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Current Surgical Treatment of Esophageal Cancer-Distal Adenocarcinoma, Multidisciplinary Approach, Evolving Minimal-Invasive Approach at High-Volume Centers

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Abstract

Even in 2020 esophageal cancer stays a severe disease and means a caesura in the life of the affected.

Early carcinoma under strict indications and conditions can be safely resected by interventional endoscopy. In locally advanced esophageal cancer of the mid and lower third radical resection stays the gold-standard. The favored approach is the transthoracic esophagectomy with 2-field lymphadenectomy and reconstruction by gastric pullup. In recent years, progress resulted in a notable decrease in morbidity and mortality of these procedures and in an acceptable life quality despite resection and reconstruction.

Additionally, multidisciplinary treatment-especially neoadjuvant chemo- and radiochemotherapy-improved long-term survival. Overall it is clear, that the treatment of esophageal cancer in high volume centers is safer and more effective.

Challenges for the future are the further development of minimally invasive procedures by laparoscopic, thoracoscopic, or robot-assisted approaches, which results in minimizing the operative trauma and reducing pulmonary complications.

With further progress in decoding the esophageal cancer gene, gene-products, and pathways more specific prevention and more targeted therapy could be applied.

Standards of treatment of esophageal cancer differ from country to country. This lies mostly in the ethnic differences like incidence, the unequal distribution of squamous cell carcinoma and adenocarcinoma, and in broad differences in concepts and the capability of the health systems. This review focuses on the current surgical diagnostic and curative treatment of esophageal cancer at the majority of high volume centers in Germany by reviewing the associated literature and imbedded by the author's own clinical and academic experiences.

Keywords: Esophageal cancer • Surgical treatment • Radiotherapy • Chemotherapy

Introduction

The incidence, localization, and histological subtype of esophageal cancer differ in Europe from other parts of the world. In Europe especially squamous cell carcinoma is much rare than in many other countries around the world. However, the incidence of distal adenocarcinoma of the esophagus in Europe is rising, so the discussion of esophageal surgery in Germany naturally centers around distal adenocarcinoma surgery. For this and other reasons, the consecutive treatment concepts vary in comparison to many others all over the world. Therefore an updated and country-specific review is required and useful for clinical and scientific work [1-4].

Methods, search strategy

PubMed (U.S. National Library of Medicine, National Center for Biotechnology Information, Bethesda MD, USA) database was selected for the search. The language was limited to English and German and the focus was on publications from the past ten years. We used the (MeSH)-search term “Esophageal Neoplasm’s” connected with “AND” and the term “Surgical

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Procedures, Operative". The current national German guideline of the associated professional societies was considered in its entirety [5].

Epidemiology

In Europe, we observe more than half of esophageal cancer in the lower third of the esophagus, less than a third in the mid third and only about 10 percent in the upper third [1]. We distinguish esophageal cancer from the Adenocarcinoma of the Esophagogastric Junction (AEG type I, II, III) according to the classification of Siewert and Hoelscher from the year 1987 [6,7].

Worldwide, the incidence of esophageal cancer is estimated at 5,00,000/year [1]. High incidence areas with more than 100 per 1,00,000 inhabitants are Central and Eastern Asia, Middle East, Turkey, India, parts of Africa, China, Japan, Korea, and the north of Iran, all together form the so-called "esophageal cancer belt" [1,2]. In these parts of the world, 90% of esophageal cancer shows the subtype squamous cell carcinoma [2]. In Europe, North America, Australia and Singapore esophageal cancer is less common with an incidence of 8-10/1,00,000 inhabitants per year, but the subtype adenocarcinoma of the lower esophagus shows a dramatic increase of up to 400% [1,2,8]. 5,700 men and 1,700 women have been registered in Germany with a newly diagnosed esophageal cancer in the year 2018; this means 3% of malignant tumors in men and 1% in women [5]. The peak age of the disease lies-corresponding to most gastrointestinal tumors-in the 6th to 7th decade. Worldwide a sex-ratio (male-female) of 3:1 for squamous cell cancer and 6:1 for adenocarcinoma is reported [2,9].

Definition, etiology, localization, pathophysiology

Esophageal cancer is defined as originating up to 2 cm proximally from the esophagogastric junction. In almost all cases esophageal cancer is an adenocarcinoma or a squamous cell carcinoma. All other malignant epithelial tumors like small-cell-carcinoma, adenoid-cystic-carcinoma, or primary melanoma are rare as are neuroendocrine carcinomas, malignant or semi malignant mesenchymal or mixed epithelial-mesenchymal tumors (e.g. sarcoma, GIST, carcinosarcoma) and benign tumors e.g. leiomyoma [1-3,5]. Squamous cell carcinoma develops more in the cervical part (about 15 cm-20 cm from the lower incisors) and thoracic part (about 20 cm-30 cm from the lower incisors) of the esophagus. Adenocarcinoma develops more at the distal third of the esophagus (about 30 cm-40 cm from the lower incisors). The macroscopic growth of esophageal cancer is irregular and either exulcerated-endophytic (majority) or polypoid-exophytic. The surface is mostly rough and cauliflowerlike [3].

Squamous cell cancer originates from the squamous cells of the intact esophageal mucosa. Adenocarcinoma originates either from the stationary or upwards migrated (heterotopic) mucosal glands of the esophagus or from Barrett's metaplastic columnar epithelium cells caused by longstanding reflux disease.

The research network of the "Global Cancer Genome Atlas Project", published in Nature, examined 164 specimens of esophageal cancer. Deletion, amplification, mutation, methylation, or epigenetic modulation of genes lead to altered repair enzymes, cell cycle regulators or receptors. In squamous cell carcinoma, they found 6 often mutated genes (TP53, NFE2L2, MLL2, ZNF750, NOTCH1, TGFBR2), in adenocarcinoma, they found 5 often mutated gene-loci (TP53, CDKN2A, ARID1A, SMAD4, ERBB2). Squamous cell carcinoma and adenocarcinoma of the esophagus are genetically two completely different entities, which supports the observed large differences in clinical behavior [10].

As concerns, the multifactorial etiology based on a genetic predisposition is sufficiently proven. On the contrary, numerous clinical risk factors for esophageal cancer have been identified (Table 1). A causal relationship between the strong increase of obesity in Europe and the US and the increasing number of adenocarcinoma of the lower esophagus may lie in the connective link of the gastroesophageal reflux disease [8]. Invasive cancer develops individually over the prestages low and high-grade dysplasia and *in situ* carcinoma [11,12].

Table 1. Identified risk factors for the development of squamous cell carcinoma or adenocarcinoma of the esophagus [2,3,5].

Adenocarcinoma	Squamous cell carcinoma
Barrett-esophagus	Tobacco Smoking[1]
Obesity	Alcohol overconsumption[2]
Symptomatic GERD (Gastro-Esophageal Reflux-Disease)	Former alkali or acid burn of the esophagus
Nitrosamine in food	Diverticulum of the esophagus, achalasia, Plummer-Vinson-Syndrome, hereditary palmoplantar keratosis, Fanconi-anemia
Mould toxin	Human Papilloma Virus?
Lack of vitamins (a few fruits, vegetables)	Gluten-sensitive Enteropathia
Former thoracic radiotherapy	Mould toxin
Tobacco Smoking	Former radiotherapy at neck/thorax
Achalasia	Low socioeconomic level
Former alkali or acid burn of the esophagus	Bad oral hygiene
	Nutritional deficiencies, folic acid deficiency, lack of zinc and vitamin A
	Very hot drinks
	Red meat

[1]By swallowed toxins of cigarette smoke; [2]Especially aldehydes as a metabolite of alcohol was identified for being a carcinogen

Prevention of esophageal cancer

A healthy lifestyle with vitamin-packed food, smoking cessation, reduction of alcohol consumption, physical activity, and prevention of obesity have been identified as relevant parameters for personal risk reduction. Subsequently, identification of symptoms in healthcare such as reflux, dysphagia, recurrent aspirations, weight loss and anemia by esophagogastroduodenoscopy continues to improve the prognosis. Of importance is the continuous and subtly preventive screening of patients with confirmed Barrett metaplasia by gastroscopy with multiple biopsies (Seattle protocol). Proton pump inhibitors, non-steroidal anti-inflammatory drugs, statins and healed helicobacter-pylori infections were identified as strong independent preventive factors [5,13-15].

Primary Staging

Accurate primary staging is the basis of an evidence-based therapy decision, assessment of the prognosis, and basis for the use of data in science. Without accurate staging patients are over or (mostly) undertreated. It is estimated, that up to 70% of the patients with newly diagnosed esophageal cancer in Europe and the US are not routed to an adequate staging process and are consequentially not treated according to the guidelines [1,7,16-19]. The pivotal questions concerning technical,

oncological, and functional resectability of esophageal cancer can only be answered by an experienced esophageal surgeon.

Signs and symptoms

Asymptomatic, early cancer of the esophagus is mainly detected randomly by routine endoscopies and/or according to diagnostics of other causes (e.g. transesophageal ultrasound of the hearth) or within the monitoring of Barrett's disease.

Dysphagia is the cardinal symptom of esophageal cancer but it occurs only when 2/3 of the lumen is already obstructed. In patients over 50 years esophageal cancer is the most common cause for a newly appearing dysphagia [5]. The typical history is discontinuous but progressive dysphagia often combined with retrosternal pain (odynophagia) or disturbance. It starts when consuming solid, and subsequently liquid food. The endpoint consists of frequent regurgitations and complete aphagia with a need for spitting out saliva [16]. The involuntary weight loss amounts to 3 kg-15 kg depending on the habitus of the patient. Due to insufficient so-called "clearing" of the esophagus by swallowing and autoperistalsis often superinfections with bacteria and/or fungi (soor-esophagitis) lead to possibly severe pain and halitosis. 90% of patients with esophageal cancer are symptomatic at the time of diagnosis, which is clinically a clear indicator for an advanced tumor stage (cT2-4). Typically many weeks or a few months pass from the first symptoms that patients remember to a histologically confirmed diagnosis.

Hoarseness and cough can be caused by affection or infiltration of the recurrent laryngeal nerve, the trachea or main bronchi due to their anatomical proximity. This is either by direct infiltration or even by affected lymph nodes [5,7,16].

Physical examination

Reduced general condition, nutritional status, and state of force are mostly noted first in patients with esophageal cancer. The documentation of body weight is of special importance. Cervical and supraclavicular lymph nodes should be examined. With the use of modern B-mode ultrasound, a scan of intraabdominal and retroperitoneal organs can be made rapidly. As such, liver metastases or ascites can easily be detected or roughly excluded [5,7,16].

Esophagogastroduodenoscopy

Most patients with esophageal cancer present with a written EGD-report and an already confirmed histological diagnosis. The EGD with biopsy should, however, be repeated because external descriptions of localisations are often unreliable, though they are highly important for correct staging.

Today we demand a high-resolution flexible video-endoscopy with digital documentation. The tumor must be described in its sublocation, vertical extension (proximal and distal margin), and circular (e.g. circular, semicircular) dimension. The distance is specified from the line of the lower incisors. Furthermore, the information on the grade of stenosis of the suspicious lesion must be given. A description of the height of the upper esophageal sphincter (norm 15 cm from the lower incisors) and the cardia (norm 40 cm from the lower incisors) is also mandatory. If there is a Barrett lesion or reflux alterations, the extent must also be described in cm, by clinical classification (short segment, long segment) and according to its morphological aspect (Prague or Los Angeles classification). The diagnosis is confirmed through biopsies from all suspect lesions and consecutive histopathological examination.

Suspicious second or multiple lesions must be described and examined by biopsy. The diagnostic value of chromoendoscopy (Lugolian solution/ methylene blue) or by the digital imitation "Narrow Band Imaging" (NBI) or other methods (autofluorescence, confocal endomicroscopy, optical coherence tomography) to improve the visualization of early carcinoma or premalignant lesions such as metaplasia and dysplasia are not well-proven. Despite this, these methods should be applied to improve the detection of premalignant lesions and early cancer in high-risk patients [17].

Computer tomography

When esophageal cancer is confirmed histologically a CT-scan of chest, abdomen and - in the case of carcinomas of the upper third-of the neck with oral and intravenous contrast must follow. This sequence is reasonable because in the case of distant metastasis an endo-sonography is obsolete. The primary diagnostic value of sectional imaging lies in the exclusion or proof of distant metastasis in preferred parenchymatous organs such as the liver and lung. But also relevant in formations about the position (e.g. distance to the carina), the extent of the tumor or infiltration of neighboring organs, vessels or structures (diaphragm, pericardium) is very relevant. However, the evidence for affected lymph nodes is limited because the size and structure do not always correlate with dignity [5,20-22].

Endoscopic Ultrasound (EUS)

EUS serves to clinically detect the depth of infiltration of the tumor (T-stage) and is obligatory in patients with intended curative treatment. Depending on the T-stage, the experience of the examiner and the standard and quality of the EUS device; the accuracy of the measurement will differ. Between T3 and T4 tumors, there is high discriminatory power with a sensitivity of 80%-93% and a specificity of 92%-96%. The lowest accuracy, however, lies between T2 and T3 tumors [2,23]. The locoregional status of lymph nodes can be determined, however with significantly lower accuracy than in the T-stage. If EUS is combined with a local puncture and fine-needle aspiration at suspected lymph nodes the accuracy of this examination from 70%-90% can be increased.

Flexible bronchoscopy

All esophageal cancer at or above the level of the carina, as well as all squamous cell cancer types, should have a flexible bronchoscopy to exclude tracheal-/broncheal involvement and to exclude an additional primary bronchial carcinoma. Additionally, in all squamous cell cancers, an ENT specialist should be consulted because of the high percentage of potential concomitant malignant disease (e.g. mouth, pharynx, larynx, tongue) [2,24-26].

PET-CT

18F-Fluorodeoxyglucose-Positron Emission Tomography-CT (18F-FDG-PET-CT) is suitable for the consequent clinical clearing of the dignity of suspected lesion expansion (assumed lymph node or distant metastasis), but it is not a standard staging tool [22]. The performance of PET-CT for the monitoring of the response under neoadjuvant treatment is discussed and observed in several clinical trials [5,22].

Advanced diagnostic investigations

Numerous further technical examinations can yield individuals finding constellations. Mostly the following diagnostics or interventions are needed selectively:

- Magnetic Resonance Imaging (MRI) of the liver, kidney, adrenal gland in case of limited validity of CT or contrast medium allergy or renal insufficiency
- CEUS of the liver in case of limited validity of CT or MRI
- Elastography of the liver (liver cirrhosis)
- Diagnostic laparoscopy (peritoneal seeding, unclear liver lesions)
- Ultrasound or CT guided puncture of lesions in the liver and lung (e.g. differential diagnosis of second cancer versus metastasis)
- Cranium MRI or CCT (brain metastasis)
- Colonoscopy (in intended reconstruction by a colon)

Clarification of functional resectability and fitness

Patients with esophageal cancer are often in highly reduced condition. Particularly in squamous cell cancers, we see concomitant diseases such as Chronic Obstructive Pulmonary Disease (COPD) or liver cirrhosis due to alcohol and tobacco abuse. In adenocarcinomas, we often have to deal with risk factors such as coronary heart disease and obesity [17,18].

Preoperative scoring

Before an operation registration and if needed, pretreatment of specific risk factors can highly decrease the rate of complications. A subtle application of validated preoperative score systems in patients with a high-risk constellation can lead to an exclusion for operative treatment due to the risk-benefit analysis (Table 2). These patients are then allocated to alternative treatment options [5]. Occasionally even high specific technically examinations are needed, such as transthoracic echocardiography, exercise ECG, coronary angiography amongst others. The preoperative condition often can be optimized by simple advice including forced respiratory training up to the point of procedures such as coronary interventions or heart valve corrections [17,18].

Table 2. Parameters of preoperative risk evaluation and physical fitness [5,17,18,27].

Variable	Characteristic/Pathological finding
General condition	
Complete blood count	Aberrations
Karnofsky performance status scale	Under 80%
Blood Screening for malnutrition	Malnutrition Yes-No
Age	Over 70 years
Body Mass Index	Women higher than 22 kg/m^2 Men higher than 25 kg/m^2
Weight loss	Higher than 10%
Alcohol consumption	Over 150 g/day
Nicotine abuse	Pack years
Cardio-vascular function	
ECG	Normal-Abnormal
Chest X-Ray	Normal-Abnormal
Cardiac assessment	Normal-Elevated risk
Pulmonary function	
COPD	Yes-No
paO_2	Under 70 mmHg
$paCO_2$	Over 45 mmHg
Vital capacity (Spirometry)	Percentage
Forced One-second-capacity (Spirometry)	Percentage
Hepatic function	
Child classification	A-C
APRI score	Over 1.0
Thrombocyte count	Under 1,00,000/microliters
GOT, GPT, Y-GT	Normal-Abnormal
Bilirubin	Normal-Abnormal
Albumin, INR	Normal-Abnormal
Renal function	
Urea	Higher than 90 mg/dl
Creatinine	Higher than 1.2 mg/dl
Creatinine clearance	Under 70 ml/min
Metabolic function	
Diabetes?	Yes-No
Others	
Neoadjuvant treatment?	Yes-No

Pre-assessment by an experienced anesthetist

After primary staging and risk analysis, patients with intended esophagectomy should be presented for anesthesiological consultation to get the approval for a 2 cavity-thoracoabdominal operation with one-lung ventilation [28]. Being aged over 80 years is generally not a contraindication for esophageal resection. Some studies showed a higher risk for esophagectomy in patients older than 70 years, but it has to be taken into account that even alternative treatments such as radiochemotherapy have an increased rate of complications. This stands in opposition to many reports of high volume centers that show, that in patients far above 80 years esophageal resections and reconstructions can be made safely and with fewer complications [29,30]. Patients over 70 years must be under very strict evaluation of functional resectability [29,30].

Multidisciplinary team meeting: "Tumor board"

After completion of the primary staging with clarification of the technical, oncological and functional resectability a multidisciplinary assessment and documented decision on a treatment plan is mandatory. This has been shown to improve clinical decision making in esophageal cancer [2,5,31-33]. The basis of discussion is formed by the tumor stage, general health and comorbidities of the patient, and many individual factors. The result is a written report and individualized consensus of experts in radiology, pathology, endoscopy, radiotherapy, and medical oncology together with the general surgeon with experience in esophageal surgery. The patients' attitude must strictly be considered. Tumor board presentation also covers forensic aspects. Tumor board meetings also should decide suitable patients recruitment for research studies [2].

A further presentation at the tumor board takes place either after the completion of neoadjuvant treatment ("re-staging") or earlier in complications under treatment or missing clinical response [34]. Tumor board decisions are also mandatory in signs of recurrence during follow up. In general, evidence-based recommendations for the individual patient require multidisciplinary

consent. Sometimes very individual decisions have to be made away from guidelines and standard treatment, e.g.:

- Salvage operation after definitive radiochemotherapy
- Decisions on radical resection in the case of oligometastatic cancer
- Recurrent esophageal cancer in follow up with newly diagnosed pulmonary or hepatic metastasis, new mediastinal or abdominal mass or local recurrence (seldomly)
- The question of adjuvant treatment in extended lymphatic spread
- The question of additive treatment in postoperative R1 or R2 situation e.g. at oral resection plane or pericardium
- Re-evaluation and radical resection after palliative treatment with excellent response and remission

Curative Therapy of Esophageal Cancer

Overview

In T2 and local advanced esophageal cancer (Figures 1 and 2), clear therapy algorithms have been implemented. Especially in young patients with esophageal cancer (<50 years) perioperative chemotherapy in cT2 adenocarcinoma and a preoperative radiochemotherapy in cT2 squamous cell carcinoma can be considered [5]. In locally advanced cancer of the upper third of the esophagus and squamous cell carcinoma of the mid third, there is an increasing trend for definitive (curative) radiotherapy with prognostically nearly equal results [35]. Arguments for this strategy are:

- Poor overall-survival of cancer in the upper third, especially in the case of squamous cell cancer (high rate of lymph node metastasis, concomitant diseases)
- Increased morbidity of cervical lymphadenectomy with up to 70% injury of the recurrent laryngeal nerve in 3 field lymphadenectomy
- Esophageal cancer higher than 4 cm distal of the upper esophageal sphincter is not resectable

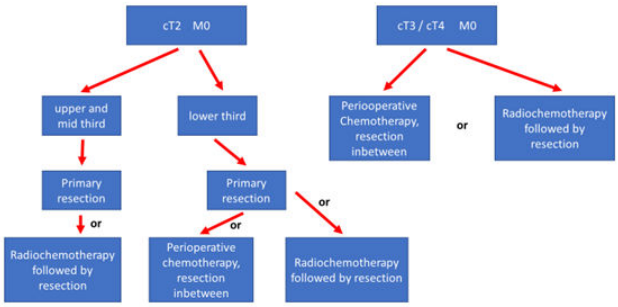

Figure 1. Recommended therapy algorithm of functional resectable patients with T2 and locally advanced (T3, T4) adenocarcinoma of the esophagus without evidence of distant metastasis.

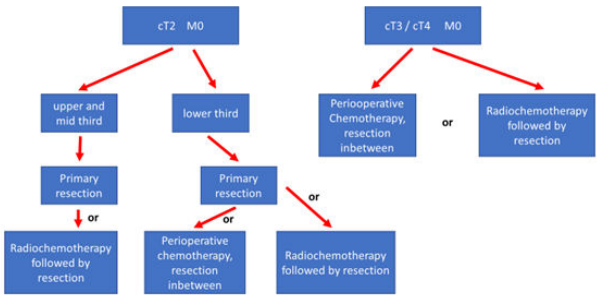

Figure 2. Recommended therapy algorithm of functional resectable patients with T2 and locally advanced (T3, T4) squamous cell carcinoma of the esophagus without evidence of distant metastasis.

Curative endoscopic treatment of early carcinoma and premalignant lesions

In contrast to the ablative procedures (radiofrequency ablation, cryoablation, argon-plasma-coagulation, photodynamic therapy) that can only be recommended in Barrett or low-grade lesions, the endoscopic resection achieves a defined, histologically investigable specimen. According to the depth of resection we differ in Endoscopic Mucosal Resection (EMR) or Endoscopic Submucosal Dissection (ESD).

In the case of high-grade dysplasia, an endoscopic resection is crucial because 50% of patients with confirmed high-grade dysplasia (biopsy) show invasive cancer in the consecutive specimen after endoscopic resection. So endoscopic resection is the method of choice for high-grade dysplasia, Carcinoma *in situ* (Cis) and under strict conditions for T1a and T1b cancer (Table 3) [4,36].

Recommendations of the associated German societies are based on stratified risk-based analyses. If they are not fulfilled, patients must undergo radical resection or definitive radiochemotherapy. The risk for regional lymph node spread correlates and rises with the grade of infiltration of the submucosa. In sm3 infiltration, 50% of patients have already affected lymph nodes. Squamous cell carcinoma poses a higher risk for lymph node metastasis in the early carcinoma of the esophagus 45% versus 26% in adenocarcinoma in T1b cancer [2,33].

Table 3. Criteria for Endoscopic Mucosa Resection (EMR, adenocarcinoma) and Endoscopic Submucosa Dissection (ESD, squamous cell carcinoma) [4,5,36].

Depth of Infiltration	• High-grade Dysplasia • T1a: m1 (intraepithelial neoplasia), m2-infiltration of lamina propria (adeno and squamous cell carcinoma) • m3-infiltration of muscularis mucosa (only adenocarcinoma) • T1b: up to sm1 and <500 µm (only adenocarcinoma)
Angiolymphatic Invasion	No L1, no V1
Grading	Only G1, G2
Foci	Unifocal
Resection-margin	R0
Macroscopic aspect	No ulceration
Size	Diameter under 20 mm

Perioperative management

Weight loss over 10% in the last 6 months before diagnosis, BMI under 19 kg/m^2, a nutritional risk score under 3 (ESPEN-Guidelines) and serum albumin under 30 g/l have proven to be strong prognostic variables for a postoperative complicated course (high “metabolic risk”) [5,37,38]. In the case of a severely reduced physical condition, the following measures have to be seized for the duration of preoperative latency which can amount up to 3 months and longer e.g. in a curative concept with neoadjuvant treatment the so-called “prehabilitation” [2,5,37-39]:

- High-calorie oral nutrition, nutritional profile and substitution
- Involvement of nutritionist/dietician
- Esophageal stents for a preoperative period in severe stenosis
- Implantation of a venous port system alongside additive or total parenteral nutrition
- Nasojenunal, endoscopic or operative implanted jejunal feeding tube
- Respiratory training, physical therapy

Experience shows, that e.g. under neoadjuvant radiochemotherapy dysphagia often rapidly decreases, patients gain weight and their physical condition improves. Moderate sports have also proven to be beneficial also from the viewpoint of psycho-mental stability. Concerning the postoperative care the following procedures have proven to be highly important [5]:

- Peridural catheter
- 2 days postoperative ICU alongside IMC monitoring to recognize early complications
- Early mobilization, beginning the evening of the day of operation
- Strict respiratory training
- Consequent, proactive drainage of pleural effusion
- Early enteral food intake (starting within 24 hours) first by jejunal feeding tube with subsequent oral food intake from the 3rd postoperative day

Neoadjuvant therapy

In locally advanced stages (cT3, cT4), according to metaanalysis, multidisciplinary treatment with preoperative or perioperative treatment offers the best prognosis with doubled or quadrupled median long term survival in subgroups in comparison to surgery alone [5,40-44].

Many former studies have shown very heterogeneous populations with unselected squamous cell- and adenocarcinoma, different forms of multimodal treatment, and different concepts of surgical treatment [43,44].

Prospective randomized trials have shown that perioperative chemotherapy according to the AIO-FLOT-4-Trial-protocol, as presented in 2017 in Chicago (Fluorouracil, leucovorin, oxaliplatin, docetaxel) or the neoadjuvant radiochemotherapy according to the 2012 CROSS-trial (carboplatin with an area under the curve of 2 mg/ml per min and 50 mg/m^2 paclitaxel for 5 weeks in conjunction with concurrent radiotherapy (41,4 Gy in 23 fractions 5 days a week) show the best results in adenocarcinoma of the mid or distal third of the esophagus [35,40,41,43-45]. In squamous cell carcinoma of the distal esophagus, there is no indication for chemotherapy alone, with squamous cell carcinoma being more radiosensitive than adenocarcinoma. Nevertheless, the neoadjuvant CROSS concept offers the best prognosis [5,40,41,46,47].

If re-staging under neoadjuvant treatment shows local tumor progress (clinical, endoscopic, CT morphologic) after half the cycles the patient is admitted to the operation immediately [5]. And it must be verified by restaging at the end of the preoperative treatment, that the qualification for curative treatment analog to primary staging still exists (e.g. exclusion of distant metastasis) [5].

The clinically strongest indicator of an excellent response to the neoadjuvant treatment is a decrease in dysphagia and an increase of weight [34]. The ideal timing for surgery following neoadjuvant treatment after the last cycle of chemotherapy or radiation dosage lies between 6 and 8 weeks, with some advocating a latency of up to 12 weeks [39].

Limited radical resection

The Merendino's operation with resection of the abdominal part of the esophagus and reconstruction by isoperistaltic interposition of jejunum is one option for limited radical resection. This method can be applied in early cancer patients or elderly patients or patients with restrictions in functional resectability. Quality of life in Merendino's procedure is superior to radical esophagectomy for several reasons including preservation of the vagal nerve however this is without oncological radicality [48]. It is also important to mention that an important limited radical procedure in early distal esophageal cancer and AEG Type I and II cancer is the antrum preserving "double tract reconstruction" with a very localized resection. It was described by Aikou et al. and earlier (Figure 3) [49]. Assuming the right indication, such as early cancer, the distal esophageal and upper gastric resection with reconstruction by the "double tract" procedure is a simple and fast operation providing a better life quality by a better reservoir, better "2 channel" emptying, fast weight gain and unaffected Vitamin B12 resorption and hematopoiesis [49].

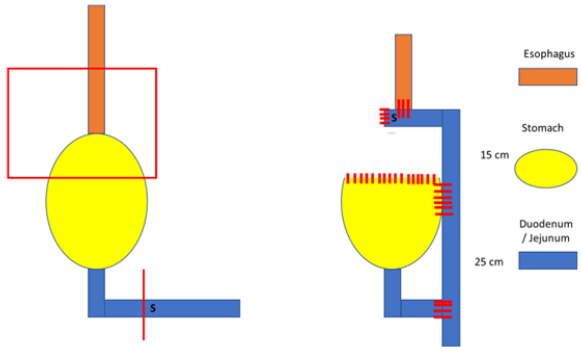

Figure 3. Double tract reconstruction [49].

Radical curative surgical resection and reconstruction

Today radical esophagectomy mostly follows neoadjuvant therapy. Primary surgery without preoperative treatment is performed in T1b cancer (e.g. after incomplete/insufficient EMR/ESD), rarely detected cT2 cancer, in locally advanced tumors (T3, T4) with contraindications for multimodal therapy or according to the patients will.

The operative principle of curative resection is the radical, subtotal, en-bloc esophagectomy with complete local excision and sufficient safety distance from the resection margin oral, aboral, and circumferential. Mandatory in esophageal cancer of the mid and lower third is the systematic, regional 2-field-lymphadenectomy (abdominal D2 and thoracic/mediastinal), in cancer of the upper third or in case of affection of cervical lymph nodes the systematic 3-field lymphadenectomy (abdominal D2, thoracic/mediastinal and cervical/paratracheal) [5]. A yield of at least 20 lymph nodes is essential and prognostically relevant (Table 4). Due to the occurrence of esophageal cancer mostly in the distal third of the esophagus the transthoracic, abdominal-right-thoracic approach with reconstruction by gastric pull up with high intrathoracic anastomosis according to Ivor-Lewis-Tanner can be considered as standard procedure. The gastric conduit lies in the retral mediastinum. The high intrathoracic anastomosis shows only mild postoperative dysphagia problems and reflux and enables a sufficient safety distance to the carcinoma by subtotal resection (3 cm-4 cm required) [5]. Intraoperative frozen section is rarely required, normally only in cancer of the upper third and in giant tumors [2].

In the first step, the abdominal cavity is inspected to exclude peritoneal cancer. The gastrocolic ligament is cut through with sparing of the gastro-epic arcade. The left gastroepiploic artery and vein and the short gastric vessels are dissected with complete mobilization of the greater curvature. The right gastroepiploic artery and vein must strictly be prevented. Then the D2-lymphadenectomy follows. The left gastric artery is dissected proximally. Next is the preparation of the esophageal hiatus with lymphadenectomy in the lower mediastinum. Sometimes the hiatus must be broadened to allow gastric pull-up. In locally extended tumors with infiltration of the diaphragm, the resection of the left or right crus can be necessary (T4a). To avoid rotation (and ischemia) and to prevent later enterothorax (colon, small bowel) the (later) adaptation of the hiatal space by non-resorbable suture and gastro-phrenic pexia but without affection of the perfusion of the conduit is recommended. The shaping of the conduit (width 5 cm, resection of the small curvature) can be made in the abdominal part or (and our preferred approach) later in the thoracic part of the operation. Terminally the right pleura is opened. Usually, we place a silicone tube (target/indicator-drainage) in the hiatal region.

For the second (thoracic) part of the operation, the patient is relocated on his left side. The thoracic approach is done by right-sided anterolateral thoracotomy (4./5. ICS). After desufflation and retraction of the right lung

(double-lumen tube, one-lung ventilation) the azygos vein is dissected after wide opening of the mediastinal pleura by ultrasound-dissector. The esophagus is dissected en-bloc and subtotally from its bed including the surrounding lymphatic tissue below the bifurcation (Figure 4). In large tumors, the resection of pericardium or pleura can be required (T4a). The thoracic duct is exposed next to the aorta on the right side, dissected, and safely ligated. Small branches from the aorta can cause severe, life-threatening bleeding. They have to be closed by metal clips or 5-0 prolene suture with a small needle. Special attention is needed by mobilization of the esophagus above the level of the carina to spare the sensitive tissue of the pars membranacea of the trachea. The vagal nerve is dissected at the lower margin of the right main bronchus. The esophagus is dissected above the level of the azygos vein. Finally, the gastric conduit is pulled up, shaped by linear stapling, and anastomosed by a 28 mm circular stapler end-to-side at the remnant esophagus [50]. We secure both the circular stapling and linear stapling line by 4-0 PDS hand suture.

If the stomach cannot be used for reconstruction (e.g. after former gastrectomy or after esophago-gastrectomy in a giant tumor), traverse colon is the second choice for reconstruction.

Cervical anastomosis (Mc Keown) features a clear advantage, by the extra-mediastinal position, that anastomotic leakage is not life-threatening. Anyway, cervical anastomosis has several functional and life quality associated disadvantages like stenosis, dysphagia, risk of aspiration and are relinquished more and more in contrast to many other countries like China [50]. Also, reconstruction with free jejunal interposition and microsurgical vascular anastomosis (inferior thyroid artery) after resection of the cervical esophagus is today a rarely performed procedure even at high-volume centers. Anyway, cervical (squamous cell) carcinomas are mainly treated with radiochemotherapy. T4b cancer with infiltration of the aorta, vertebral body, or trachea is technically not resectable [48-52].

Table 4. Lymphnodestations for considering in radical esophagectomy.

Abdominal	Thoracic
Paracardial lymphnodes	Mediastinal infrabifurcal aortic, pericardial (standard)
Lymph nodes along the celiac trunk, common hepatic artery, splenic artery, left gastric artery	Paraesophageal, right paratracheal, along the right recurrent vagal nerve, along the azygos vein (extended)
Lower mediastinum	Left paratracheal, along the left recurrent vocal nerve and sub-aortic (total)

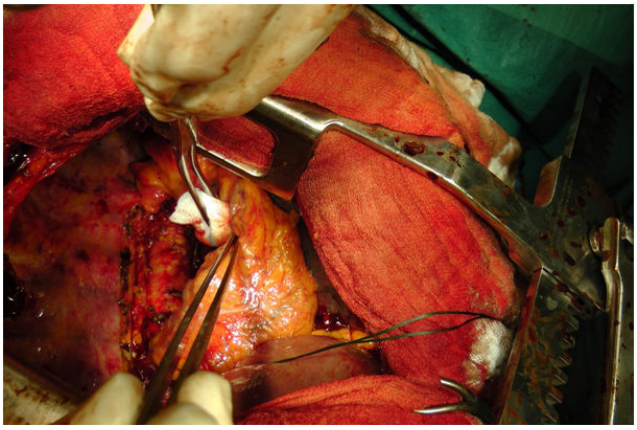

Figure 4. Right thoracic anterolateral thoracotomy, after mediastinal lymphadenectomy, gastric conduit already anastomosed at the remnant esophagus (Source: Fetzner UK, own patient).

Minimal-invasive access

Both the abdominal and the thoracic part of resection and reconstruction can be performed minimal-invasive with the same oncological radicality and safety than the open access. The minimal-invasive "Hybrid" procedure combines laparoscopic abdominal and open trans-thoracic approach, the total-minimal-invasive approach combines complete laparoscopic and thoracoscopic access.

Minimal-invasive esophagectomy started in the nineties. In 2003 Luketich and colleges from Pittsburg (US) presented the first excellent results of minimal-invasive thoracic and abdominal esophagectomy in over 200 patients with a 30 day-lethality rate of 1.4% [53]. Outstanding was the dramatic decrease in postoperative pulmonary complications under 8%. Further spread of minimal-invasive techniques in esophageal surgery in Europe grew rapidly. In the Netherlands, the rate of minimal-invasive esophagectomy was over 60% in 2014. Oncologic radicality (R0-rate, lymph node count, survival) today counts equal to the open surgical approach. Therefore indication for minimal-invasive esophagectomy corresponds to that for the open technique. Today at many high-volume centers minimal-invasive esophagectomy, at least the hybrid-technique is the standard procedure.

The rate of anastomotic leakage with 8%-12% corresponds to approximately the open approach. Some studies describe a higher rate of re-operations or re-interventions needed in minimal-invasive esophagectomy. The learning curve for minimal-invasive esophagectomy rates 30-60 esophagectomies [54]. In 2006 Palanivelu and coworkers suggested the prone position for the minimal-invasive thoracoscopic part [55]. Advantages are:

- No one-lung ventilation needed
- No retraction of the lung needed
- Excellent view over all relevant mediastinal structures

The disadvantage is only the time-consuming relocation in case of complications with the need for conversion to thoracotomy (e.g. severe bleeding).

Nevertheless, it must be mentioned, that concerning minimal-invasive esophagectomy no randomized oncological long term data exist. The current, valid German guideline ("S3-Leitlinie") of the associated societies gives no unlimited recommendation for minimal-invasive esophagectomy [5]. Significant improvement of life quality in minimal-invasive esophagectomy versus open surgical access seems obvious but is not proven strictly scientifically [53-55].

Robot Assisted Minimal-invasive Esophagektomie (RAMIE)

RAMIE is the youngest chapter in the evolution of esophageal surgery. Most experience exists at specialized centers in the thoracic part of the operation. Robot-assisted operations facilitate high-grade freedom of movement combined with excellent 3-dimensional and enhanced view, the basis for a safe and effective lymphadenectomy. In RAMIE the esophago-gastrostomy is mostly completed by hand suture.

Common in RAMIE technique is the combination of conventional minimal-invasive laparoscopic part and the robot-assisted transthoracic part (esophagectomy, gastric pull up) in prone position [53-55].

Even the abdominal part can be done robot-assisted, however, there is a lack of studies with a higher number of cases. The first results showed a high number of lymph node harvesting, low complication rate, and corresponding long term results [56].

TNM classification of esophageal cancer

Histological classification and stage grouping of esophageal cancer follow the 8th edition of TNM classification. Concerning stage grouping, there is a differentiation between adenocarcinoma and squamous cell carcinoma [57].

Complications and management of complications

In addition to an experienced, subtle, non-traumatic and efficient operative technique the early clinical (e.g. fever, tachyarrhythmia, restlessness, increase of CRP), endoscopic and radiologic recognition and the appropriate, interdisciplinary management of postoperative complications is the key to increase the safety of these complex operative procedures in oncological esophageal surgery. This has a crucial influence on early survival, patient comfort, and even long term prognosis.

The treatment of complications encompasses conservative, interventional, and operative measures [4,7,27,30,48,58,59]. Anastomotic leakage is the most common technical-surgical complication. The rate ranges about 10 percent independent on the kind of technique used. The exact technique, avoiding tension and low perfusion of the stomach, colon, or small bowel conduit can decrease the rate of leakages.

Covered leakage can mostly be managed with a covered, self-expandable stent, potentially combined with an interventionally (CT or ultrasound-guided) abscess drain. Endo-Vac-therapy (intracavitary or intraluminal sponge) additionally strongly decreased the number of required operative revisions. Not covered leakages and especially conduit necrosis must undergo operative revision (e.g. cervical esophago-stoma, chest-tubes). Postoperative bleeding, tracho-bronchial lesions/fistulas, chylothorax, or enterothorax are rare, their management can be elaborate and demand profound expertise in centers. The most common non-surgical complication is postoperative pneumonia, which can be avoided and treated by effective pain management (PDA), special techniques of postoperative ventilation, and especially early mobilization and forced respiratory training. Postoperative delayed gastric emptying is common after esophagectomy usually suspends after single endoscopic pneumatic dilatation of the pylorus. Postoperative anastomotic stricture can be a protracted complication and sometimes require an often repeated endoscopic pneumatic dilatation [4,7,27,30,48,58,59].

Morbidity, mortality, high-volume-care and quality assessment in esophageal surgery

In the nineties, perioperative mortality after esophagectomy in low-volume centers in the US amounted higher than 20% [60]. Over the years the percentage decreased in the US and Europe by:

- Improved operative techniques
- Improved anesthesiologic management (e.g. PDA)
- Improved perioperative management (e.g. mobilization)
- Development of high-volume centers

The mortality of esophagectomy ranges estimated between 1.5%-10%. In German centers, mortality under 5% is claimed by the societies. The estimated mortality in German high volume centers lies between 1.5% and 3%. A clear correlation between hospital volume and especially surgeons volume annually by one surgeon and mortality is prooved. So it is indisputable that operative treatment of esophageal cancer should be performed in high volume centers, due to a significant decrease in mortality and morbidity with increasing frequency of operations. This lies in the shortened duration of the operation, less transfusion of blood preservation units, decreased rate of postoperative infections, and a higher oncological radicality. Even the hospital stay is shorter and the costs of treatment are lower. Clinical studies can be performed more effectively at centers and clinical and scientific training of young consultants and academics in esophageal surgery proceeds significantly faster. 10-20 esophagectomies a year count as a minimum to keep the surgeon and interdisciplinary team in a sufficient trained condition [2,4,5,33,48,58-62]. Counter-arguments concerning the centralization-debate are the treatment close to the patient's home and the preservation of the plurality of clinical and scientific approaches [63].

Indicators of quality assessment encompass tumor board presentations, caseload, completeness, and quality of histopathological examination and documentation, RO-resection rate, radicality (lymph node harvesting), interdisciplinary treatment, rate and classification of anastomotic leakage and the mortality within 30 and 90 days after surgery [5,33].

Adjuvant therapy

Patients with a good response after neoadjuvant chemotherapy (e.g. FLOT) should continue this 4-6 weeks latency after the operation (perioperative treatment). Tumor-regression of specimen is classified according to Becker and colleagues from 1a (complete regression) to 3 (low/no regression, >50% remnant tumor) [34,64].

Additive therapy

If postoperative histopathologic examination of the specimen results in R1 or (seldomly) R2 margins there might be the indication for additive radiochemotherapy (alternatively "watch and wait"). The indication for postoperative, additive radiochemotherapy also can evolve of the situation of an intraoperative frozen section that results in "R1" (resection margin or circumferential) but for technical/anatomical reasons with no option of re-resection [5,48,65].

Salvage Concept

The salvage concept contains the primary, definitive (curative) radiochemotherapy (50 Gy) in basically curative resectable esophageal cancer with subsequent "wait and watch" strategy. If local recurrence occurs (risk about 40%-60%) or in case of low response under treatment, the patient can be admitted to surgery secondary. However, studies showed higher morbidity and mortality under operations following the salvage concept. Additionally, the salvage strategy holds the risk of sudden metastatic dissemination [34,66].

Synchronous Oligometastasis

In general, synchronously distant metastasis at the time of primary staging excludes from curative treatment. Anyway more and more personalized concepts and even improved imaging methods confront us with the question of suitable treatment-paths in case of e.g. very small solitary hepatic or pulmonal metastasis. Despite the German guidelines recommend palliative treatment in preoperatively histologically confirmed metastasis, radical curative resection with simultaneous resection of solitary hepatic or pulmonal metastasis can be reasonable under the premise of tumor board conscensus, monitoring by clinical trial and preoperative exclusion of secondary cancer (e.g. colorectal, bronchial carcinoma). In the case of unsuspected intraoperatively recognized metastasis, solitary metastasis should be resected if resection is achievable with low additional operative load [4,5,48,67].

Postoperative Care

After primary curative treatment patients should be admitted to rehabilitation. Rehabilitation embraces individual medical, nursing care, educative, physical training and oncopsychological aspects [5].

Follow Up

98% of recurrence occurs in the first 36 months after the first diagnosis. The value of a structured follow up after radical surgical treatment of esophageal cancer in terms of extension of a lifetime is not proven.

Most important clinical questions target bodyweight and the general condition of the patient. However physical examination, abdomen ultrasound, blood sample, EGD and chest ray should be undertaken in appropriate intervals. The high psychological value of a structured follow-up program must also be taken into account and the value should not be underestimated. Apart from the oncological view by follow up early and late operative complications and long-term consequences can be detected (e.g. incisional hernias, enterothorax, stenosis of the anastomosis, lack of vitamins, reflux) and effectively eliminated. Follow up should be symptom orientated. Heavy underweight without evidence of recurrence can be counteracted with a high caloric dietary supplement if necessary implantation of a jejunal feeding tube or venous port system [5]. Tumor markers (CA19-9, CEA, SCC) do not play a role for screening and play an underpart role in follow up and by the way only if elevated pre-therapeutically. In terms of follow up after endoscopic resections, there is a strict and close endoscopic follow up obligate, because of the increased risk of local recurrence [5].

Life Quality

Life quality in esophageal cancer is initially very poor. This starts with the first diagnosis and the information of a malignant and only elaborately to treat disease. Disturbance of elementary body functions accompanies a reduced general condition [1,50]. The first weeks and months after esophagectomy are embossed from the aftereffects of a severe surgical intervention. Late postoperative complications might need further treatment (e.g. stenosis as a consequence of subclinical anastomotic leakages). So re-interventions like endoscopic pneumatic dilatations might be needed, often patients are underweight. Complicating courses with a prolonged stay in intensive care units are severe traumas, which have to be overcome. Overall the oncological fear of death, accompanied with insomnia up to the point of panic, reduced social functioning. Not seldomly financial worries (employment) come along, interpersonal relationships are heavily stressed (life events) [1,2]. Then a phasis follows of new-learning of eating in terms of kind of food, quantity (loss of stomach reservoir), frequency (up to 6 meals a day). A dietitian can effectively help and support in these months, vitamin B and folate must be supplemented life long [5]. Patients should be motivated to do sports orientated on their individual capability, this effectively reduces fatigue [5]. Anyway cough, dry mouth, reflux, emotional changes an increased risk of developing psychiatric disorders are ongoing problems [2,68-70]. There is a significant improvement in life-quality between 9 months and 1 year after surgery. The anxiety-level decreases, routine follow up without evidence of recurrence give patients a feeling of safety. Stenosis is removed, diet-mistakes are well known and are avoided. In longterm-survivors life quality of patients after esophagectomy approximates the life quality of a normal population after about 2 years [1,5,68,69,71]. It is difficult to capture life quality in complex diseases like esophageal cancer with all effects. By standardized life quality HRQL questionnaires (Health-Related Quality of Life) like EORTC QLC-OES18 scientific clinical research tries to measure and compare life quality at different phases of disease and with different treatment paths [68,69].

Prognosis of Esophageal Cancer

In adenocarcinoma of the esophagus, the prognosis is slightly advantageous in comparison to squamous cell carcinoma. It is unexplained if this lies in the biology of the cancer types or the higher rate of concomitant diseases in squamous cell cancer. A multitude of further prognostic factors, e.g. number of resected lymph nodes, ratio of affected/unaffected lymph nodes are identified [1,2,5].

- Today, overall 5 year survival over all stages and therapies: 15%-25%
- Curative resection rate 50%-60%
- 5-year survival after a curative, radical operation in stage I and stage II disease: >40%
- 5-year survival after curative, radical operation stage III and stage IV disease: <20%

Research Perspective

The increasing incidence of distal adenocarcinoma of the esophagus is expressed by the volume of associated scientific literature. In the year 2009, there were 2,040 papers published concerning esophageal cancer. In 2019 already 3,590 papers deal with esophageal cancer, mainly from the U.S., followed by China, Japan, and Germany [72].

Better prevention by identifying persons at risk would be the best treatment. Sharpening of indications for local endoscopic therapy could spare subgroups from radical overtreatment. This concerns also subgroups with occult distant metastasis. By improved imaging, these also could be protected from overtreatment.

The further promotion and development of minimal-invasive and robot-assisted esophageal surgery stand in the focus of clinical research, as well as the decision making in oligometastatic cases.

In patients with excellent, complete response/remission after multimodal treatment, which ranges by 5%-10% we have to ask if an operation is still beneficial. Conversely, about 50% of neoadjuvant treated patients are “Non-Responder”. Chemotherapy or chemoradiotherapy in these patients only delays the operation and patients suffer from needless side effects and risks of radio, and chemotherapy. An improved evaluation of molecular response predictors would be eligible [34].

Concerning the further development of chemotherapeutic agents, angiogenetic inhibitors, or EGF-inhibitors seem promising.

Genomic medicine with personalized immunotherapy and understanding of intratumor heterogeneity allows the hope of more targeted therapies.

Finally and last, still unclear is the cause of the gender preference of esophageal cancer.

Conflict of Interest

The authors declared no conflicts of interest concerning the authorship and/or publication of this article.

Permission

Pictures of the patient's situs was taken with permission.

References

1. Pennathur, Arjun, Michael K Gibson, Blair A Jobe, and James D Luketich. "Oesophageal Carcinoma." *The Lancet* 381 (2013): 400-412.

2. Lagergren, Jesper, Elizabeth C Smyth, David Cunningham, and Pernilla Lagergren, et al."Oesophageal Cancer." *The Lancet* 390 (2017): 2383-2396.

3. Hoelscher, AH, and UK Fetzner. "Carcinoma of the Esophagus, Esophagogastric Junction, and Stomach. Cooperation between Pathology and Surgery." *The Pathologist* 33 (2012): 246-252.
4. Fetzner, UK, G Saada, and M Löhnert. "Current Diagnostics and Therapy of Esophageal Cancer Part 1." *CME Chaz* 19 (2018): 21-29.
5. Porschen, R, A Buck, W Fischbach, and I Gockel, et al. "S3-Guidelines Diagnosis and Treatment of Squamous Cell Carcinoma and Adenocarcinoma of the Esophagus." *J Gastroentero*l 53 (2015): 1288-1347.
6. Siewert, JR, AH Hoelscher, K Becker, and W Gössner. "Cardia Cancer: Attempt at a Therapeutically Relevant Classification." *J Areas Operative Med* 58 (1987): 25-32.
7. Hoelscher, AH, and UK Fetzner. "Modern Diagnostics and Stage-Appropriate Surgery." *Surgeon* 83 (2012): 702-711.
8. Lagergren, Jesper, and Pernilla Lagergren. "Recent Developments in Esophageal Adenocarcinoma." *Cancer J Clinicians* 63 (2013): 232-248.
9. Xie, Shao-Hua, and Jesper Lagergren. "A Global Assessment of the Male Predominance in Esophageal Adenocarcinoma." *Oncotarget* 7 (2016): 38876-38883.
10. Cancer Genome Atlas Research Network. "Integrated Genomic and Molecular Characterization of Cervical Cancer." *Nature* 541 (2017): 169-175.
11. Anderson, Lynn L, and Thomas E Lad. "Autopsy Findings in Squamous Cell Carcinoma of the Esophagus." *Cancer* 50 (1982): 1587-1590.
12. DeMeester, Tom R, and Bernard Levin. "Cancer of the Esophagus." *WB Saunders Company* (1985).
13. Islami, Farhad, and Farin Kamangar. "Helicobacter pylori and Esophageal Cancer Risk: A Meta-Analysis." *Cancer Prevention Res* 1 (2008): 329-338.
14. Liu, Jun, Jian Wang, Ye Leng, and Changxing Lv. "Intake of Fruit and Vegetables and Risk of Esophageal Squamous Cell Carcinoma: A Met-Analysis of Observational Studies." *Int J Cancer* 133 (2013): 473-485.
15. Codipilly, DC, AK Chandar, S Singh, and S Wani, et al."The Effect of Endoscopic Surveillance in Patients With Barrett's Esophagus: A Systematic Review and Meta-Analysis." *Gastroentero*l 154 (2018): 2068-2086.
16. Lightdale, Charles J. "Esophageal Cancer." *Am J Gastroenterol* 94(1999): 20-29.
17. Qumseya, Bashar J, Haibo Wang, Nicole Badie, and Rosemary N Uzomba, et al. "Advanced Imaging Technologies Increase Detection of Dysplasia and Neoplasia in Patients with Barrett's Esophagus: A Meta-Analysis and Systematic Review." *Clin Gastroenterol Hepatol* 11 (2013): 1562-1570.
18. Blank, S, F Lordick, M Dobritz, and L Grenacher, et al. "A Reliable Risk Score for Stage IV Esophagogastric Cancer." *Eur J Surg Oncol* 39 (2013): 823-830.
19. Gockel, I, F Lordick, O Lyros, and N Kreuser, et al. "Pretherapeutic Misclassification of Esophageal Cancer and Adenocarcinoma of the Esophagogastric Junction: Possibilities and Clinical Consequences." *The Surgeon* 91 (2020): 41-50.
20. Sons, HU, and F Borchard. "Cancer of the Distal Esophagus and Cardia. Incidence, Tumorous Infiltration, and Metastatic Spread." *Annals Surg* 203 (1986): 188-195.
21. Choi, Jeongmin, Sang Gyun Kim, Joo Sung Kim, and Hyun Chae Jung, et al. "Comparison of Endoscopic Ultrasonography (EUS), Positron Emission Tomography (PET), and Computed Tomography (CT) in the Preoperative Locoregional Staging of Resectable Esophageal Cancer." *Surg Endosc* 24 (2010): 1380-1386.
22. Lowe, Val J, Fargol Booya, Joel Garland Fletcher, and Mark Nathan, et al. "Comparison of Positron Emission Tomography, Computed Tomography, and Endoscopic Ultrasound in the Initial Staging of Patients with Esophageal Cancer." *Mol Imaging Biol* 7 (2005): 422-430.
23. Luo, Lin-Na, Long-Jun He, Xiao-Yan Gao, and Xin-Xin Huang, et al. "Endoscopic Ultrasound for Preoperative Esophageal Squamous Cell Carcinoma: A Meta-Analysis." *PLoS One* 11 (2016): e0158373.
24. Omloo, Jikke MT, Mark Van Heijl, Jacques JGHM Bergman, and Mia GJ Koolen, et al. "Value of Bronchoscopy after EUS in the Preoperative Assessment of Patients with Esophageal Cancer at or above the Carina." *J Gastrointest Surg* 12 (2008): 1874-1879.
25. Findlay, JM, KM Bradley, EJ Maile, and B Braden, et al. "Pragmatic Staging of Oesophageal Cancer using Decision Theory Involving Selective Endoscopic Ultrasonography, PET and Laparoscopy." *Br J Surg* 102 (2015): 1488-1499.
26. Allum, William H, Jane M Blazeby, S Michael Griffin, and David Cunningham, et al. "Guidelines for the Management of Oesophageal and Gastric Cancer." *Gut* 60 (2011): 1449-1472.
27. Hoelscher, AH, UK Fetzner, M Bludau, and J Leers. "Complications and Management of Complications in Oesophageal Surgery." *Cent Sheet Surg* 136 (2011): 213-223.
28. Carney, Adam, and Matt Dickinson. "Anesthesia for Esophagectomy." *Anesthesiol Clin* 33 (2015): 143-163.
29. Low, Donald E. "Evolution in Surgical Management of Esophageal Cancer." *Digestive Dis* 31 (2013): 21-29.
30. Moenig, Stefan Paul, Hans-Joachim Meyer, William H Allum, and Giovanni De Manzoni, et al. "Third International Conference of the European Union Network of Excellence on Gastric and Esophagogastric Junction Cancer, Cologne, Germany, June 2012." *Gastric Cancer* 81 (2015): 193-199.
31. Schmidt, Henner M, John M Roberts, Artur M Bodnar, and Sonia Kunzet al. "Thoracic Multidisciplinary Tumor Board Routinely Impacts Therapeutic Plans in Patients with Lung and Esophageal Cancer: A Prospective Cohort Study." *Ann Thoracic Surg* 99 (2015): 1719-1724.
32. Boniface, Megan M, Sachin B Wani, Tracey E Schefter, and Phillip J Koo, et al. "Multidisciplinary Management for Esophageal and Gastric Cancer." *Cancer Manag Res* 8 (2016): 39-44.
33. Hoelscher, Arnulf H, and Ulrich K Fetzner. "Quality Assessment, Education and Training in Esophageal Surgery" *Innovat Esophageal Surg* (2012): 119-125.
34. Grimminger, Peter P, Martin KH Maus, Juliane Bergenthal, and Christoph Wandhoefer, et al. "Prognostic Impact of Blood Biomarkers TS and DPD in Neoadjuvant-Treated Esophageal Cancer Patients." *Anticancer Res* 35 (2015): 1297-1302.
35. Stahl, Michael, Martin Stuschke, Nils Lehmann, and Hans-Joachim Meyer, et al. "Chemoradiation with and without Surgery in Patients with Locally Advanced Squamous Cell Carcinoma of the Esophagus." *J Clin Oncol* 23 (2005): 2310-2317.
36. Cao, Y, C Liao, A Tan, and Y Gao et al. "Meta-Analysis of Endoscopic Submucosal Dissection versus Endoscopic Mucosal Resection for Tumors of the Gastrointestinal Tract." *Endoscopy* 41 (2009): 751-757.
37. Kondrup, JESPEN, Simon P Allison, Marinos Elia, and Bruno Vellas, et al. "ESPEN Guidelines for Nutrition Screening 2002." *Clin Nutr* 22 (2003): 415-421.
38. Weimann, A, S Breitenstein, JP Breuer, and SE Gabor, et al. "Clinical Nutrition in Surgery." *Surgeon* 85 (2014): 320-326.
39. Shapiro, Joel, Pieter van Hagen, Hester F Lingsma, and Bas PL Wijnhoven, et al. "Prolonged Time to Surgery after Neoadjuvant Chemoradiotherapy Increases Histopathological Response without Affecting Survival in Patients with Esophageal or Junctional Cancer." *Ann Surg* 260 (2014): 807-814.
40. Hagen P, van, MC Hulshof, van Lanschot JJ, and EW Steyerberg, et al. "Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer." *N Engl J Med* 366 (2012): 2074-2084.
41. Al-Batran, Salah-Eddin, Ralf D Hofheinz, Claudia Pauligk, and Hans-Georg Kopp, et al. "Histopathological Regression after Neoadjuvant Docetaxel, Oxaliplatin, Fluorouracil, and Leucovorin versus Epirubicin, Cisplatin, and Fluorouracil or Capecitabine in Patients with Resectable Gastric or Gastro-Oesophageal Junction Adenocarcinoma (FLOT4-AIO): Results from the

Phase 2 Part of a Multicentre, Open-Label, Randomised Phase 2/3 Trial." The *Lancet Oncol* 17 (2016): 1697-1708.

42. Sjoquist, Katrin M, Bryan H Burmeister, B Mark Smithers, and John R Zalcberg, et al. "Survival after Neoadjuvant Chemotherapy or Chemoradiotherapy for Resectable Oesophageal Carcinoma: An Updated Meta-Analysis." *Lancet Oncol* 12 (2011): 681-692.
43. Hoelscher, AH, UK Fetzner, FG Uzunoğlu, and JR Izbicki. "Multimodal Therapy of Esophageal Carcinoma: Pros and Cons." *Gen Visceral Surg Up2date* 8 (2014): 199-214.
44. Hoelscher, AH, and UK Fetzner. "Multimodal Therapy with Curative Approach." *Viseral Med* 28 (2012): 113-120.
45. Al-Batran, Salah-Eddin, Nils Homann, Harald Schmalenberg, and Hans-Georg Kopp, et al. "Perioperative Chemotherapy with Docetaxel, Oxaliplatin, and Fluorouracil/Leucovorin (FLOT) versus Epirubicin, Cisplatin, and Fluorouracil or Capecitabine (ECF/ECX) for Resectable Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (FLOT4-AIO): A Multicenter, Randomized Phase 3 Trial." *Amer Soc Clin Oncol Annual Meeting* 35 (2017): 4004.
46. Burmeister, Bryan H, B Mark Smithers, Val Gebski, and Lara Fitzgerald, et al. "Surgery Alone versus Chemoradiotherapy Followed by Surgery for Resectable Cancer of the Oesophagus: a Randomised Controlled Phase 3 Trial." *Lancet Oncol* 6 (2005): 659-668.
47. Tepper, Joel, Mark J Krasna, Donna Niedzwiecki, and Donna Hollis, et al. "Phase III Trial of Trimodality Therapy with Cisplatin, Fluorouracil, Radiotherapy, and Surgery Compared with Surgery alone for Esophageal Cancer: CALGB 9781." *J Clin Oncol* 26 (2008): 1086-1092.
48. Fetzner, UK. Current Diagnostics and Therapy of Esophageal Cancer Part 2. *CHAZ* 19 (2018): 89-95.
49. Aikou, Takashi, Shouji Natsugoe, Hisaaki Shimazu, and Mitsumasa Nishi. "Antrum Preserving Double Tract Method for Reconstruction Following Proximal Gastrectomy." *Jpn J Surg* 18 (1988): 114-115.
50. Fetzner, UK, and AH Hoelscher. "A Prospective Randomized Controlled Trial of Semi-Mechanical versus Hand-Sewn or Circular Stapled Esophagogastrostomy for Prevention of Anastomotic Stricture." *World J Surg* 37 (2013): 2246-2247.
51. Davies, AR, H Sandhu, A Pillai, and P Sinha, et al. "Surgical Resection Strategy and the Influence of Radicality on Outcomes in Oesophageal Cancer." *Br J Surg* 101 (2014): 511-517.
52. Lagergren, Jesper, Fredrik Mattsson, Janine Zylstra, and Fuju Chang, et al. "Extent of Lymphadenectomy and Prognosis after Esophageal Cancer Surgery." *JAMA Surg* 151 (2016): 32-39.
53. Luketich, James D, Miguel Alvelo-Rivera, Percival O Buenaventura, and Neil A Christie, et al. "Minimally Invasive Esophagectomy: Outcomes in 222 Patients." *Ann Surg* 238 (2003): 486-495.
54. Wullstein, C. "Scope and Limitations of Minimally Invasive Resections of the Oesophagus and Stomach." *Cent Sheet Surg* 139 (2014): 37-42.
55. Palanivelu, Chinnusamy, Anand Prakash, Rangaswamy Senthilkumar, and Palanisamy Senthilnathan, et al. "Minimally Invasive Esophagectomy: Thoracoscopic Mobilization of the Esophagus and Mediastinal Lymphadenectomy in Prone Position-Experience of 130 Patients." *J Am College Surgeons* 203 (2006): 7-16.
56. Van der Sluis, PC, JP Ruurda, RJJ Verhage, and S van der Horst, et al. "Oncologic Long-Term Results of Robot-Assisted Minimally Invasive Thoraco-Laparoscopic Esophagectomy with Two-Field Lymphadenectomy for Esophageal Cancer." *Ann Surg Oncol* 22 (2015): 1350-1356.
57. Brierley, James D, Mary K Gospodarowicz, and Christian Wittekind. "TNM Classification of Malignant Tumours, 8th Edition". *Wiley-Blackwell* (2016): 272.
58. Babic, Benjamin, Evangelos Tagkalos, Ines Gockel, and Florian Corvinus, et al. "CRP Levels after Esophagectomy are Associated with Increased Surgical Trauma and Complications." *Ann Thoracic Surg* 109 (2020): 1574-1583.
59. Hoelscher, AH, and UK Fetzner. "Surgery of the Esophagus. In: Bauch J, Bruch HP, Heberer J, Jähne J Malpractice and Liability in General Surgery." *Springer* (2011): 61-76.
60. Birkmeyer, John D, Andrea E Siewers, Emily VA Finlayson, and Therese A Stukel, et al. "Hospital Volume and Surgical Mortality in the United States." *N Engl J Med* 346 (2002): 1128-1137.
61. Brusselaers, Nele, Fredrik Mattsson, and Jesper Lagergren. "Hospital and Surgeon Volume in Relation to Long-Term Survival after Oesophagectomy: Systematic Review and Meta-Analysis." *Gut* 63 (2014): 1393-1400.
62. Derogar, Maryam, Omid Sadr-Azodi, Asif Johar, and Pernilla Lagergren, et al. "Hospital and Surgeon Volume in Relation to Survival after Esophageal Cancer Surgery in a Population-Based Study." *J Clin Oncol* 31 (2013): 551-557.
63. Hoelscher, AH. "Esophageal Cancer Operative Treatment in Centers." *Cent Sheet Surg* 98(2013): A1890-A1894.
64. Herskovic, A, Martz K, Al-Sarraf M, and Leichman L, et al. "Cimbined Chemotherapy and Radiotherapy Compared with Radiotherapy alone in Patients with Cancer of the Esophagus." *N Engl J Med* 326 (1992): 1593-1598.
65. Liu, Jingeng, Zhiru Wei, Yuebin Wang, and Zongjiang Xia, et al. "Hepatic Resection for Post-Operative Solitary Liver Metastasis from Oesophageal Squamous Cell Carcinoma." *ANZ J Surg* 88 (2018): E252-E256.
66. Levinsky, Nick C, Koffi Wima, Mackenzie C Morris, and Syed A Ahmad, et al. "Outcome of Delayed versus Timely Esophagectomy after Chemoradiation for Esophageal Adenocarcinoma." *J Thoracic Cardiovas Surg* 9 (2019): 169.
67. Schmidt, T, and SP Mönig. "Therapeutic Approach in Oligometastatic Gastric and Esophageal Cancer." *J Areas Operative Med* 88 (2017): 1024-1032.
68. Rutegard, M, J Lagergren, I Rouvelas, and M Lindblad, et al. "Population-Based Study of Surgical Factors in Relation to Health-Related Quality of Life after Oesophageal Cancer Resection." *Br J Surg* 95 (2008): 592-601.
69. Derogar, M, Orsini N, Sadr-Azodi O, and Lagergren P. "Influence of Major Postoperative Complications on Health-Related Quality of Life Among Long-Term Survivors of Esophageal Cancer Surgery." *J Clin Oncol* 30 (2012): 1615-1619.
70. Wikman, Anna, Rickard Ljung, Asif Johar, and Ylva Hellstadius, et al. "Psychiatric Morbidity and Survival after Surgery for Esophageal Cancer: A Population-Based Cohort Study." *J Clin Oncol* 33 (2015): 448-454.
71. Gutschow, Christian A, Arnulf H Hölscher, Jessica Leers, and Hans Fuchs, et al. "Health-Related Quality of Life after Ivor Lewis Esophagectomy." *Langenbeck's Archives Surg* 398 (2013): 231-237.
72. Amdal, Cecilie Delphin, Anne-Birgitte Jacobsen, Berit Sandstad, and Trond Warloe, et al. "Palliative Brachytherapy with or without Primary Stent Placement in Patients with Oesophageal Cancer, a Randomised Phase III Trial." *Radiother Oncol* 107 (2013): 428-433.

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