of carboplatin und paclitaxel for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions) followed by surgery was performed.

Statistical analysis: The χ^2 test (Fisher's exact test) and the binary logistic regression in case of categorical variables, as well as Mann-Whitney U test and Kruskal-Wallis H test in case of non- parametric, not normally distributed continuous variables were performed. The distribution of continuous variables was tested with the Kolmogorov- Smirnov test. Statistical significance was set at $p \leq 0.05$. Survival data were recorded partially contacting the Cancer Registry of Saarland and partially contacting the house doctors. Log rank test and Cox-regression were performed for survival analysis. Statistical analysis was conducted using IBM SPSS Statistics V22.0.

3. Results:

3.1. Descriptive Analysis:

320 patients with esophageal cancer were treated in the University Clinic of Saarland from 01.01.2001 until 31.12.2014. Overall, the men/ women ratio was 268:52 (83.8%:16.2%), and the median age of patients at the time of operation was 63 years (min. 28 years, max. 88 years). Regardless of the tumor stage or its localisation, median overall survival was 17 months (0- 146.5 months). The 1-, 3- and 5 –year survival was 65.2%, 41.7% and 30.7%, the 30- day, 60- day and 90- day mortality rates were 5.9% (19/320), 9.4% (30/320) and 12.8% (41/320), respectively.

3.1.1. Patient characteristics. Patient characteristics are shown in table 6. 37.8% of the patients had a squamous- cell esophageal cancer (SCC), while 62.2% (199/320) suffered from adenocarcinoma of the esophagus. In 44.6% of patients with a SCC (54/121) and 62.8% with an esophageal adenocarcinoma (125/199) an abdomino-thoracic esophageal resection with intrathoracic anastomosis was performed (TAE intrathoracic group). 25.6% (82/320) patients had a chronic obstructive pulmonary disease (COPD) at the time of surgery, 21.3% (68/320) a history of coronary heart disease (CHD) and 20.9% (67/320) were obese. Overall, 51.9% of the patients (166/320) received neoadjuvant therapy.

Table 6. Esophagectomies for esophageal cancer (n= 320). Patient characteristics						
Parameters	***THE intraabdominal*** *59, 18.4%*	***THE cervical*** *30, 9.4%*	***TAE intrathoracic*** *179, 55.9%*	***TAE cervical*** *52, 16.2%*	***Total*** *320, 100%*	***P***
Age in years (median, range)	67 (38)	70 (37)	61 (54)	61 (39)	63 (60)	0.149
Men/women ratio (n, %)	45/14 76.3%/27%	25/5 83.3%/16.7%	156/23 87.1%/12.9%	42/10 80.8%/19.2%	268/52 83.8%/16.2%	0.23
Adenocarcinoma of esophagus (n, %)	56 (94.5%)	12 (40%)	125 (69.8%)	6 (11.5%)	199 (62.2%)	**<0.001*****
Squamous- cell carcinoma of esophagus (n, %)	3 (5.5%)	18 (60%)	54 (30.2%)	46 (88.5%)	121 (37.8%)	**<0.001*****
COPD (n, %)	11 (18.7%)	10 (33.3%)	47 (26.3%)	14 (26.9%)	82 (25.6%)	0.47
Coronary Heart Disease (n, %)	15 (25.4%)	12 (40%)	33 (18.4%)	8 (15.4%)	68 (21.3%)	**0.032***
Obesity (n, %)	18 (30.5%)	6 (20%)	34 (19%)	9 (17.3%)	67 (20.9%)	0.251
Neoadjuvant therapy (n, %)	29 (49.2%)	13 (43.3%)	100 (55.9%)	24 (46.2%)	166 (51.9%)	0.529

TAE cervical: abdomino- thoracic esophageal resection with cervical anastomosis, **TAE intrathoracic:** abdomino- thoracic esophageal resection with intrathoracic anastomosis, **THE cervical:** transhiatal esophagectomy with cervical anastomosis, **THE intraabdominal:** transhiatal esophagectomy with intraabdominal anastomosis, **SCC:** squamous- cell esophageal carcinoma, **AEG:** adenocarcinoma of the gastroesophageal junction.

** p <0.05, *** p< 0.001*

3.1.2. Tumor characteristics.

Table 7. Esophagectomies for esophageal cancer (n= 320). Histology and tumor localization		
	n	***%***
SCC	**121**	**37.8**
SCC upper 1/3	12	3.7
SCC middle 1/3	57	17.8
SCC lower 1/3	52	16.3
AEG	**199**	**62.2**
AEG I	106	33.1
AEG II	56	17.5
AEG III	37	11.6
Total	320	100

121 patients (37.8%) had a squamous- cell esophageal carcinoma (SCC). In 12 patients the SCC was located in the upper 1/3 of the esophagus (3.7%), in 57 patients in the middle 1/3 (17.8%) and in 52 in the lower 1/3 (16.3%). 199 patients (62.2 %) had an esophageal adenocarcinoma; in 106 adenocarcinoma of the esophago -gastric junction Type I (AEG I) according the Siewert classification (33.1%), in 56 AEG of Type II (17.5%) and in 37 AEG of Type III (11.6%), as given in table 7.

The median value of dissected lymph nodes was 17 (min= 2, max= 65).

Table 8. Esophagectomies for esophageal cancer (n= 320). UICC tumor stage		
Stage	***n***	***%***
0	33	10.3
I	53	16.6
II	97	30.3
III	113	35.3
IV	24	7.5
Total	320	100

Table 8 shows tumor staging data of the patients. The majority of patients experienced a tumor stage III (35.3%, 113/320), followed by stage II (30.3 %, 97/320), stage I (16.6 %, 53/320) and stage IV (7.5 %, 24/320). Interestingly, 10.3% of patients (33/320) experienced stage 0 in the postoperative pathological assessment.

3.1.3. Operative data and postoperative outcome.

In more than half of our patients, abdomino- thoracic esophageal resection (TAE) with intrathoracic anastomosis was performed (179 patients, 55.9%), transhiatal esophagectomy (THE) with intraabdominal anastomosis in 59 patients (18.4 %), abdomino- thoracic esophageal resection (TAE) with cervical anastomosis in 52 patients (16.3 %) and transhiatal esophagectomy (THE) with cervical anastomosis in 30 patients (9.4 %), as given in table 6.

In 222 patients (69.4 %) hand- sewn, double- row, end- to- end anastomosis, and in 98 patients (30.6 %) a stapled, end- to- side anastomosis was performed (table 9). Table 10 depicts the type of surgery performed for each histological type and localization of the tumor.

106 patients (33.1 %) had an esophageal adenocarcinoma type I (AEG I). In these, TAE with intrathoracic anastomosis was performed in 79 patients (24.7%), THE with cervical anastomosis in 11 patients (3.4%), THE with intraabdominal anastomosis in 11 patients (3.4%), and TAE with cervical anastomosis in 5 patients (1.6%), respectively (table 10).

Table 9. Esophagectomies for esophageal cancer (n= 320). Surgical procedure and type of anastomosis			
	Hand- sewn, double- row end-to-end *n (%)*	***Stapled, end-to-side (circular stapler)*** *n (%)*	***Total*** *n (%)*
TAE cervical	52 (16.2%)	0 (0%)	52 (16%)
TAE intrathoracic	129 (40.3%)	50 (15.6%)	179 (55.9%)
THE cervical	30 (9.5%)	0 (0%)	30 (9.5%)
THE intraabdominal	11 (3.4%)	48 (15%)	59 (18.4%)
Total	222 (69.4%)	98 (30.6%)	320 (100%)

TAE cervical: abdomino- thoracic esophageal resection with cervical anastomosis, **TAE intrathoracic:** abdomino- thoracic esophageal resection with intrathoracic anastomosis, **THE cervical:** transhiatal esophagectomy with cervical anastomosis, **THE intraabdominal:** transhiatal esophagectomy with intraabdominal anastomosis.

Table 10. Esophagectomies for esophageal cancer (n= 320). Surgical procedure, histology and localization of the tumor							
	SCC upper 1/3 *n (%)*	***SCC middle 1/3*** *n (%)*	***SCC lower 1/3*** *n (%)*	***AEG I*** *n (%)*	***AEG II*** *n (%)*	***AEG III*** *n (%)*	***Total***
TAE cervical	5 (1.6%)	33 (10.3%)	8 (2.5%)	5 (1.6%)	1 (0.3%)	0 (0%)	52 (16.3%)
TAE intrathoracic	0(0%)	19 (5.9%)	35 (10.9%)	79 (24.7%)	36 (11.3%)	10 (3.1%)	179 (55.9%)
THE cervical	7 (2.2%)	4 (1.3%)	7 (2.2%)	11(3.4%)	1 (0.3%)	0 (0%)	30 (9.4%)
THE intraabdominal	0 (0%)	1 (0.3%)	2 (0.6%)	11 (3.4%)	18 (5.6%)	27 (8.4%)	59 (18.4%)
Total	12 (3.8%)	57 (17.8%)	52 (16.2%)	106 (33.1%)	56 (17.5%)	37 (11.6%)	320, 100 %

TAE cervical: abdomino- thoracic esophageal resection with cervical anastomosis, **TAE intrathoracic:** abdomino- thoracic esophageal resection with intrathoracic anastomosis, **THE cervical:** transhiatal esophagectomy with cervical anastomosis, **THE intraabdominal:** transhiatal esophagectomy with intraabdominal anastomosis, **SCC:** squamous- cell esophageal carcinoma, **AEG:** adenocarcinoma of the gastroesophageal junction.

Table 11. Esophagectomies for esophageal cancer (n= 320). Surgical procedure and type of gastric tube			
	Conventional gastric tube Kirschner/ Akiyama *n (%)*	***Fundus rotation gastroplasty*** *n (%)*	***Total*** *n (%)*
TAE cervical	27 (8.4%)	25 (7.8%)	52 (16.2%)
TAE intrathoracic	176 (55%)	3 (0.9%)	179 (55.9%)
THE cervical	14 (4.5%)	16 (5%)	30 (9.5%)
THE intraabdominal	59 (18.4%)	0 (0%)	59 (18.4%)
Total	276 (86.2%)	44 (13.8%)	320 (100%)

The majority of gastric conduits were conventionally performed (86.2%), whereas in 44 patients (44/320, 13.8%) a fundus rotation gastroplasty was performed in order to achieve a longer gastric tube with an improved vascular perfusion. As shown in table 11, a fundus rotation gastroplasty was performed in case of cervical anastomosis and only 3 times in case of an intrathoracic anastomosis (3/320, 0.9%).

The morbidity and mortality during patients' first hospital stay is thoroughly described in the tables 12- 14. A total of 167 patients (52.2%) suffered from at least one postoperative complication. 47 patients (14.7 %) suffered from anastomotic leak, whereas 96 patients (30%) suffered from a respiratory complication (table 12). The 30- day, 60- day and 90- day mortality rates were 5.9% (19/320), 9.4% (30/320), and 12.8% (41/320) respectively.

There was observed significant difference among the different types of surgery concerning duration of surgical procedure, and rates of postoperative complications Clavien- Dindo III-IV, respiratory complications, reoperation, palsy of N. recurrens, and 90- day mortality ($p=0.01$, $p< 0.001$, $p<0.001$, $p=0.013$, $p<0.001$, and $p<0.001$ respectively, x^2 exact test), as shown in table 12. More specially, the postoperative morbidity and 90- day mortality after cervical anastomosis, either in the frame of TAE or THE, was significantly higher in comparison to other types of surgery.

Table 12. Esophagectomies for esophageal cancer (n= 320). Operative data and postoperative outcome among different types of surgery

Parameters	***THE intraabdominal*** 59 (18.4%)	***THE cervical*** 30 (9.4%)	***TAE intrathoracic*** 179 (55.9%)	***TAE cervical*** 52 (16.2%)	***Total*** 320 (100%)	***P***
Duration of surgical procedure median [min., max.]	201 [77, 354]	242.5 [125, 548]	269 [128, 532]	333 [168, 675]	257 [77, 675]	**0.01****
Blood loss in ml median [min., max.]	200 [20, 1500]	500 [50, 6000]	300 [5, 4000]	350 [100, 1200]	300 [5, 6000]	0.797
Number of dissected lymph nodes median [min., max.]	19 [6, 65]	14 [3, 49]	17 [3, 62]	14 [2, 49]	17 [2, 65]	0.388
Minor postoperative complications Clavien- Dindo Grade I-II *n (%)*	4 (6.8%)	3 (10%)	23 (12.8%)	10 (19.2%)	40 (12.5%)	0.25
Major postoperative complications Clavien- Dindo Grade III-IV *n* (%)	21 (35.6%)	9 (30%)	29 (16.2%)	27 (51.9%)	86 (26.9%)	**p<0.001 *****
Respiratory complications *n* (%)	9 (15.3%)	16 (53.3%)	47 (26.3%)	24 (46.1%)	96 (30%)	**p<0.001 *****
Reoperation *n* (%)	18 (30.6%)	16 (53.3%)	47 (26.3%)	21 (40.4%)	102 (31.9%)	**0.013***
Anastomotic leak *n* (%)	9 (15.3%)	9 (30%)	22 (12.3%)	7 (13.5%)	47 (14.7%)	0.11
Anastomotic stricture *n* (%)	3 (5%)	3 (10%)	20 (11.2%)	4 (7.7%)	30 (9.4%)	0.543
Palsy of N. recurrens *n* (%)	0 (0%)	7 (23.3%)	3 (1.7%)	14 (26.9%)	24 (7.5%)	**p<0.001*****
30- day mortality *n* (%)	2 (3.4%)	5 (16.7%)	6 (3.4%)	6 (11.5%)	19 (5.9%)	0.103
60- day mortality *n* (%)	4 (6.8%)	8 (26.7%)	11 (6.1%)	7 (13.5%)	30 (9.4%)	**0.007 ****
90- day mortality *n* (%)	4 (6.8%)	11 (36.7%)	18 (10.1%)	8 (15.4%)	41 (12.8%)	**p<0.001*****
Hospital stay (days) median [min., max.]	19 [8, 118]	29 [8, 127]	20 [9, 198]	25 [10, 114]	22 [8, 198]	0.164

** p <0.05, ** p<0.01, *** p< 0.001*

3.1.4. Postoperative complications according to Clavien- Dindo.

To assess the severity of postoperative morbidity, we recorded the postoperative complications according to Clavien- Dindo classification. 40 patients (12.5%) suffered from a minor postoperative complication (Clavien- Dindo grade I- II), whereas 86 patients (26.9%) experienced a major postoperative complication (Clavien- Dindo grade III- IV), thus requiring surgical, endoscopic or radiological intervention or readmission in the Intensive Care Unit (ICU). A total of 41 patients (12.8%) suffered from a lethal postoperative complication (Clavien- Dindo grade V), as shown in table 13.

Table 13. Esophagectomies for esophageal cancer (n= 320).
Classification of postoperative complications after Clavien- Dindo

Grade	***n***	***%***
No complication	153	47.8
I	19	5.9
II	21	6.6
III	60	18.8
IV	26	8.1
V	41	12.8
Total	320	100

Patients with minor postoperative complication (grade I- II according to Clavien- Dindo) suffered mainly from respiratory complication (24/40 patients, 60%). On the contrary, surgical complications (anastomotic leak, necrosis of the gastric tube) led predominantly to major and lethal postoperative morbidity (Clavien- Dindo grade III- V). In particular, 23 out of 86 patients with Clavien- Dindo III- IV complications suffered from anastomotic leak (26.7%), whereas 24 patients (27.9%) suffered from palsy of N. recurrens. Surgical complications (anastomotic leak in 21 patients, necrosis of gastric tube in 9 patients) were predominantly responsible for lethal complications Clavien- Dindo grade V, as shown in table 14.

Table 14. Esophagectomies for esophageal cancer (n= 320). Postoperative morbidity among different types of surgery					
	THE intraabdominal	***THE cervical***	***TAE intrathoracic***	***TAE cervical***	***Total***
	59 (18.4%)	30 (9.4%)	179 (55.9%)	52 (16.2%)	320 (100%)
Minor postoperative complications Clavien- Dindo Grade I&II n (%)	4 (6.8%)	3 (10%)	23 (12.8%)	10 (19.2%)	40 (12.5%)
Anastomotic leak treated conservatively	1 (1.7%)	0 (0%)	0 (0%)	2 (3.8%)	3 (0.9%)
Esophageal fistula	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	1 (0.3%)
Chyle leak treated conservatively	0 (0%)	1 (3.3%)	4 (2.2%)	2 (3.8%)	7 (2.2%)
Wound infection	0 (0%)	0 (0%)	3 (1.7%)	2 (3.8%)	5 (1.6%)
Pneumonia	1 (1.7%)	1 (3.3%)	7 (3.9%)	0 (0%)	9 (2.8%)
Pleura effusion treated with diuretics	2 (3.4%)	0 (0%)	8 (4.5%)	2 (3.8%)	12 (3.8%)
Pneuothorax with no need for extra chest tube	0 (0%)	0 (0%)	1 (0.6%)	2 (3.8%)	3 (0.9%)
Major postoperative complications Clavien- Dindo Grade III&IV n (%)	21 (35.6%)	9 (30%)	29 (16.2%)	27 (51.9%)	86 (26.9%)
Anastomotic leak	6 (10.2%)	3 (10%)	7 (3.9%)	0 (0%)	16 (5%)
Anastomotic leak+ mediastinitis	0 (0%)	0 (0%)	5 (2.8%)	0 (0%)	5 (1.6%)
Anastomotic leak+ respiratory insufficiency	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	1 (0.3%)
Anastomotic leak+ hiatal hernia	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	1 (0.3%)
Necrosis of the gastric tube	0 (0%)	0 (0%)	4 (2.2%)	0 (0%)	4 (1.3%)
Peforated ulcus of the					

gastric tube	1 (1.7%)	0 (0%)	1 (0.6%)	0 (0%)	2 (0.7%)
Necrosis of the colon interposition	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)	1 (0.3%)
Hemorrhage	4 (6.8%)	1 (3.3%)	0 (0%)	1 (1.9%)	6 (1.9%)
Insufficiency of the duodenal stump	1 (1.7%)	0 (0%)	0 (%)	0 (0%)	1 (0.3%)
Pancreatic fistula	1 (1.7%)	0 (0%)	0 (%)	0 (0%)	1 (0.3%)
Biliary leak	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	1 (0.3%)
Intra-abdominal abscess	1 (1.7%)	0 (0%)	0 (%)	0 (0%)	1 (0.3%)
Hiatal hernia	1 (1.7%)	0 (0%)	1 (0.3%)	0 (0%)	2 (0.6%)
Wound dehiscence	0 (0%)	1 (3.3%)	7 (3.9%)	0 (0%)	8 (2.5%)
Adhesion ileus	0 (0%)	0 (0%)	1 (1.9%)	0 (0%)	1 (0.3%)
Chyle leak with need for Reoperation	0 (0%)	0 (0%)	6 (3.4%)	5 (9.6%)	11 (3.4%)
Iatrogene perforation of small intestine	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	1 (0.3%)
Palsy of N. recurrens	0 (0%)	7 (23.3%)	3 (1.7%)	14 (26.9%)	24 (7.5%)
Pneumonia resulting in respiratory insufficiency	1 (1.7%)	2 (6.7%)	7 (3.9%)	5 (9.6%)	15 (4.7%)
Pleura effusion with need for draining tube	1 (1.7%)	1 (3.3%)	7 (3.9%)	0 (0%)	9 (2.8%)
Pneumothorax with need for draining tube	2 (3.4%)	3 (10%)	0 (0%)	0 (0%)	5 (1.6%)
Pulmonary embolism	1 (1.7%)	1 (3.3%)	1 (0.6%)	3 (5.8%)	6 (1.9%)
Sepsis after aspiration	0 (0%)	1 (3.3%)	0 (0%)	3 (5.8%)	4 (1.3%)
Pericardial tamponade	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)	1 (0.3%)
Lethal postoperative complications Clavien- Dindo Grade V, n (%)	4 (6.8%)	11 (36.7%)	18 (10.1%)	8 (15.4%)	41 (12.8%)
Anastomotic leak	0 (0%)	2 (6.7%)	3 (1.7%)	3 (5.8%)	8 (2.5%)
Anastomotic leak+ fistula	0 (0%)	0 (0%)	3 (1.7%)	1 (1.9%)	4 (1.2%)
Anastomotic leak+ mediastinitis	2 (3.4%)	4 (13.3%)	2 (1.1%)	1 (1.9%)	9 (2.8%)

Necrosis of the gastric tube	2 (3.4%)	5 (16.7%)	1 (0.6%)	1 (1.9%)	9 (2.8%)
Hemorrhage from gastric tube	0 (0%)	0 (0%)	2 (1.2%)	0 (0%)	2 (0.6%)
Sepsis after aspiration	0 (0%)	1 (3.3%)	3 (1.7%)	1 (1.9%)	5 (1.5%)
Massive pulmonary embolism	0 (0%)	0 (0%)	3 (1.7%)	0 (0%)	3 (0.9%)
Pericardial tamponade	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	1 (0.3%)

3.1.5. Complications at 6 months´ follow- up: 24 out of 320 patients (7.5%) suffered from N. recurrens palsy at the time of discharge (Clavien- Dindo IIId complications); 21/320 of patients (6.6%) were subjected to cervical anastomosis. Furthermore, 30 patients (9.4%) suffered from anastomotic stricture, of which 20 patients (6.3%) had undergone abdomino-thoracic esophagectomy with intrathoracic anastomosis.

3.2. Impact of anastomotic technique (intrathoracic stapler versus hand- sewn esophagogastric anastomosis) on postoperative outcome after abdomino-thoracic esophagectomy for cancer.

We investigated in particular, whether the type of anastomosis (hand- sewn, or stapler) influenced the postoperative outcome. For this purpose, we analyzed 179 patients, who underwent abdomino-thoracic resection with intrathoracic anastomosis. Three patients with a fundus rotation gastroplasty were excluded, and the remaining 176 patients were divided into two groups: group 1 hand- sewn, double row, end-to-end anastomosis (with 4-0 PDS and 5-0 PDS stitches), group 2 one row end-to-side, stapler. Both groups were compared in terms of morbidity and mortality. Demographic, operative and postoperative data were recorded for both groups.

3.2.1. Patient characteristics, operative data and postoperative outcome. Hand- sewn anastomosis was carried out in 126 patients (group 1) and stapler anastomosis in 50 patients (group 2). Patient characteristics were similar in both groups (table 15): Median age of patients at the time of surgery was 61 years [34- 88], with more men than female patients

(153/ 23). 52 patients (29.5%) suffered from squamous- cell esophageal cancer (SCC), and 124 patients (70.5%) from esophageal adenocarcinoma. 45 patients (25.6%) had chronic obstructive pulmonary disease (COPD) at the time of surgery, 33 patients (18.9%) coronary heart disease (CHD) and 34 patients (19.3%) were obese. The preoperative rates of COPD (p=0.13), CHD (p=0.20) and obesity (p=0.42) were not significantly different among both groups. A total of 93 patients (52.8%) were admitted to neoadjuvant therapy due to preoperative staging (group 1: 47.6% vs. group 2: 66%, p=0.11).

Table 15. Esophagectomies for esophageal cancer (n= 176). Patient characteristics

Characteristic	***Hand-sewn*** *126*	***Stapler*** *50*	***Total*** *176*	**P** ***value***
Age in years, median [min, max.]	62 [42,88]	61 [34,84]	61 [34,88]	0.34
Men/women ratio n (%)	111/15 (88%/12%)	42/8 (84%/16%)	153/23 (86.9%/13.1%)	0.23
Adenocarcinoma of esophagus n (%)	86 (68.3%)	38 (76%)	124 (70.5%)	0.21
Squamous- cell carcinoma of esophagus n (%)	40 (31.7%)	12 (24%)	52 (29.5%)	0.21
COPD n (%)	35 (27.8%)	10 (20%)	45 (25.6%)	0.13
Coronary Heart Disease n (%)	26 (20.6%)	7 (14%)	33 (18.9%)	0.20
Obesity n (%)	24 (19%)	10 (20%)	34 (19.3%)	0.42
Neoadjuvant therapy n (%)	60 (47.6%)	33 (66%)	93 (52.8%)	0.11

Median duration of surgery was 269 min. [128- 532 min.], whereas the median intraoperative blood loss was 300 ml [5- 4000 ml], as shown in table 16. The median number of dissected lymph nodes was 17 [3- 62].

Table 16. Esophagectomies for esophageal cancer (n=176): Operative data and postoperative outcome				
Parameters	***Hand- sewn*** *126*	***Stapler*** *50*	***Total*** *176*	**P** ***value***
Duration of surgical procedure median [min, max]	280 [128, 532]	261 [160, 376]	269 [128, 532]	0.49
Blood loss in ml median [min, max]	300 [50, 4000]	200 [5, 1500]	300 [5, 4000]	0.12
Number of dissected lymph nodes (median, [min, max])	17 [3, 62]	17 [6,34]	17 [3, 62]	0.59
Minor postoperative complications Clavien- Dindo Grade I-II, n (%)	13 (10.3%)	10 (20%)	23 (13%)	0.2
Major postoperative complications Clavien- Dindo Grade III-IV, n (%)	25 (19.8%)	4 (8%)	29 (16.5%)	0.12
Reoperation, n (%)	43 (34.1%)	4 (8%)	47 (26.7%)	**0.001*** **
Respiratory complications, n (%)	35 (27.8%)	12 (24%)	47 (26.3%)	0.36
Anastomotic leak, n (%)	18 (14.3%)	4 (8%)	22 (12.5%)	0.22
Anastomotic stricture, n (%)	17 (13.5%)	3 (6%)	20 (11.4%)	0.1
30- day mortality, n (%)	6 (4.8%)	0 (0%)	6 (4.8%)	0.13
60- day mortality, n (%)	12 (9.6%)	1 (2%)	13 (7.4%)	0.08
90- day mortality, n (%)	17 (13.5%)	1 (2%)	18 (10.2%)	**0.02 ***
Hospital stay in days median [min, max]	21 [9, 198]	18 [12, 114]	20 [9, 198]	0.26

** p <0.05, ** p<0.01, *** p< 0.001*

23 patients (13%) suffered from minor postoperative complication (Clavien- Dindo Grade I-II), whereas 29 patients (16.5%) suffered from major postoperative complication (Clavien-Dindo Grade III- IV). 18 patients (10.2%) suffered from lethal postoperative complication (Clavien- Dindo Grade V) within 90 days after surgery.

Minor surgical complications included wound infection and chyle leak treated conservatively, while minor cardiopulmonary complications included pleura effusion treated with diuretics, pneumothorax with no need for draining tube, pneumonia and atrial fibrillation. The minor postoperative morbidity did not differ significantly among both groups (p=0.2). On the other hand, major surgical complications included anastomotic leak, necrosis of gastric tube, hiatal hernia, wound dehiscence, bile leak and chyle leak with need for reoperation. Surgical complications (anastomotic leak, necrosis of the gastric conduit) led predominantly to major and lethal postoperative morbidity (Clavien- Dindo Grade III- V).

47 patients (26.7%) were reoperated during first hospital stay. The rate of reoperations differed substantially between both groups (group 1: 34.1% vs. group 2: 8%), p= 0.001). The incidence of anastomotic leak was 12.5% (22/176) and did not differ significantly among both groups (group 1: 14.3% vs. group 2: 8%, p= 0.22). The median hospital stay was 20 days [9, 198] and did not significantly differ among both groups (p=0.26). The rate of anastomotic stricture in the 6 months´ follow-up was also similar among both groups (group 1: 13.5% vs. group 2: 6%, p= 0.1). 30-, 60- and 90- day mortality was 4.8% (n=6), 7.4% (n=13), and 10.2% (n=18) respectively. The 90- day mortality was significantly lower in group 2 (group 1: 13.5% vs. group 2: 2%, p= 0.02). The rate of reoperation, and consequently the 90- day mortality differed significantly among both groups.

Management of anastomotic leak: In the stapler anastomosis group, anastomotic leaks were treated with endoscopic stent insertion: 4/ 50 patients after stapler anastomosis suffered from anastomotic leak, of whom only one was reoperated. On the contrary, in the hand- sewn anastomosis group, anastomotic leaks were predominantly treated with reoperation: 18 patients after hand- sewn anastomosis suffered from anastomotic leak, of whom 14 were reoperated. Consequently, 90 days´ mortality (Clavien- Dindo grade V complications) and overall survival was statistically significantly different among both groups of patients.

3.2.2. Risk factors for major and lethal postoperative complications (Clavien- Dindo grade III- V) after abdomino- thoracic esophageal resection*:* Type of anastomosis and duration of surgery significantly influenced the incidence of major and lethal postoperative complications (Clavien- Dindo grade III- V) in the multivariate analysis (binary logistic regression, table 17).

Table 17. Univariate and multivariate analysis of predictors of major postoperative complications (Clavien- Dindo III- IV) after resection for esophageal cancer

	Univariate analysis		***Multivariate analysis***	
Parameter	***OR (CI 95%)***	**P *value***	***OR (CI 95%)***	**P *value***
Age	1.022 (0.998-1.057)	0.200		
Sex	1.745 (0.703-4.331)	0.230		
CHD	1.847 (0.838-4.071)	0.130		
COPD	1.633 (0.802-3.327)	0.180		
Obesity	1.057 (0.465-2.403)	0.900		
Neoadjuvant therapy	0.984 (0.486-1.993)	0.964		
Duration of surgery	0.992 (0.987-0.997)	**0.003****	0.991 (0.986-0.997)	**0.002 ****
Type of anastomosis (hand-sewn vs. stapler)	3.296 (1.369-7.937)	**0.008****	3.666 (1.499-8.963)	**0.004 ****
Intraoperative blood loss	1.000 (0.999-1.001)	0.68		

*** p<0.01*

3.2.3. Risk factors for anastomotic leak after abdomino -thoracic esophageal resection. Obesity**,** neoadjuvant therapy and anastomotic method did not significantly influence the incidence of anastomotic leak in the univariate analysis (table 18).

Table 18. Risk factors for anastomotic leak after abdomino- thoracic resection for esophageal cancer

	Univariate analysis	
Parameter	***OR (CI 95%)***	**P** ***value***
Age	0.984 (0.940-1.031)	0.506
Obesity	1.390 (0.47-4.101)	0.551
Neoadjuvant therapy	2.250 (0.775-6.534)	0.136
Type of anastomosis (hand-sewn vs. stapler)	1.746 (0.557-5.469)	0.34

3.2.4. Survival. Overall median patient survival was 18 months [0, 121]. In group 1 median survival was 22 months [0, 119], whereas in group 2, median survival was 16 months [1, 121]. Patients subjected to hand- sewn anastomosis experienced worse overall survival, as well as patients with advanced UICC tumor stage (p= 0.001, and p=0.002 respectively, log rank test), as shown in table 19 and figure 3.

In the multivariate analysis, type of anastomosis and advanced UICC tumor stage were independent factors, that significantly influenced overall survival (table 20, figure 4).

Table 19. Risk factors for worse overall survival after abdomino- thoracic resection for esophageal cancer -univariate analysis

	Log rank for categorical parameters		***Cox regression for continuous parameters***	
Parameter	**P *value***	***x*** ²	***OR (CI 95%)***	**P *value***
Age			1.07 (0.997-1.036)	0.098
Sex	0.528	0.398		
CHD	0.950	0.004		
COPD	0.153	2.039		
Obesity	0.118	2.446		
Neoadjuvant therapy	0.060	3.595		
Duration of surgery			1.002 (0.999-1.004)	0.197
Type of anastomosis (hand-sewn vs. stapler)	**0.001*** **	**22.866**		
Anastomotic leak	0.790	0.070		
Reoperation	0.150	2.108		
Intraoperative blood loss			1.000 (0.999-1.000)	0.658
Minor postoperative complication (Clavien-Dindo I&II)	0.810	1.060		
Major postoperative complication (Clavien-Dindo III-V)	0.100	0.001		
Histology (SCC vs. adenocarcinoma)	0.310	1.034		
UICC tumor stage	**0.002** **	**16.971**		

*, ** p<0.01, p< 0.001*

Table 20. Risk factors for survival after abdomino- thoracic resection for esophageal cancer- multivariate analysis		
	Cox regression	
Parameter	***OR (CI 95%)***	**P** ***value***
Type of anastomosis	**0.165 (0.067- 0.409)**	**<0.001 *****
UICC tumor stage	**1.371 (1.130- 1.663)**	**0.001*****
**** p< 0.001*		

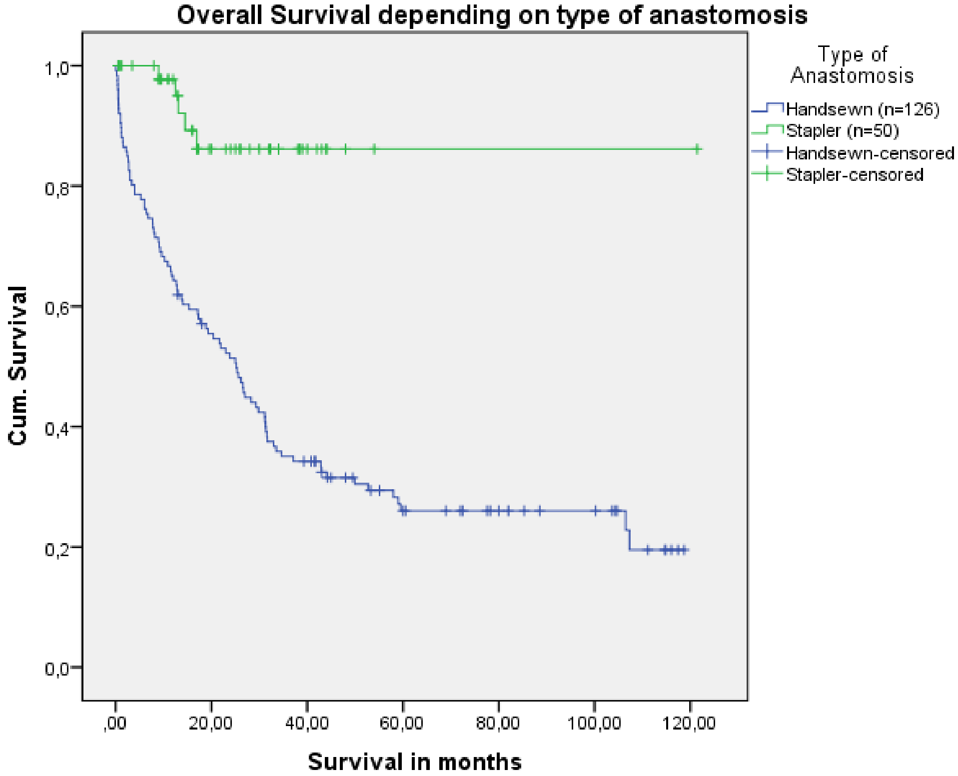

Figure 3: Overall survival after abdomino- thoracic resection for esophageal cancer depending upon the type of anastomosis (p< 0.001, log rank test).

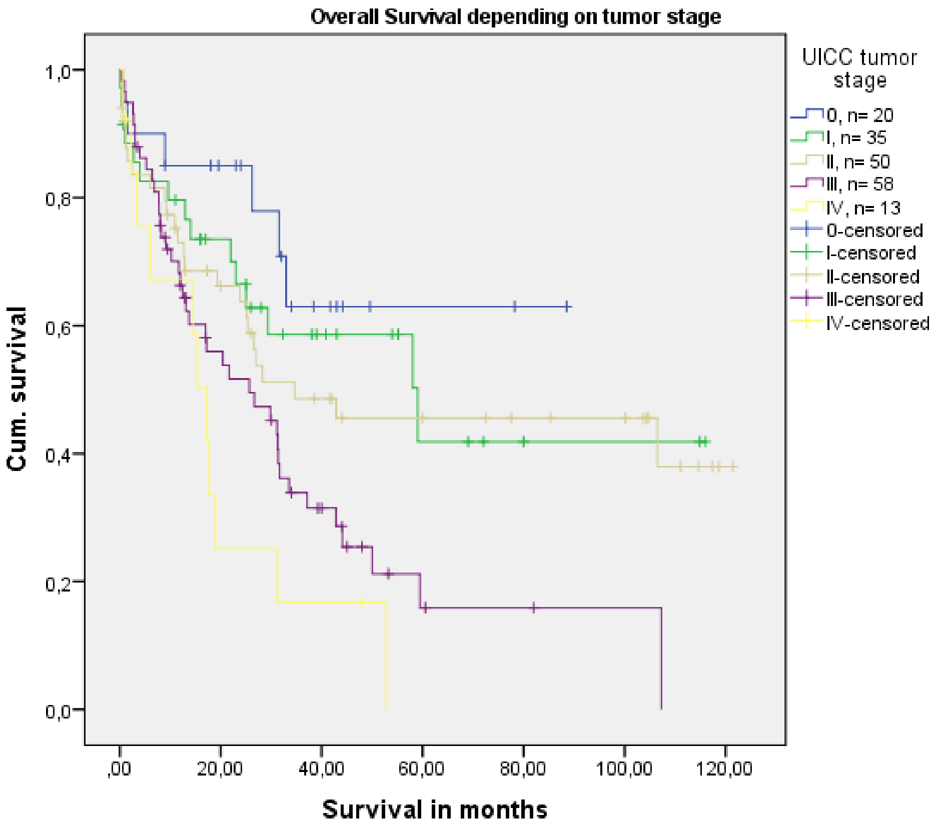

Figure 4: Overall survival after abdomino- thoracic esophageal resection for cancer depending upon UICC tumor stage (p=0.001, log rank test)

3.3. Impact of cervical anastomosis upon postoperative outcome after esophagectomy for cancer.

When analyzing operative data and postoperative morbidity among the different types of esophagectomies (transhiatal esophagectomies with intraabdominal esophagojejunostomy, transhiatal esophagectomies with cervical esophagojejunostomy, abdomino- thoracic esophagectomies with intrathoracic anastomosis and abdomino- thoracic esophagectomies with cervical anastomosis), we observed that in patients subjected to cervical anastomosis the rate of respiratory complications was significantly higher ($p < 0.001$, OR=20.88, binary logistic regression), compared to patients subjected to intrathoracic or intraabdominal anastomoses.

As described in table 12, patients subjected to cervical anastomosis (either in the frame of transhiatal or after abdomino- thoracic esophageal resection) suffered singnificantly more often from major and lethal postoperative complications (Clavien- Dindo grade III- V) in comparison to intrathoracic and intraabdominal anastomosis ($p < 0.001$). In the THE cervical subgroup 20 patients (66.7%) suffered from postoperative complications grade III-V, compared to 35 patients (67.3%) in the TAE cervical subgroup. Moreover, in the THE cervical subgroup, 16 patients (53.3%) experienced postoperatively respiratory complication, 16 patients (53.3%) underwent reoperation, 7 patients (23.3%) suffered from palsy of the N. recurrens, whereas in the TAE cervical subgroup, the rates were 46.1% (24/52 patients), 40.4% (21/52 patients), and 26.9% (14/52 patients), respectively. Furthermore, the 90-day mortality in the THE cervical subgroup was 11/30 (43.3%), while in the TAE cervical subgroup it was only 15.4% (8/52 patients). In summary, patients subjected to cervical anastomosis experienced significantly higher rates of major and lethal complications, significantly more respiratory complications, and palsies of N. recurrens.

3.4.1. Response to neoadjuvant therapy (NAT).

We investigated whether the histological subtype influenced the response to neoadjuvant treatment (NAT) and its effect upon disease free interval (DFI) and overall survival (OS) in patients with esophageal cancer treated in our institution.

Included into the study were patients undergoing esophageal resection in curative intention following NAT with a postoperative survival of at least 90 days. Indication for NAT was tumor stage ≥ T3 and/or N+ as diagnosed in preoperative endosonography (EUS). Excluded were patients in UICC stage IV, or no R0 resection.

Out of 117 patients who underwent NAT, 3 groups were analyzed: group 1, "complete responders", if T0N0 tumor stage was diagnosed in the postoperative histopathological examination of the specimen (n= 26, 22.2%), group 2, "partial responders", if a less advanced tumor stage was postoperatively diagnosed in comparison to preoperative EUS staging (n= 55, 47%) and group 3, "no responders", if no change or progression was observed (n= 36, 30.8%). As mentioned before, until 2012, PLF protocol consisting of cisplatin, folic acid, 5-fluorouracil (5-FU) was used. In case of squamous cell carcinoma, simultaneous irradiation [45 Gy (1.5 per day)] was added. Since 11/2012, NAT consists of weekly doses of carboplatin and paclitaxel for 5 weeks and simultaneous radiotherapy (41.4 Gy in 23 fractions) followed by surgery after four weeks.

72 out of the 117 patients (61.5 %) suffered from AC, whereas 45 patients (38.5%) from SC. 3 tumors were located in the upper 1/3 of esophagus (n= 2.6%), 61 tumors in the middle 1/3 of esophagus (n= 52.1%), and 53 tumors in the lower 1/3 of esophagus (45.3%). Table 21 shows the correlation between histological subtype and response to NAT: the response of patients with SCC to neoadjuvant treatment was significantly higher in comparison to patients with adenocarcinoma of esophagus (p= 0.002, x^2 exact test).

Table 21. Response to neoadjuvant therapy (NAT) among patients with adenocarcinoma (AC) and squamous cell carcinoma (SC) of esophagus (n=117 patients)

Response	***Adenocarcinoma*** *72*	***SCC*** *45*	***Total*** *117*	***P value***
No response, n (%)	30 (41.7%)	6 (13.3%)	36 (30.8%)	**0.002****
Partial response, n (%)	31 (43.1%)	24 (53.3%)	55 (47%)	
Complete response, n (%)	11 (15.3%)	15 (33.3%)	26 (22.2%)	

*** p<0.01*

3.4.2. Tumor disease free interval (DFI) and median overall survival (MS) depending on response to NAT.

We analyzed the influence of response to NAT on tumor- free disease interval and median overall survival. Following parameters were included in the multivariate survival analysis: age, sex, presence of coronary heart disease or obstructive lung disease, obesity, response to NAT, tumor localization, histological subtype, intraoperative blood loss, anastomotic leak, major postoperative complications Clavien- Dindo grade III- IV.

41 patients (35%) suffered from tumor progress in follow- up despite NAT and R0 esophageal resection. Median disease free interval (DFI) of group 1 (complete responders) was 34 months [9- 139], DFI of group 2 (partial responders) was 25 months [1- 134], and DFI of group 3 (no responders) was 13 months [0- 124]. Response to NAT was the only significant, independent factor that influenced DFI (p= 0.004, log rank test). Histological subtype and tumor localization did not significantly influence DFI (p= 0.85, and p= 0.64 respectively, log rank test). Whereas the difference in DFI depending on response to NAT was consistent if AC was the histological subtype (group 1: 11 patients, group 2: 30 patients, group 3: 30 patients, p = 0.02, log rank test), the difference in DFI in the subgroup of patients with SC could not be shown (group 1, n=15 patients, group 2: 25 patients, group 3: 6 patients, p = 0.27, log rank test), due to the very high rate of response to NAT in the SCC subgroup (n=39, 86.7%). The DFI curves are given in figures 5- 7.

Interestingly, 6 out of 26 patients (23%) experienced tumor progress, despite initial complete response observed in the postoperative histopathologic specimen.

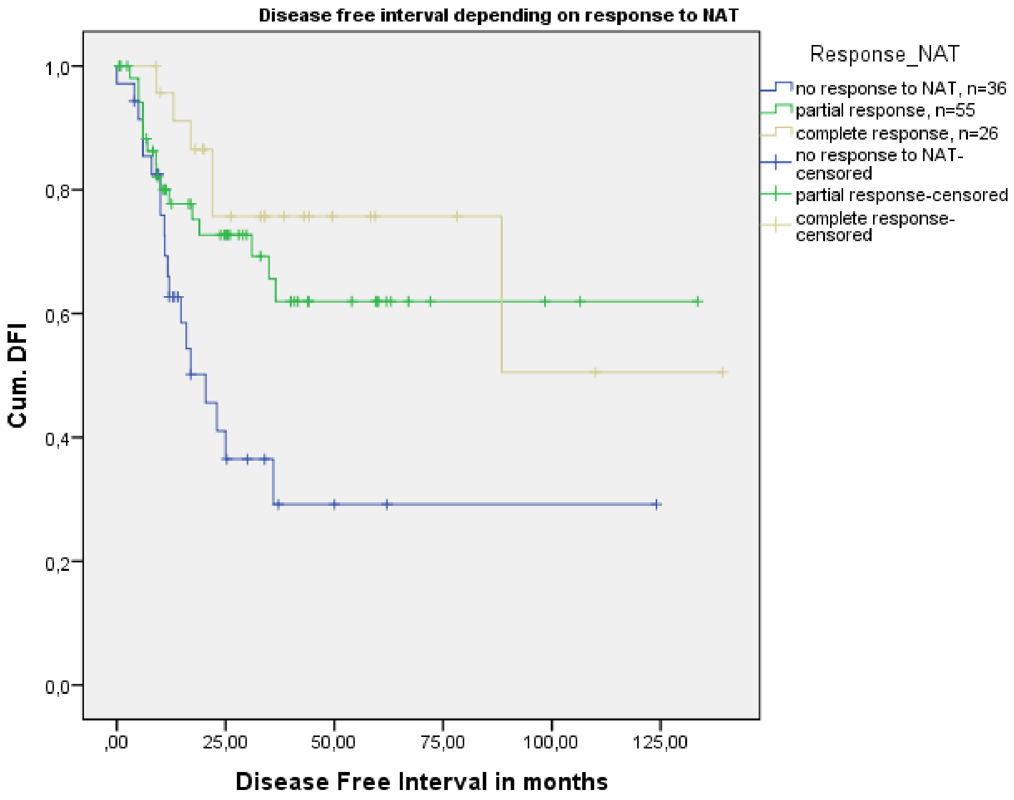

Figure 5: Significant influence of response to NAT on disease free interval (n=117, p= 0.004, log rank test)

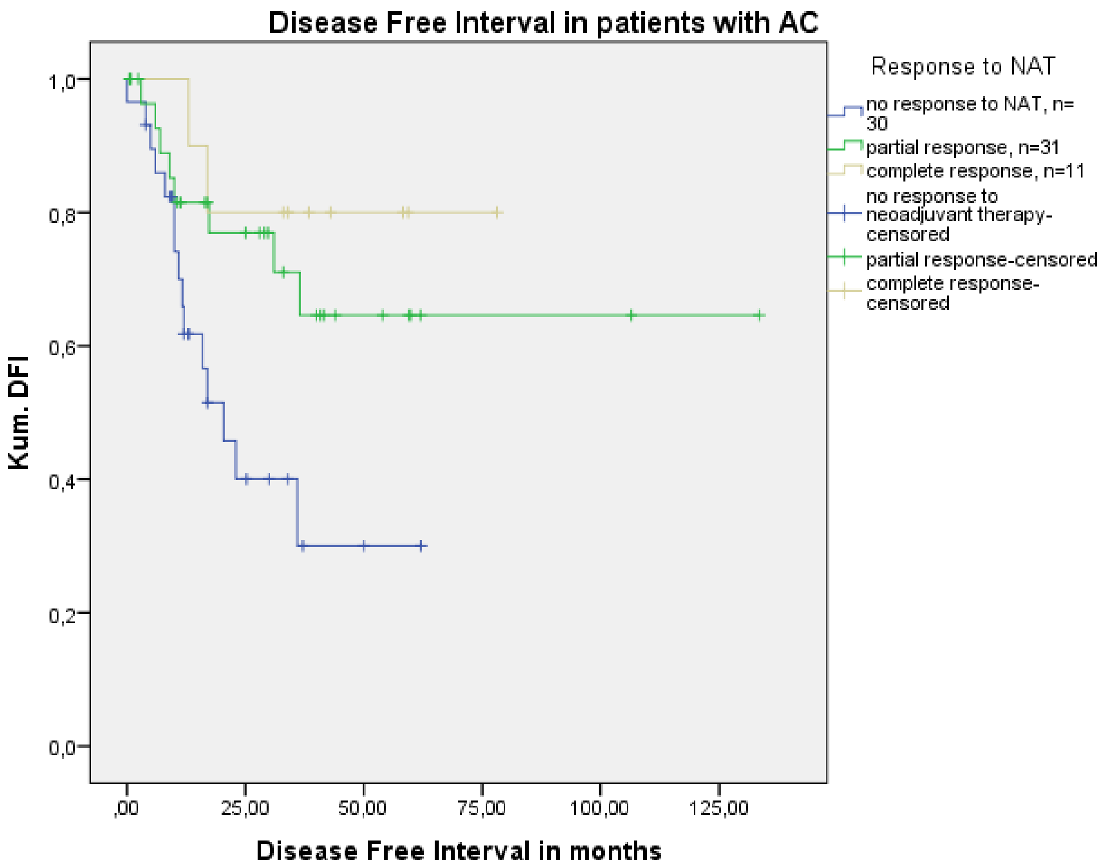

Figure 6: Significant influence of response to NAT on disease free interval in patients with AC (n=72, p= 0.02, log rank test)

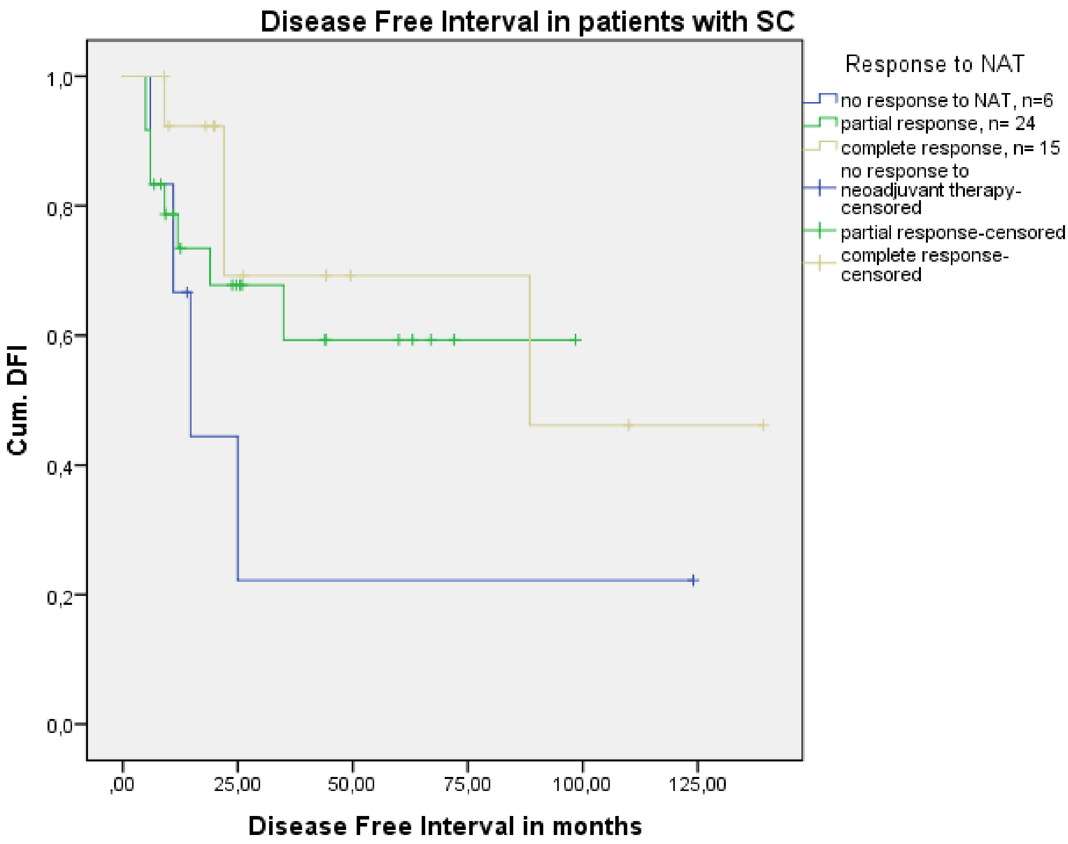

Figure 7: Influence of response to NAT on disease free interval in patients with SC (n=45, p= 0.27, log rank test)

Median survival of group 1 was 33 months [4- 139], 25 months [1- 134], and 14 months [4- 124], respectively (p = 0.02, log rank test). The following parameters were included in the survival analysis: age, sex, presence of coronary heart disease or obstructive lung disease, obesity, response to NAT, tumor localization, histological subtype, intraoperative blood loss, anastomotic leak, major postoperative morbidity and reoperation. In the same line of evidence, NAT was the only significant, independent factor that influenced OS (p= 0.015) in the multivariate Cox regression analysis (tables 22- 23). The survival curves are given in figures 8- 10.

Table 22. Univariate survival analysis for patients subjected to NAT and esophageal resection (n=117)

	Log rank for categorical parameters		*Cox regression for continuous parameters*	
Parameter	**P** ***value***	x^2	***OR (CI 95%)***	**P** ***value***
Age			1.025 (0.993-1.057)	0.124
Sex	0.721	0.127		
CHD	0.349	0.004		
COPD	0.427	0.630		
Obesity	0.956	0.003		
Histological subtype	0.805	0.061		
Response to NAT	**0.016***	**8.289**		
Tumor localization	0.614	0.975		
Anastomotic leak	0.149	2.080		
Reoperation	**0.015***	**5.860**		
Intraoperative blood loss			1.000 (1.000-1.001)	0.127
Major postoperative complication (Clavien-Dindo III -IV)	0.874	0.025		

* *p <0.05*

Table 23. Multivariate survival analysis for patients subjected to NAT and esophageal resection (n=117)

	Cox regression	
Parameter	***OR (CI 95%)***	**P** ***value***
Response to NAT	**0.615 (0.416- 0.909)**	**0.015 ***
Reoperation	1.671 (0.960- 2.909)	0.069

* *p <0.05*

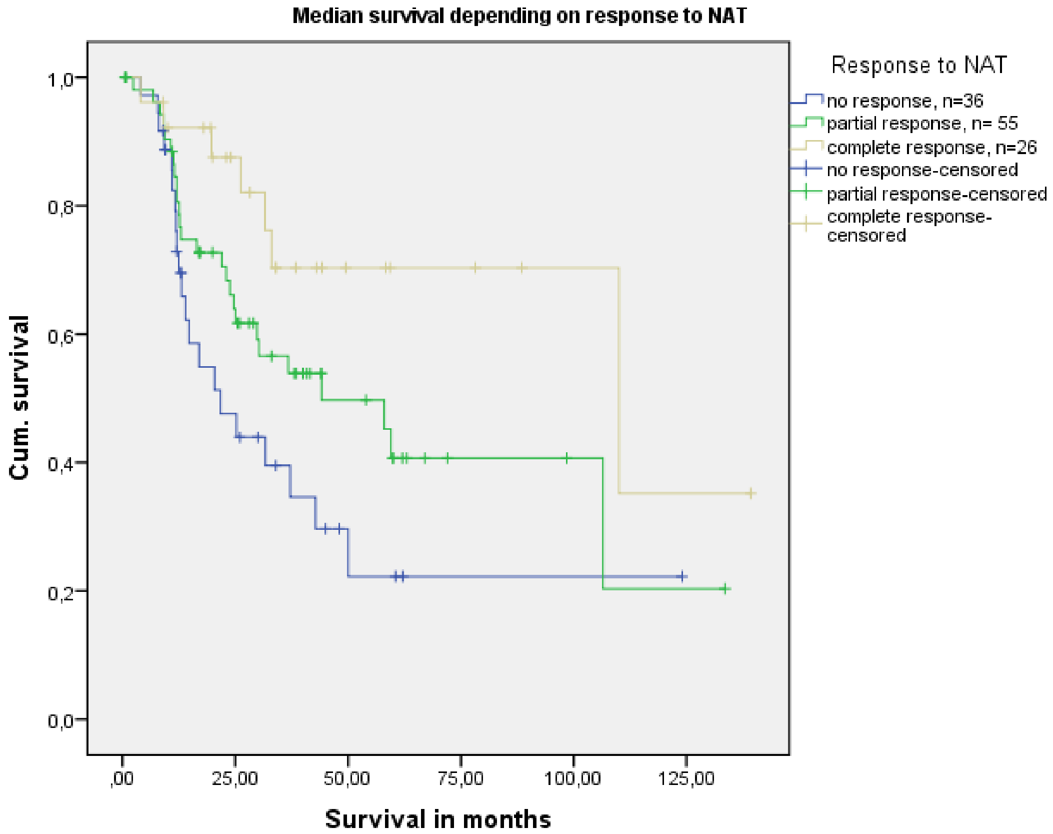

Figure 8: Significant influence of response to NAT on overall median survival (n=117, p= 0.016, log rank test)

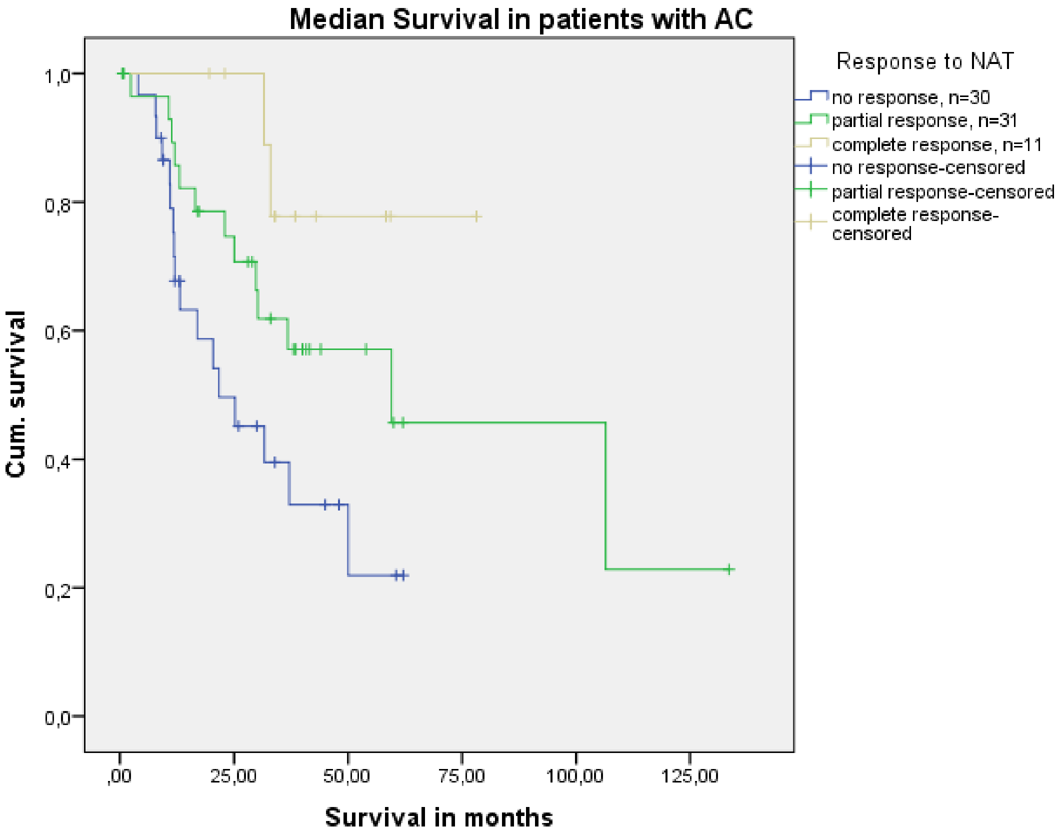

Figure 9: Significant influence of response to NAT on overall median survival in patients with esophageal AC (n=72, p= 0.013, log rank test)

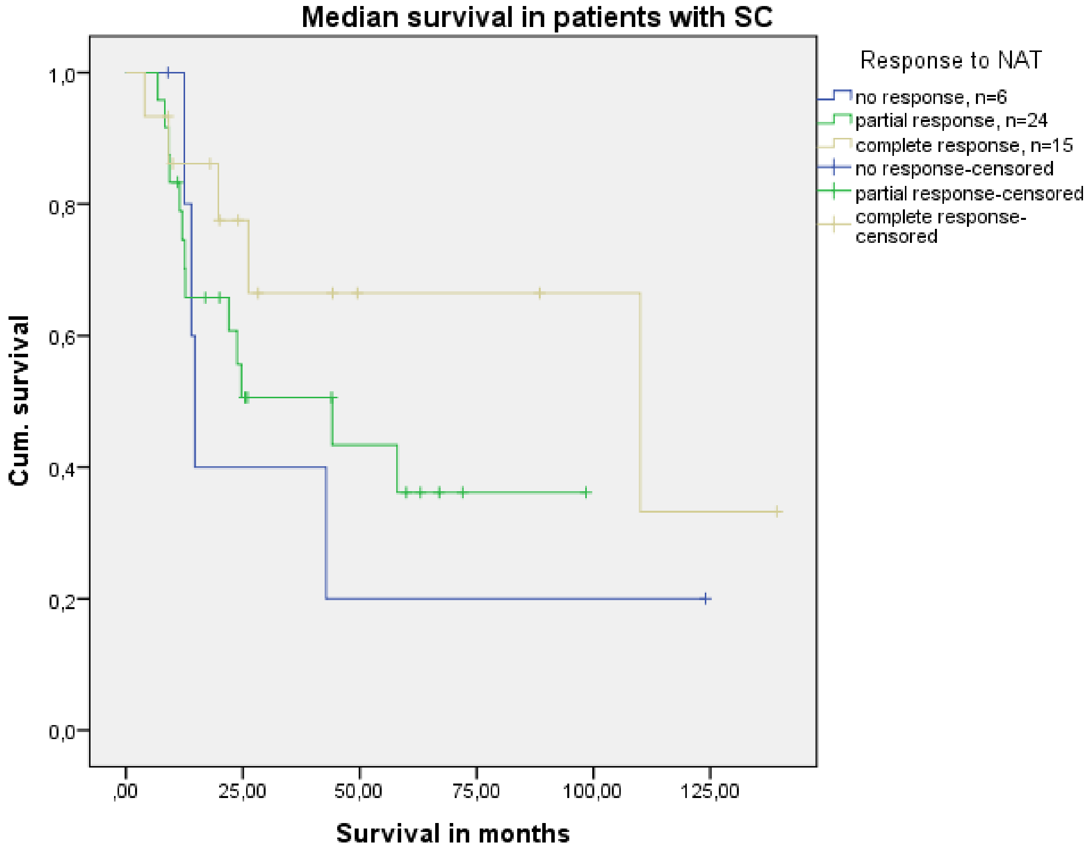

Figure 10: Influence of response to NAT on overall median survival in patients with SC (n=45, p= 0.400, log rank test)

As mentioned above, until 2012 patients with AC were subjected only to chemotherapy according to PLF protocol (n= 41). Up this point, combined chemoradiation according to CROSS protocol was given (n=31). The response to NAT was also compared among these subgroups. Despite the addition of radiation in the NAT, no significant difference in response rates was observed (p= 0.979, x^2 exact test). The response rates are given in table 24.

Table 23. Comparison of response to NAT in patients with AC treated according to PLF vs. CROSS protocol

Response	***PLF*** 41	***CROSS*** 31	***Total*** 72	***P value***
No response, n (%)	17 (41.5%)	13 (41.9%)	30 (41.7%)	0.979
Partial response, n (%)	18 (43.9%)	13 (41.9%)	31 (43%)	
Complete response, n (%)	6 (14.6%)	5 (16.1%)	11 (15.3%)	

Summarizing, our results highlight the different tumor biology among the two main histological subtypes of esophageal cancer. Patients with SC experienced better response rates in comparison to patients with AC, due to the higher radiosensivity of SC. The additional radiation preoperatively in patients with AC, according to CROSS protocol after 2012, did not significantly influence the response to NAT (p= 0.979, x^2 exact test). Response to NAT was the only significant, independent factor that influenced patient survival (p= 0.015, OR= 0.615, 95% CI= 0.416- 0.909).

3.5. Role of surgical experience.

We investigated whether surgical experience influences the postoperative outcome after esophagectomy for esophageal cancer. All esophagectomies in our surgical department were performed either by chief surgeon or by a senior surgeon. We divided the operations into 3 groups: group 1: operations performed by chief surgeon, group 2: operations performed by experienced senior surgeons (>20 esophagectomies), and group 3: operations performed by senior surgeon (surgical experience <20 esophaegectomies).

No statistical significance was observed regarding the postoperative morbidity comparing the different groups of surgeons (table 25).

Table 25. Esophagectomies for esophageal cancer (n= 320). Operative data and postoperative outcome depending on surgical experience

Parameters	*Chief surgeon* 124 (38.8%)	*Senior surgeon >20 esophagectomies* 135 (42.2%)	*Senior surgeon <20 esophagectomies* 61 (19%)	*Total* 320 (100%)	*P value*
Duration of surgical procedure median [min., max.]	235 [77, 432]	281 [104, 675]	295 [161, 548]	257 [77, 675]	0.357
Blood loss in ml median [min., max.]	300 [5, 2500]	300 [20, 4000]	250 [50, 6000]	300 [5, 6000]	0.395
Number of dissected lymph nodes median [min., max.]	17 [3, 65]	16 [2, 62]	18 [3, 47]	17 [2, 65]	0.821
Minor postoperative complications Clavien- Dindo Grade I-II, *n (%)*	17 (13.7%)	14 (10.4%)	9 (14.8%)	40 (12.5%)	0.604
Major& lethal postoperative complications Clavien- Dindo Grade III-V, *n (%)*	46 (37.1%)	60 (44.4%)	21 (34.4%)	127 (39.7%)	0.312
Respiratory complications *n (%)*	38 (30.6%)	42 (31.1%)	16 (26.3%)	96 (30%)	0.772
Reoperation, *n (%)*	34 (27.4%)	46 (34%)	22 (36%)	102 (31.9%)	0.381
Anastomotic leak, *n (%)*	13 (10.5%)	24 (17.8%)	9 (14.8%)	46 (14.4%)	0.246
Anastomotic stricture, *n (%)*	11 (8.9%)	14 (10.4%)	5 (8.2%)	30 (9.4%)	0.863
Palsy of N. recurrens, *n (%)*	8 (6.5%)	11 (8.1%)	5 (8.2%)	24 (7.5%)	0.863
30- day mortality, *n (%)*	6 (4.8%)	10 (7.6%)	9 (14.8%)	25 (7.8%)	0.06
60- day mortality, *n (%)*	12 (9.6%)	14 (10.7%)	11 (18%)	37 (11.6%)	0.211
90- day mortality, *n (%)*	17 (13.7%)	22 (16.8%)	14 (23%)	53 (16.6%)	0.281
Hospital stay (days) median [min., max.]	21 [8, 133]	22, [8, 198]	21, [9, 127]	22, [8, 198]	0.66

3.6. Predictors for major& lethal postoperative complications (Clavien- Dindo grade III-V), anastomotic leak, and overall patient survival

The median overall survival was 17 months (0- 147 months, n=320). The 1-, 3- and 5 year survival was 65.2%, 41.7%´, and 30.7% respectively (figure 11).

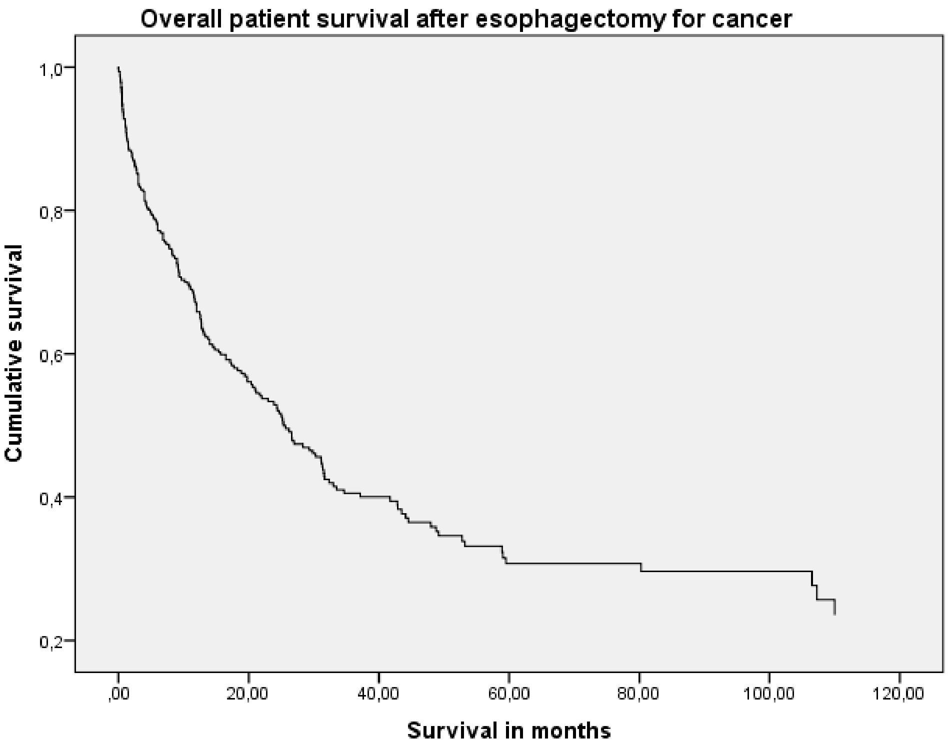

Figure 11: Overall patient survival (OS) after resection for esophageal cancer in UKS (n= 320 patients).

3.6.1. Predictors for major postoperative complications of grade III- V and anastomotic leak

Female gender, anastomotic leak and respiratory complications were significant, independent factors for higher rate of major and lethal postoperative complications (Clavien- Dindo III- V) after resection for esophageal cancer in the multivariate regression analysis with $p = 0.002$, OR= 0.417, $p < 0.001$, OR= 0.028, and $p < 0.001$, OR= 0.121, respectively (table 26).

Interestingly, anastomotic leak was significantly related with presence of COPD ($p = 0.026$, OR= 2.109, 95% CI= 1.096- 4.061), as shown in table 27. Neoadjuvant therapy, surgical experience, type of surgical procedure and type of anastomosis did not significantly influence the rate of anastomotic leak ($p = 0.853$, OR= 0.942, $p = 0.274$, OR= 1.264, $p = 0.893$, OR= 1.023, and $p = 0.471$, OR= 0.772, respectively).

Table 26. Univariate and multivariate analysis of predictors of major& lethal postoperative complications (Clavien- Dindo III- V) after resection for esophageal cancer (n=320 patients, binary logistic regression)

	Univariate analysis		***Multivariate analysis***	
Parameter	***OR (CI 95%)***	**P** ***value***	***OR (CI 95%)***	**P** ***value***
Age	1.016 (0.993-1.039)	0.171		
Sex	**1.992 (1.094-3.625)**	**0.024***	**0.417 (0.199-0.873)**	**0.02***
CHD	1.168 (0.679-2.012)	0.574		
COPD	1.264 (0.760-2.102)	0.366		
Obesity	1.033 (0.596-1.789)	0.908		
Neoadjuvant therapy	**0.604 (0.384-0.949)**	**0.029***	1.359 (0.767-2.408)	0.293
Advanced tumor stage (UICC III& IV)	1.150 (0.745-1.775)	0.529		
Tumor localization	0.865 (0.581- 1.287)	0.474		
Duration of surgery	0.999 (0.997-1.002)	0.626		
Intraoperative blood loss	1.000 (0.999-1.000)	0.874		
Surgical experience	1.000 (0.737-1.357)	1.000		
Type of operation	1.142 (0.900-1.450)	0.275		
Anastomotic leak	**23.625 (8.207- 68.007)**	**<0.001*****	**0.028 (0.009-0.086)**	**<0.001*****
Respiratory complications	**6.422 (3.789- 10.884)**	**<0.001*****	**0.121 (0.066-0.221)**	**<0.001*****

** when p <0.05, *** when p< 0.001*

Table 27. Univariate analysis of predictors of anastomotic leak after resection for esophageal cancer (n=320 patients, binary logistic regression)

	Univariate analysis	
Parameter	***OR (CI 95%)***	**P** ***value***
Age	0.998 (0.968-1.030)	0.903
Sex	1.100 (0.481-2.518)	0.821
CHD	1.569 (0.774-3.180)	0.212
COPD	**2.109 (1.096-4.061)**	**0.026***
Obesity	1.223 (0.585-2.560)	0.592
Neoadjuvant therapy	0.942 (0.504-1.761)	0.853
Duration of surgery	1.000 (0.997-1.004)	0.862
Intraoperative blood loss	1.000 (0.999-1.001)	0.443
Surgical experience	1.264 (0.831-1.925)	0.274
Type of surgery	1.023 (0.735-1.423)	0.893
Type of anastomosis (hand-sewn vs. stapler)	0.772 (0.381-1.563)	0.471
Tumor localization	1.487 (0.838-2.640)	0.175

* *p <0.05*

3.6.2. Predictors for overall patient survival (OS) after resection for esophageal cancer

Advanced tumor stage, SC histological subtype and presence of major/ lethal postoperative complications Clavien- Dindo grade III- V were significant, independent factors for worse OS ($p < 0.001$, OR= 0.239, $p = 0.028$, OR= 1.506, and $p = 0.005$, OR= 0.582 respectively), as shown in tables 27 and 28, and figures 12 and 13.

Table 28. Univariate analysis of predictors of overall patient survival after resection for esophageal cancer (n=320 patients)

	Log rank for categorical parameters		***Cox regression for continuous parameters***	
Parameter	**P *value***	***x*** ^{2}	***OR (CI 95%)***	**P *value***
Age			1.012 (0.998-1.027)	0.092
Sex	0.679	0.171		
CHD	0.251	1.317		
COPD	0.102	2.680		
Obesity	0.831	0.045		
Histology (SC vs. AC)	**0.015***	**5.880**		
UICC tumor stage	**<0.001*****	**21.119**		
Tumor localization	0.990	0.021		
Duration of surgery			1.001 (0.999-1.002)	0.265
Type of operation	**0.002****	**14.888**		
Intraoperative blood loss			1.000 (1.000-1.000)	0.230
Anastomotic leak	0.885	0.021		
Respiratory complications	**0.007****	**7.367**		
Minor postoperative complications (Clavien-Dindo I&II)	0.965	0.002		
Major& lethal postoperative Complications (Clavien-Dindo III-V)	**<0.001*****	**22.613**		
Reoperation	**0.001****	**10.120**		

** p <0.05, ** p<0.01, *** p< 0.001*

Table 29. Multivariate analysis of predictors of overall patient survival after resection for esophageal cancer (n=320 patients)

	Cox regression	
Parameter	***OR (CI 95%)***	**P** ***value***
Histology (SC vs. AC)	**1.506 (1.045-2.170)**	**0.028***
Tumor stage	**0.239 (0.113-0.505)**	**<0.001 *****
Type of surgical procedure	1.004 (0.551-1.830)	0.090
Major& lethal postoperative complication (Clavien-Dindo III-V)	**0.582 (0.398-0.851)**	**0.005 ****
Respiratory complications	0.935 (0.658-1.328)	0.706
Reoperation	0.923 (0.651-1.310)	0.655

** p <0.05, ** p<0.01, *** p< 0.001*

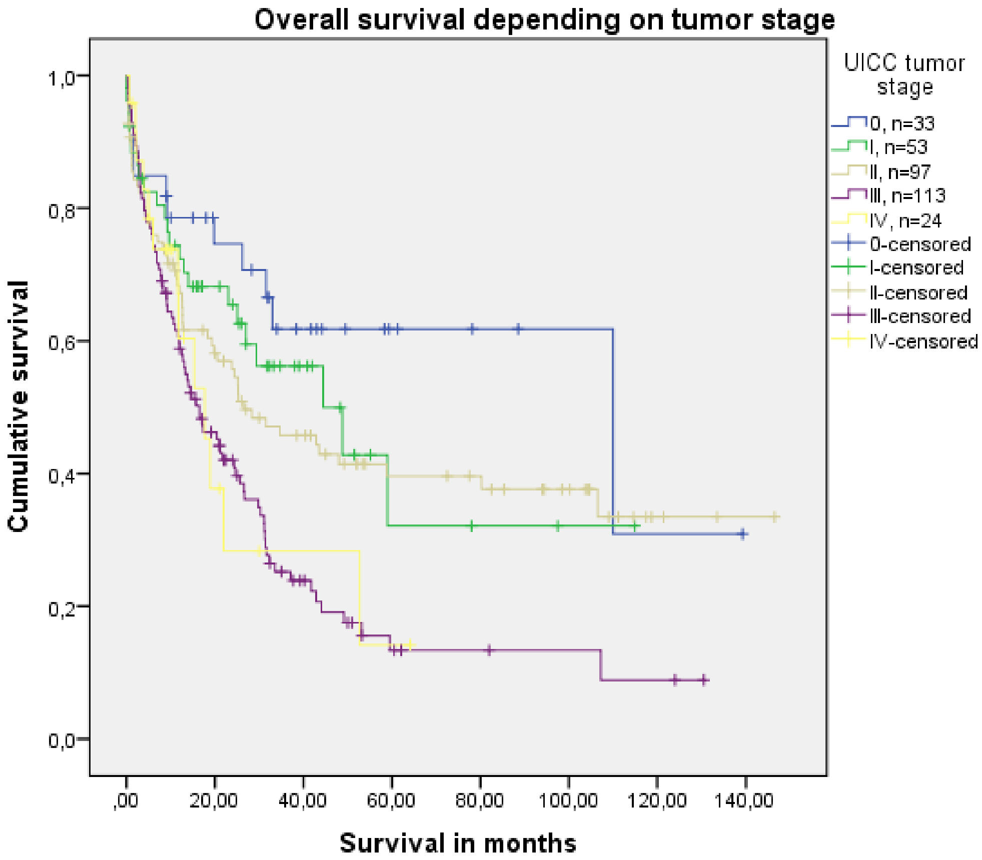

Figure 12: Overall patient survival (OS) after resection for esophageal cancer depending on UICC tumor stage (n= 320 patients, p<0.001, OR=0.239, multivariate cox regression analysis).

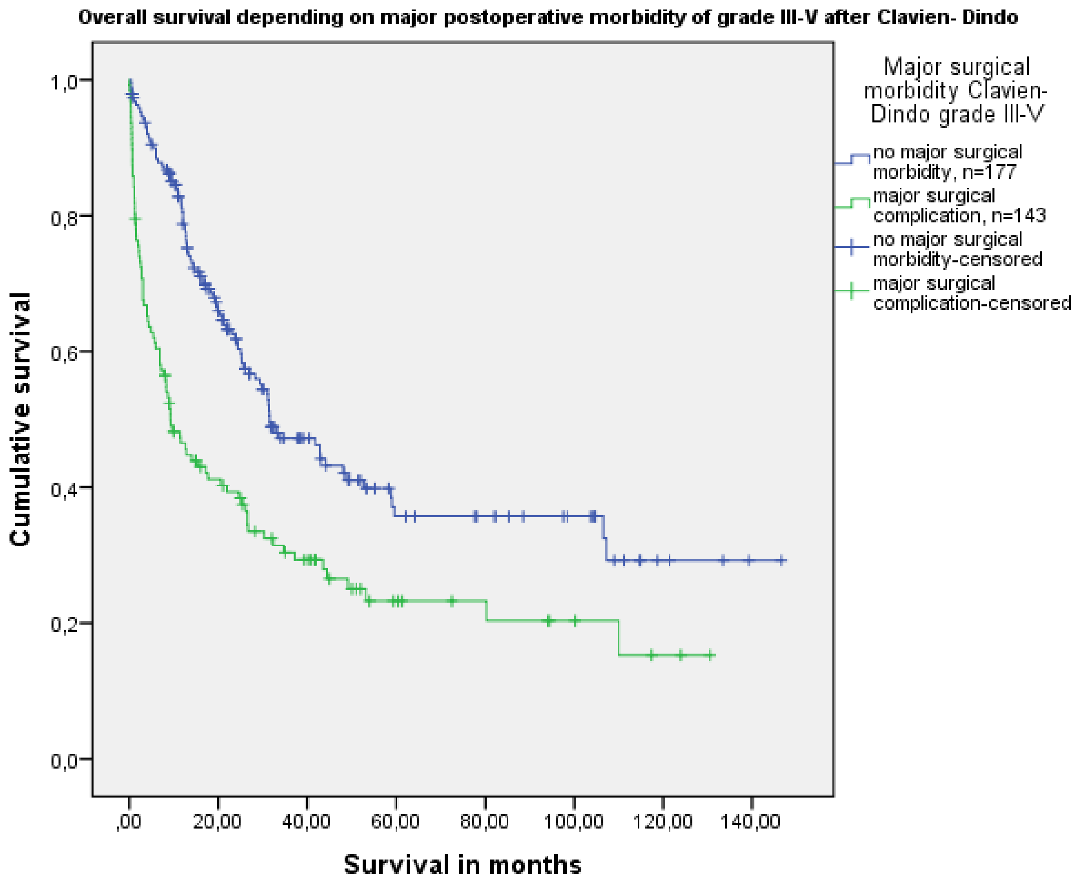

Figure 13: Overall patient survival (OS) after resection for esophageal cancer depending on major and lethal morbidity (Clavien- Dindo grade III-V, n= 320 patients, p=0.005, OR=0.582, multivariate cox regression analysis).

4. Discussion:

Aim of the present retrospective study was to assess the postoperative outcome and survival after surgery for esophageal cancer in our department in a time period from 2001- 2014. Our plan was to evaluate the results of surgical therapy and identify potential risk factors for worse postoperative outcome and overall patient survival (OS).

4.1. Overall results: Advanced tumor stage, SC histological subtype and presence of major or lethal postoperative complications (Clavien- Dindo grade III-V) were significant, independent factors for worse overall patient survival ($p<0.001$, OR= 0.239, $p=0.028$, OR= 1.506, and $p=0.005$, OR= 0.582, respectively). As expected, anastomotic leak and respiratory complications were significant, independent factors for higher rate of major or lethal postoperative complications Clavien Dindo grade III- V ($p<0.001$, OR= 0.028, and $p< 0.001$, OR=0.121, respectively).

Our results confirm the results of the prospective, population- based study of Rutegard et al., who reported that surgical complications are independent predictors for worse long- term survival, even in patients who survived after the initial postoperative period [34]. However, our study indicates that major postoperative morbidity grade III- V according to Clavien- Dindo, not minor postoperative morbidity (Clavien- Dindo grade I& II), led to poor long- term survival and therefore confirm the statement of Luc et al., that major postoperative complications influence long- term survival after esophagectomy [35].

4.1.1. Impact of type of surgery (transhiatal esophagectomy with cervical anastomosis) on postoperative outcome after resection for esophageal cancer.

A significantly higher postoperative morbidity was observed, if transhiatal esophagectomy with cervical anastomosis was performed. The mortality and morbidity rates in patients with a cervical anastomosis were significantly increased in our series, reaching 36.7%, and 70% respectively. Moreover, approximately 25 % of the patients suffered from palsy of N. recurrens in the 6 months´ follow- up, a procedure- specific postoperative complication.

In 3 extensive series with 3129 patients undergoing surgery, the rate of anastomotic leak after cervical anastomosis ranged from 12% to 21% [36-38]. The severity of anastomotic leak may be very disparate, from asymptomatic patients in type I leaks (localized leaks) to very severe symptoms such as systemic inflammatory reaction or septic shock in type IV leaks [39]. This variation depends on the size of leak, how it spreads and the presence of ischaemia, necrosis of the gastric conduit [40], or presence of systemic inflammatory reactions. In the present study, anastomotic leaks were more frequently treated with reoperation in this group of patients (32/46, 69.6%). Moreover, the number of patients who died within 90 days postoperatively was significantly increased, reaching up to one third of patients (36.7%).

4.1.2. Impact of respiratory complications on postoperative outcome.

Respiratory complications were summarized as minor postoperative morbidity (Clavien-Dindo grade I- II) in our cohort. Interestingly, we found no significant difference in the incidence of respiratory complications regarding transthoracic or intraabdominal esophageal resections, despite operative manipulation in the thorax within the transthoracic approach. This result is in accordance with the results of other studies, where minimally invasive esophagectomies did not lead to a lower rate of respiratory complications [41, 42]. In minimally invasive esophagectomies, similarly to intraabdominal esophageal resections the thorax is not opened. However, a metaanalysis by Zhou et al. showed superiority of minimally invasive esophagectomy in reducing in -hospital mortality of patients with resectable esophageal cancer [43]. 48 studies involving 14311 cases of resectable oesophageal cancer were included in the meta-analysis. Compared to patients undergoing open esophagectomy, patients undergoing minimally invasive esophagectomy had statistically decreased incidence of in-hospital mortality (OR=0.69, 95%CI =0.55 -0.86). Patients undergoing minimally invasive esophagectomy also suffered from significantly less pulmonary complications (RR=0.73, 95%CI = 0.63-0.86), pulmonary embolism (OR=0.71, 95%CI= 0.51-0.99) and tachyarrhythmia (OR=0.79, 95%CI = 0.68-0.92). Non-significant differences were observed among the included studies in the occurrence of anastomotic leak (OR=0.93, 95%CI =0.78-1.11), or necrosis of the gastric conduit (OR=0.89, 95%CI =0.54-1.49) [43].

4.2. Special aspects concerning surgical technique:

4.2.1. Hand- sewn versus stapler esophagogastric anastomosis after abdomino- thoracic resection for esophageal cancer.

Special focus was given upon the impact of anastomotic technique (intrathoracic stapler versus hand- sewn esophagogastric anastomosis) after abdomino-thoracic esophagectomy for cancer. The heterogeneity of previously published studies, their contradictory results [44-52] and the fact that the use of stapler devices in the context of abdomino- thoracic resection for cancer increased substantially in our institution in the time period 2010- 2014 were the reasons to focus on this topic. Our data showed similar rates of revealed anastomotic leak and stricture between intrathoracic stapler and hand- sewn esophagogastric anastomosis. Female gender, presence of anastomotic leak and presence of respiratory complications were identified to be independent factors for higher rate of major/ lethal postoperative morbidity (Clavien- Dindo grade III-V). Furthermore, histological subtype (SC), advanced tumor stage (UICC grade III& IV) and presence of major/ lethal postoperative morbidity (Clavien- Dindo grade III-V) were identified to be statistically significant independent factors for worse overall patient survival in the multivariate analysis. Important to note, that histological subtype and tumor stage cannot be influenced by the surgeon, whereas the surgical performance belongs to the entire field of specialty.

Regarding anastomotic leak rates after abdomino- thoracic esophageal resection, our incidence of 12.5% is similar to other reported rates [34, 53, 54]. Major/ lethal postoperative complications (Clavien- Dindo grade III- V) were significantly lower in the stapler anastomosis group, obviously due to the lower reoperation rate. Important to note, that in the hand- sewn anastomosis group, anastomotic leaks almost required reoperation (14/18 patients with anastomotic leak), contrary to the stapler anastomosis group, and thus leading to higher mortality (34.1% reoperation and 13.5% Clavien- Dindo V complications in the hand- sewn anastomosis group, compared to 8%, and 2% in the stapler group respectively). In the same line of evidence, no patient died from anastomotic leak in the stapler anastomosis group due to successful treatment with endoscopic stent insertion. Both, intraoperative blood loss and duration of surgery were comparable among both groups in contrary to the results of other observational studies, claiming that stapler anastomosis is faster performed than hand- sewn anastomosis [48].

There are numerous other studies comparing hand- sewn with stapled esophagogastric anastomosis (table 30). The majority consists in retrospective, non- randomized studies. Primary end points in these studies were anastomotic leak and stricture rate. The reported results are contradictory. Several reports showed no difference in anastomotic leak comparing both anastomotic methods [44, 55-62], while other reports demonstrated decreased anastomotic leak with stapler anastomosis [49, 63-67]. Kim et al. concluded in their systematic review of eight randomized, controlled trials, that there was no significant difference in the anastomotic leakage or early mortality [48]. One study demonstrated a difference in stricture rates, with fewer after hand-sewn anastomosis (9% vs. 40%, $p= 0.003$) [47]. Two metaanalyses found no significant difference in the rate of anastomotic leak comparing both anastomotic techniques[48, 52]. However, retrospective and randomized trials vary substantially in the performed surgical technique, stapler size, end- to- end vs. end- to- side esophagogastric anastomosis, cervical vs. intrathoracic anastomosis, one- row vs. double- row anastomosis, or application of neoadjuvant therapy prior to surgery. Our analysis showed no significant differences concerning anastomotic leaks and strictures between both types of anastomosis, however both occurred less frequent (with a 50% reduction) after stapler anastomosis. Moreover, we should also notice, that 30- day mortality underestimates in- hospital mortality, as shown in previous reports [68]. Our data also indicate, that 90- day mortality represents more accurately the in-hospital mortality. This was significantly reduced after stapler anastomosis (2 vs. 13.5%). Obviously, the stapler anastomosis is superior, providing better patient outcomes.

Table 30. Summary of non- randomized studies comparing hand- sewn with stapler esophagogastric anastomosis

Study	***Number of patients***	***Basic findings***
I. Retrospective studies		
Cooke et al. [67]	1133	↓ anastomotic insufficiency (AI) for stapler (OR=0.40, p<0.001), transhiatal esophagectomy with cervical esophagogastric anastomosis, side-to-side stapler anastomosis, 241 of patients had benign disease
Zhu et al. [62]	1194	↓ AI for two- layer hand- sewn anastomosis (0% vs. 3.5%, p<0.001), groups not equal (1024 two-layer hand-sewn vs. 170 stapler anastomoses), cervical and intrathoracic anastomoses included in the study, preoperative radio-, chemotherapy was not given for all patients
Kondra et al. [69]	168	↓ AI for stapler (13% vs. 27%, p=0.021), partially stapled (posterior stapled wall and anterior hand-sewn wall) anastomosis vs. hand-sewn cervical anastomosis
Blackmon et al. [70]	214	↓ anastomotic strictures and dysphagia for stapler (OR=3.39), 214 intrathoracic anastomoses included in the study, 3 groups: 44 side-to-side stapler vs. 147 circular stapler vs.23 hand- sewn anastomoses, propensity-matching
Viklund et al. [61]	275	No difference among both anastomotic methods, different type of surgery and localization of the anastomosis, anastomotic methods not described
Ercan et al. [44]	170	No difference in AI, ↓ anastomotic strictures for stapler (88% vs. 63%, p<0.001), 86 modified Collard esophagogastric cervical (partially stapled, partially hand-sewn anastomotic technique, terminalized, semimechanical, side-to-side cervical esophagogastrostomy) vs. 188 handsewn cervical anastomoses, propensity-matching
Furukawa et al. [64]	31	No difference among the three anastomotic methods, 3 groups: 11 triangular, with TA-30 liner stapler vs. 8 with circular stapler vs. 12 handsewn- cervical anastomoses
Casson et al. [56]	91	No difference among both anastomotic methods, (7.9% stapler vs. 22.6% hand-sewn, p=0.08), 53 hand-sewn vs. 38 partially cervical esophagogastric stapler anastomoses
Singh et al. [66]	93	↓ AI for stapler (3% vs. 23%, p<0.05), ↓ anastomotic strictures for stapler (18% vs. 58%, p<0.05), 67 transhiatal and 26 McKewon esophagectomies included in the study, 43 hand-sewn vs.16 partially stapler (modified Collard) vs. 34 linear stapler cervical anastomoses
Honkoop et al. [71]	269	↑ anastomotic strictures for stapler (48% vs. 35%, p=0.04), 269 transhiatal esophagectomies with cervical anastomosis included in the study, 114 one-layer hand-sewn vs. 154 circular stapler cervical anastomoses
Mc Manus et al. [49]	221	↓ AI for stapler (7.1% vs. 17.2%, p<0.05), ↑anastomotic strictures for stapler (15.3% vs. 2.7%, p<0.02)
Sugimachi et al. [60]	40	No difference among both anastomotic methods, 12 hand-sewn vs. 17 “Russian” stapler vs. 11 “American” stapler
Present study	176	Reduction of AI among both anastomotic methods (8% vs. 14.3%, p=0.22), 126 hand-sewn vs. 50 circular stapler intrathoracic anastomoses
II. Non-randomized prospective studies		
Fok et al. [57]	785	No difference among both anastomotic methods
Lam et al. [59]	411	No difference among both anastomotic methods
Peracchia et al. [65]	242	↓ AI for stapler (4.2% vs. 17.9%, p=0.013)

Wong et al. [55]	174	No difference in AI ↑ anastomotic strictures with stapler (11.3% vs. 5.6%, p not referred)
III. Meta-analyses		
Urschel et al. [45]	5 randomized controlled trials	No difference among both anastomotic methods
Kim et al. [48]	8 randomized controlled trials	No difference among both anastomotic methods
Honda et al. [52]	12 randomized controlled trials	No difference in AI (OR=1.02) ↑ anastomotic strictures with stapler (OR= 1.67) ↓ duration of surgical procedure (mean: - 15.3 minutes)

An important methodological advantage of this comparison is the qualitative homogeneity of the included patients. We chose to include into the analysis only patients subjected to open Ivor- Lewis abomino- thoracic esophageal resection with intrathoracic anastomosis. The therapeutic protocol used in our department was also standardized and given in detail. An esophagogastroduodenoscopy was routinely performed in all of our patients to control the anastomosis in the 6 months' follow- up. We did not analyze only the rate of anastomotic leak; a thorough comparison of various parameters including intraoperative blood loss, duration of surgical procedure, number of reoperations and 30-, 60- and 90- day mortality rates was performed.

The paramount methodological disadvantage of the present study is the retrospective non-randomized character. Furthermore, the number of hand-sewn and stapler esophagogastric anastomoses was not equal (126 vs. 50). The majority of esophagogastric anastomoses were hand-sewn until May 2012. From this time point, most of the anastomoses were performed using a 25 mm circular stapler in our institution. A prospective randomised trial is therefore more appropriate to draw more valid conclusions and answer the question which anastomotic method is better.

4.2.2. Role of postoperative radiologic examination and endoscopy in the detection and management of anastomotic leak.

In a prospective, controlled study, Schaible et al. suggested superiority of endoscopy to radiographic diagnosis of potential anastomotic leak after esophageal reconstruction [72]. The authors claim, that radiologic contrast swallow in the early postoperative days is often not feasible, has no further relevance, and therefore should be replaced by endoscopy. Contrary to this claim, we left the nasogastric tube routinely for 5 days postoperatively. If the anastomosis was patent in the postoperative radiographic control at the fifth postoperative day, nasogastric tube was removed and enteral feeding with liquids was started. Postoperative chest X- rays were performed before and after removing the intraoperatively placed chest tubes. From our data, we cannot show if there is additional benefit from performing the gastrografin swallow, because this radiologic examination was always performed.

Postoperative endoscopy played an important role in the management of anastomotic leak. In the stapler anastomosis group, anastomotic leaks were successfully endoscopically treated. In the hand- sewn anastomosis group, anastomotic leaks were treated mainly with reoperation. Consequently, 90 days´ mortality (Clavien- Dindo grade V complications) and overall survival was statistically significantly different among both anastomotic methods. Dasari et al. in their review of 27 case series (340 patients) recommend esophageal stent insertion as treatment option in the management of anastomotic leak with limited mediastinal or pleural contamination [73]. If we focus on the abdomino- thoracic esophageal resections performed in our department, 50 stapled and 126 hand- sewn anastomoses were performed. 4 patients (8%) after stapler anastomosis suffered from anastomotic leak, of whom only one was reoperated. On the contrary, 18 patients (14.3%) after hand- sewn anastomosis suffered from anastomotic leak, of whom 14 were reoperated. Our results confirm that less reoperations obviously led to lower 90 days´ mortality and consequently increased patient overall survival in the stapler anastomosis group. As previously mentioned, endoscopy was performed in the 6 months´ follow- up to control potential local tumor recurrence and treat potential anastomotic strictures with balloon dilatation.

4.2.3. Transthoracic vs. transhiatal resection for esophageal cancer.

Several studies compare transthoracic to transhiatal esophagectomy [74, 75]. In a randomized-controlled trial by Omloo et al. [74], no statistical advantage in overall 5-year survival could be found in patients with adenocarcinoma of the middle /distal esophagus (AEG I/ II) subjected to extended transthoracic compared to patients subjected to transhiatal esophageal resection. However, in contrast to transhiatal esophageal resection, extended transthoracic esophagectomy for type I esophageal adenocarcinoma shows an ongoing trend towards better 5-year survival, reaching nearly 36% in a recently published trial [74]. Moreover, patients with a limited number of positive lymph nodes in the resection specimen seemed to benefit from an extended transthoracic esophagectomy [74]. Two meta-analyses by Yang et al. and Boshier et al. [76] could also not demonstrate statistically significant differences in survival and postoperative morbidity and mortality in patients with AEG undergoing transthoracic or transhiatal resection [75]. However, the type of the selected procedure depends on the localization of the tumor, accounting for a significant selection bias, when comparing TTE to THE without considering the localization of the tumor. Moreover, the lymph nodes of lower mediastinum are often resected when performing THE, so that the performed lymphadenectomy is more extended than the standard D2 lymphadenectomy. Mönig et al. could demonstrate, that the main topographical distribution of lymph node metastasis in adenocarcinoma of gastroesophageal junction is towards the abdomen and the lower mediastinum. In 50 specimens, 1730 lymph nodes were evaluated regarding metastatic infiltration. Lymph node metastases of the lower mediastinum were found in 24% of type I carcinoma, in 11% of type II carcinoma and in 13% of type III carcinoma, whereas the lymph nodes of the upper mediastinum were tumor free in all patients with transthoracic en bloc resection and 2-field lymphadenectomy (n = 13). In all cases with lymph node metastasis abdominal lymph nodes were infiltrated independently from the localization of the primary tumor [77].

179 abdomino- thoracic esophageal resections and 59 transhiatal esophagectomies were performed in our department. Our data demonstrate similar postoperative outcome comparing both surgical procedures. We observed no statistically significant difference regarding anastomotic leaks, major surgical complications, 90 day mortality or overall patient survival (p= 0.107, 0.192, 0.270, and 0.51, respectively). Respiratory complications appeared more frequently in the "abdomino- thoracic esophageal resection" group, though not reaching statistical significance (p= 0.06, chi square test).

4.2.4. Extended LN- dissection.

In Japan, extensive lymph- node dissections with curative intent are widely performed, including the upper and middle mediastinal lymph nodes (two- field lymphadenectomy) or occasionally three- field lymphadenectomy including also the cervical lymph nodes [78]. The incidence of squamous- cell esophageal cancer is higher in Asia compared with Western countries, which could explain why three- field lymphadenectomies are more often performed in Japan in association with R0 resection. Interestingly, Igaki et al. suggested that three- field lymphadenectomy should also be performed for squamous cell carcinomas of the lower thoracic esophagus [78]. A prospective randomized trial showed high rates of neck recurrence in patients with SCC, supporting D3 lymphadenectomy in this group of patients [79]. Lerut et al. showed, that overall morbidity was 58% and 5 years´ overall survival was 41.9% after three-field lymphadenectomy [80]. Several meta-analyses suggested extended D3 lymphadenectomy, especially for tumors with lymph node metastasis [81], however with higher anastomotic leaks and N. recurrens palsy [82]. The role of 3-field lymphadenectomy in distal third esophageal adenocarcinoma remains a case of controversy [80].

Extended lymph node dissection is performed according to the Japanese society for gastric cancer for Siewert type II adenocarcinoma of the esophagogastric junction [28]. Mine et al. investigated the lymph node involvement and prognosis in patients with Siewert type II cancers treated by surgical resection, with regard to lymphadenectomy around the left renal vein [83]. Out of 150 patients with type II esophagogastric adenocarcinoma, 94 had left renal vein lymphadenectomy. In these patients, the incidence of involvement was 17 %, and the 5-year survival rate was 19 %. Multivariate analysis showed left renal vein lymphadenectomy to be an independent prognostic factor in patients with histopathological tumor category T3-4 (OR= 0.51, 95% CI= 0.26- 0.99, $p= 0.048$) [83]. The authors concluded that left renal vein nodal involvement is similar to that seen along the splenic artery, in the lower mediastinum and celiac trunk, with similar impact on patient survival.

Yamashita et al. explored the extent of lymphadenectomy in 225 patients with AEG II tumors [84]. They also dissected the para- aortic lymphatic nodal station 16a2 in 73 patients and the nodal station 16b in 38 patients. The incidence of positive lymph nodes was 11% for 16a2 and 18 % for 16b. The 5- year survival rate in patients with positive lymph nodes was 12.5% for 16a2 and 0% for 16b. It is subsequently questionable, whether a more extended lymphadenectomy with dissection of para- aortic nodes should be routinely performed, due to the low incidence and the low survival rate, as concluded by the authors [85].

88 patients with AEG II tumor were operated in our department with a median survival of 23 months. As previously mentioned, we routinely performed the D2 lymphadenectomy. Moreover, lymph nodes of lower mediastinum were also resected when performing THE. Postoperative lymph node status significantly influenced overall patient survival ($p< 0.001$, log rank test).

There is only one report (n= 4 cases) regarding salvage lymphadenectomy for recurrent esophageal cancer after lymphadenectomy [85]. In this study, salvage esophagectomy was indicated for locoregional recurrence without distant metastases after failed definitive chemoradiation (RCT) [85]. In case 1, right supraclavicular lymph node was tumor infiltrated and R0 resection was carried out; the patient was alive without recurrence (follow- up 18 months). In case 2, metastases in the left cervical paraesophageal and the left supraclavicular lymph nodes were found; residual tumors were R1 in both lesions. The patient was alive despite esophageal recurrence (follow- up 32 months). In case 3, a lymphadenectomy was performed on his thoracic para-aortic lymph nodes; however, the tumor was removed incompletely, and the patient died 4 months after salvage lymphadenectomy from tumor disease progression. In case 4, a subcarinal lymph node was considered metastatic, and was dissected but turned out to be tumor free. The patient died 17 months postoperatively from pneumonia. The authors concluded, that their experiences suggest that some patients may survive relatively long with salvage lymphadenectomy [85].

4.3. Role of neoadjuvant therapy or definitive chemoradiation on postoperative outcome

4.3.1. Impact of histological subtype on response to neoadjuvant therapy (NAT), disease free interval (DFI) and OS.

In addition, special attention was given in the impact of histological subtype upon response to NAT, DFI, and OS.

Neoadjuvant chemoradiation became a standard part of the multimodal therapy of esophageal cancer, because of the results of large randomized trials that reported improved long- term outcomes [32, 86-92]. The Chemoradiation for Oesophageal Cancer Followed by Surgery Study (CROSS) Group, included patients with either esophageal adenocarcinoma or squamous cell carcinoma who were clinical stage T1N1 or T2-3, N0-1, and showed that squamous cell carcinoma hat more favorable outcomes compared to esophageal adenocarcinoma [32]. Consequently, patients with both histological subtypes (adenocarcinoma of esophagus, squamous cell carcinoma of esophagus) are currently subjected to the same neoadjuvant therapy regardless of histological subtype.

However, Deng et al. separated the patients with SC and the patients with AC concerning neoadjuvant therapy. After conducting a meta- analysis, they suggested neoadjuvant chemoradiation as standard preoperative treatment strategy for locally advanced esophageal SC. In patients with esophageal AC, the authors concluded, that neoadjuvant chemotherapy alone may be the best preoperative treatment strategy to avoid the adverse effects of radiotherapy [93]. Contrary to this assumption, Alnaji et al. supported the neoadjuvant chemoradiation for esophageal AC, and demonstrated the value of pathologic complete response in long- term outcomes.[94] Hoeppner et al. supported chemotherapy alone for patients with locally advanced esophageal AC in their retrospective study, claiming, that there was no survival benefit in comparison to patients treated with neoadjuvant chemoradiation, despite better histologic response after chemoradiation [95]. The additional irradiation preoperatively in our patients with locally advanced AC, according to CROSS protocol after 2012, did not significantly influence the response to NAT (p= 0.979, x^2 exact test). Moreover, our study demonstrates, that not only complete response, but also partial response to NAT contributes significantly to overall patient survival after esophageal resection for cancer, regardless of histological subtype (p= 0.015, OR= 0.615, 95% CI= 0.416- 0.909).

Concerning overall survival benefit of patients receiving neoadjuvant therapy, we refer to the metaanalysis of Gebski et al., where the influence of neoadjuvant chemoradiation on survival rates of patients with squamous- cell carcinoma and the influence of preoperative chemotherapy on survival of patients with adenocarcinoma of the esophagus were separately examined (10 randomized studies with 1209 patients and 8 randomized studies with 1724 patients, respectively) [96]. This metaanalysis reported significant survival benefit (13% difference after 2-years) in case of squamous- cell carcinoma, but not in case of esophageal adenocarcinoma.

The favorable effects of neoadjuvant therapy were shown in a Cochrane database review from 2013, where 14 randomized controlled trials with a total of 2422 eligible patients were analysed. Perioperative chemoradiation was associated with longer disease-free survival, higher rates of R0 resection, and more favorable tumor stage at the time of resection, while there was no association to perioperative morbidity and mortality for resectable adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus [97]. In our study, response to NAT was the only independent factor that influenced disease free interval and overall patient survival regardless of histological subtype.

A significant restriction of our analysis, apart from its retrospective character, is the relative small number of study population. From 320 patients operated in our department from 2001-2014, only 117 patients met the inclusion criteria. We excluded patients who died within the first 90 days postoperatively, or suffered from UICC Stage IV esophageal cancer, to investigate tumor progress and long- term survival.

In addition, the need for tailored neoadjuvant therapy depending on histological subtype is demonstrated in the present study. We expect therefore with great interest the results of the ESOPEC trial, a prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus [98].

Previous observational studies have reported that neoadjuvant therapy did not lead to increased surgical morbidity [48]. Mungo et al. compared 30- day mortality and postoperative morbidity after esophagectomy in patients who had received neoadjuvant therapy and patients without neoadjuvant therapy in a time-period from 2005- 2011 [99]. They concluded that the incidence of postoperative complications was similar in both groups. However, they reported less blood loss and thromboembolic events in the "surgery- alone" group (5.71% vs. 8.27%, p= 0.027; 6.89% vs. 10.57%, p= 0.004).

Interestingly, 6 out of 26 patients (23%) experienced tumor progress, despite initial complete response observed in the postoperative histopathologic specimen. 2 out of 6 patients suffered from esophageal adenocarcinoma.

The impact of neoadjuvant therapy on postoperative outcome after esophageal resection was assessed in a European multicenter study [100]. 2944 patients treated for esophageal cancer between 2000 and 2010 in 30 European centers were included in this study. There was no difference in anastomotic leak among patients subjected to neoadjuvant therapy or patients without neoadjuvant therapy. Our study basically confirms these results. Neoadjuvant therapy, as well as surgical experience, type of surgical procedure or type of anastomosis did not significantly influence the rate of anastomotic leak (p= 0.853, OR= 0.942, p= 0.274, OR= 1.264, p= 0.893, OR= 1.023, and p= 0.471, OR= 0.772, respectively).

4.3.2. Role of definitive chemoradiation (RCT) in esophageal cancer.

In view of the high morbidity after esophageal surgery for cancer (44.7% major postoperative morbidity of grade III-V after Clavien- Dindo classification in our patients), alternative therapeutic strategies could be considered. Especially for patients with locally advanced SCC of the upper 1/3 of esophagus and comorbidities, it was suggested to apply definitive RCT for patients not suitable for surgery as first line treatment and salvage surgery only in cases without response or with locoregional recurrence after definitive RCT for this group of patients [101]. There are two randomized controlled trials comparing the benefit of adding surgery to definitive RCT [101, 102]. Only patients with squamous cell carcinoma of the esophagus were included. The study of Bedenne et al. randomized patients with response after RCT either to a surgery or an observation group [103]. 259 patients were evaluated (129 surgical, 130 definitive RCT; 11% adenocarcinoma). Median survival in the surgical and non-surgical groups was 17.7 months and 19.3 months, respectively, and 2-year overall survival was 34% versus 40%, respectively (OR=0.90, p=0.44). In the surgical group, improved locoregional control and less palliative procedures (such as stent insertion) were found. Mortality analyzed at 90 days was 9.3% in the surgical group versus 0.8% in the non-surgical group. The fact that improved locoregional control in the surgical group did not lead to an increase in overall survival implies the difficulty to adequately stage patients before treatment and the biological heterogeneity inherent to esophageal cancer.

The study of Stahl et al. adopted induction chemotherapy prior to RCT in an effort to decrease formation of remnant metastases [101]. This study randomized 172 patients (86 to RCT followed by surgery versus 86 treated with definitive RCT). The results showed better locoregional disease control with surgery and longer disease-free survival with surgery compared to observation after definitive chemoradiation (64% versus 41% at 2 years; p= 0.003). However, in contrast to the Bedenne trial, the Stahl trial (which randomized all patients rather than responders only) demonstrated a survival advantage in the surgery group (31% versus 24% at 3 years; p= 0.02). This study also found a significant increase in treatment-related mortality in the surgical group (12.8% versus 3.5%; p=0.03). An interesting finding on the sub-group analysis was that non-responders with (R0) resection reached 32% 3 -year survival. This markedly contrasted to responders who achieved more than 50% 3 -year survival regardless of the treatment modality.

Markar et al. reported that salvage esophagectomy (SALV) is associated with poor short-term outcomes when compared to scheduled esophagectomy following neoadjuvant RCT (NCRS). This metaanalysis included eight studies comprising 954 patients; 242 (SALV) and 712 (NCRS). SALV was associated with a significantly increased incidence of post-operative mortality (9.5 vs. 4 %; pooled odds ratio [POR] = 3.02; $p < 0.001$), anastomotic leakage (24 vs. 15 %; POR = 1.99; $p = 0.005$), pulmonary complications (30 vs. 17 %; POR = 2.12; $p < 0.001$), and an increased length of hospital stay (weighted mean difference = 8.3 days; 95 % CI 7.08–9.5; $p < 0.001$) [102].

In our study, we did not include patients who received definitive RCT for squamous- cell esophageal cancer. However, the postoperative morbidity and the overall survival following transhiatal esophagectomy with cervical anastomosis with advanced tumor stage was disappointing. Retrospectively, we may reconsider, that these patients would probably benefit more from a definitive RCT instead of surgery.

Whether a definitive RCT compared to surgical resection results in less mortality, morbidity, and longer survival for older patients with esophageal cancer, was also subject to investigation. Morita et al. retrospectively explored this issue in a total of 1.002 patients with thoracic esophageal cancer undergoing esophagectomy. Three groups were formed: I (≤ 74 years old, n=898); II (75-79 years, n=81); and III (≥ 80 years, n=23). Historical changes were related to as a first (1964-1989) and a second period (1990-2011). The morbidity rates were 40%, 41% and 26% in the respective groups. Pulmonary complications decreased historically in groups II and III (36% to 15% and 43% to 0%, respectively). The mortality was higher in the older groups (4.8%, 8.6% and 13.0%, respectively); however, there was a marked historical decrease in groups II (18.2% to 5.1%) and III (28.6% to 6.3%). The 5-year survival improved from 5% to 35% in group II and from 0% to 17% in group III. They concluded that the outcomes of esophagectomy for elderly patients have markedly improved over time [104]. The postoperative results after resection for esophageal cancer in older patients were comparable to those obtained in younger patients in our study. The preoperative age of patients should not be considered a contraindication to surgery according to our results.

4.4. Pros and Cons of retrospective studies.

Our study is a retrospective cohort study; a major limitation of retrospective studies are significant biases which may have affected the results. Among these biases that may put in doubt the results of this type of study are the selection bias and the misclassification or information bias. Selection bias is a statistical bias in which there is an error in choosing the individuals or groups to take part in a scientific study. Information bias (epidemiology) means bias arising in a clinical study because of misclassification of the level of exposure to the agent or factor being assessed and/or misclassification of the disease or other outcome parameters [105, 106]. Furthermore, exposure or outcome assessment cannot directly be controlled, but depends upon accurate record-keeping. Retrospective studies can require very large sample sizes, if rare events are examined [107].

On the other side, important advantages of observational studies are, that they are conducted on a smaller scale, they typically require less time to complete, they are better in comparison with prospective studies for analyzing multiple factors, and they can potentially address rare diseases, which would require extremely large cohorts in prospective studies. Retrospective studies are especially helpful in addressing diseases of low incidence [107]. Retrospective studies are also less expensive than prospective studies, because the resources are mainly directed at collection and statistical analysis of data only.

To assess the OS we selected patients operated until 31.12.2014; in order to be able to use censored data, we accept the hypothesis that censoring is independent or unrelated to the likelihood of developing the event of interest. This is called non-informative censoring [108].

Appropriate use of the Kaplan-Meier estimation relies on the assumption that censoring is independent of the likelihood of developing the event of interest and that survival probabilities are comparable in participants who attend early and later into the study. When comparing several groups, it is also important that these assumptions are applied in each group and that censoring is not more likely in one group than another [108].

5. Note of thanks

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II. Complementary material/ data:

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