ESOPHAGEAL CANCER AND ASSOCIATED NUTRITIONAL DEFICITS - TREATMENT AND EFFECT ON PROGNOSIS

TOMMI JÄRVINEN
ACADEMIC DISSERTATION

To be presented with the permission of the Medical Faculty of the University of Helsinki, for public examination in lecture room 3, Biomedicum, on 29th of March 2019, at 12 noon

Helsinki 2019
Supervised by:
Docent Jari Räsänen, MD, PhD
University of Helsinki

Dr. Ilkka Ilonen, MD, PhD
University of Helsinki

Reviewed by:
Professor Markku Voutilainen, MD, PhD
University of Turku

Docent Juha Saarnio, MD, PhD
University of Oulu

Opponent:
Professor Daniela Molena, MD
Weill Cornell Medical College and Memorial Sloan Kettering Cancer Center

Helsinki 2019
Unigrafia

ISBN 978-951-51-4964-0 (nid.)
ISBN 978-951-51-4965-7 (PDF)
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ABBREVIATIONS</td>
<td>5</td>
</tr>
<tr>
<td>2 LIST OF ORIGINAL PUBLICATIONS</td>
<td>7</td>
</tr>
<tr>
<td>3 ABSTRACT</td>
<td>8</td>
</tr>
<tr>
<td>3.1 Background</td>
<td>8</td>
</tr>
<tr>
<td>3.2 Patients and methods</td>
<td>8</td>
</tr>
<tr>
<td>3.3 Results</td>
<td>8</td>
</tr>
<tr>
<td>3.4 Conclusions</td>
<td>9</td>
</tr>
<tr>
<td>4 INTRODUCTION</td>
<td>10</td>
</tr>
<tr>
<td>5 REVIEW OF THE LITERATURE</td>
<td>10</td>
</tr>
<tr>
<td>5.1 Gross anatomy of the esophagus</td>
<td>10</td>
</tr>
<tr>
<td>5.2 Epidemiology of esophageal cancer</td>
<td>12</td>
</tr>
<tr>
<td>5.3 Risk factors for development of esophageal cancer</td>
<td>13</td>
</tr>
<tr>
<td>5.3.1 Modifiable risk factors</td>
<td>13</td>
</tr>
<tr>
<td>5.3.2 Non-modifiable risk factors</td>
<td>15</td>
</tr>
<tr>
<td>5.4 Diagnosis</td>
<td>16</td>
</tr>
<tr>
<td>5.4.1 Clinical presentation</td>
<td>16</td>
</tr>
<tr>
<td>5.4.2 Staging principles</td>
<td>16</td>
</tr>
<tr>
<td>5.4.3 Endoscopy</td>
<td>18</td>
</tr>
<tr>
<td>5.4.5 Histologic subtypes of esophageal cancer</td>
<td>20</td>
</tr>
<tr>
<td>5.5 Treatment</td>
<td>21</td>
</tr>
<tr>
<td>5.5.1 Mucosal tumors</td>
<td>21</td>
</tr>
<tr>
<td>5.5.2 Locally advanced tumors</td>
<td>23</td>
</tr>
<tr>
<td>5.5.3 Advanced tumors</td>
<td>27</td>
</tr>
<tr>
<td>5.5.4 Stents in esophageal cancer</td>
<td>30</td>
</tr>
<tr>
<td>5.6 Prognosis of esophageal cancer</td>
<td>32</td>
</tr>
<tr>
<td>5.7 Nutritional deficits and sarcopenia in esophageal cancer</td>
<td>33</td>
</tr>
<tr>
<td>5.7.1 Definitions</td>
<td>33</td>
</tr>
<tr>
<td>5.7.2 Prevalence</td>
<td>33</td>
</tr>
<tr>
<td>5.7.2. Mechanism</td>
<td>33</td>
</tr>
<tr>
<td>5.7.3 Diagnosis</td>
<td>34</td>
</tr>
<tr>
<td>5.7.4 Effect on oncological and surgical outcomes</td>
<td>35</td>
</tr>
<tr>
<td>6 AIMS OF THE PRESENT STUDY</td>
<td>37</td>
</tr>
</tbody>
</table>
7 PATIENTS AND METHODS..............................................................................................................................................................................38
  7.1. PATIENTS..............................................................................................................................................................................................................38
  7.2. Methods ............................................................................................................................................................................................................38
    7.2.1. Staging ..............................................................................................................................................................................................................38
    7.2.2 Definition of sarcopenia ........................................................................................................................................................................39
    7.2.3. Neoadjuvant therapy ........................................................................................................................................................................39
    7.2.4. Stent insertion ........................................................................................................................................................................................................40
    7.2.5. Nutritional evaluation and treatment ..................................................................................................................................................40
    7.2.6. Surgical therapy ................................................................................................................................................................................40
    7.2.7. Adjuvant therapy ...........................................................................................................................................................................................................41
    7.2.8. Follow-up ........................................................................................................................................................................................................41
    7.2.9. Statistical methods ..............................................................................................................................................................................41
    7.2.10. Study endpoints ................................................................................................................................................................................42
8 RESULTS .................................................................................................................................................................................................................43
  8.1. STUDY I ..............................................................................................................................................................................................................43
  8.2. STUDY II ..............................................................................................................................................................................................................44
  8.3. STUDY III ..............................................................................................................................................................................................................46
  8.4. STUDY IV ..............................................................................................................................................................................................................48
9 DISCUSSION ...........................................................................................................................................................................................................51
  9.1. ESOPHAGEAL STENTING AS A BRIDGE TO SURGERY IN RESECTABLE ESOPHAGEAL CANCER ...........................................51
  9.2. SKELETAL MUSCLE MASS AND SARCOPE NIA AS A PREDICTOR OF POOR PROGNOSIS IN ESOPHAGEAL CANCER PATIENTS RECEIVING NEOADJUVANT TREATMENT ........................................................................................................52
  9.3. SKELETAL MUSCLE MASS LOSS & SARCOPE NIA IN ADVANCED ESOPHAGEAL CANCER TREATED WITH PALLIATIVE STENT INSERTION ........................................................................................................................................................................53
  9.4. STENT FAILURE IN MALIGNANT AND BENIGN ESOPHAGEAL DISEASE ........................................................................................................................54
10 SUMMARY ...........................................................................................................................................................................................................56
11 CONCLUSIONS ......................................................................................................................................................................................................57
12 ACKNOWLEDGEMENTS ..................................................................................................................................................................................60
13 REFERENCES ........................................................................................................................................................................................................62
ORIGINAL PUBLICATIONS ...................................................................................................................................................................................78
# 1 ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE</td>
<td>Barrett’s esophagus</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CRT</td>
<td>Chemoradiotherapy</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CCI</td>
<td>Charlson comorbidity index</td>
</tr>
<tr>
<td>EAC</td>
<td>Esophageal adenocarcinoma</td>
</tr>
<tr>
<td>EC</td>
<td>Esophageal cancer</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>EMR</td>
<td>Endoscopic mucosal resection</td>
</tr>
<tr>
<td>EOX</td>
<td>Epirubicin – Oxaliplatin – Cabecitabin</td>
</tr>
<tr>
<td>ESCC</td>
<td>Esophageal squamous cell carcinoma</td>
</tr>
<tr>
<td>EUS</td>
<td>Endoscopic ultrasound</td>
</tr>
<tr>
<td>FDG</td>
<td>18F-fluorodeoxy-D-glucose</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>18F-fluorodeoxy-D-glucose positron emission tomography</td>
</tr>
<tr>
<td>FDG-PET-CT</td>
<td>18F-fluorodeoxy-D-glucose positron emission tomography with computed tomography</td>
</tr>
<tr>
<td>GEJ</td>
<td>Gastroesophageal junction</td>
</tr>
<tr>
<td>HGD</td>
<td>High grade dysplasia</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>LNM</td>
<td>Lymph node metastases</td>
</tr>
<tr>
<td>MIE</td>
<td>Minimally invasive Ivor Lewis esophagectomy</td>
</tr>
<tr>
<td>NAT</td>
<td>Neoadjuvant treatment</td>
</tr>
<tr>
<td>OEGD</td>
<td>Upper gastrointestinal endoscopy</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PEG</td>
<td>Percutaneous endoscopic gastrostomy</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>RFA</td>
<td>Radiofrequency ablation</td>
</tr>
<tr>
<td>RFS</td>
<td>Recurrence free survival</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
</tr>
<tr>
<td>SEMS</td>
<td>Self-expanding metallic stent</td>
</tr>
<tr>
<td>SMI</td>
<td>Skeletal Muscle Index</td>
</tr>
<tr>
<td>SUV</td>
<td>Standardized uptake values</td>
</tr>
</tbody>
</table>
2 LIST OF ORIGINAL PUBLICATIONS

This thesis is based on following original publications, which are referred to in the text by their Roman numerals.


3 ABSTRACT

Background
Esophageal cancer (EC) is one of the most lethal malignancies, with long-term survival rates lower than 15% in western countries. Nutritional deficits, muscle wasting and swallowing disorders are commonly associated with EC. The aims of this study were to 1) assess the safety and efficacy of esophageal stent insertion as a bridge to surgery in EC, 2) the impact of muscle wasting and low muscle mass in EC patients undergoing Neoadjuvant treatment (NAT), 3) and in patients undergoing palliative stent insertion for EC. In addition, 4) we weighed the factors affecting esophageal stent failure rates across in all indications for stenting.

Patients and methods
We analyzed 174 patients with EC of clinical T-stage of 2 or more operated at Helsinki University Central Hospital (HUCH) between 2006-2014 in study I. A total of 30 patients that had received a self-expanding metallic stent (SEMS) preoperatively were 1:1 propensity matched to 30 non-stented patients and the groups were compared. In study II, 115 EC patients that had been operated at HUCH and had undergone NAT between 2010 and 2014 were analyzed for sarcopenia, muscle mass and muscle mass loss during NAT by using routine computed tomography (CT) scans taken during the treatments. Study III comprised of 238 patients undergoing SEMS insertion for palliative treatment of advanced EC between 2005 and 2013. We used CT scans to assess the patients’ sarcopenia status and muscle mass. For study IV, we collected data on 469 patients with SEMS inserted at HUCH between 2005 and 2013 for EC, non-esophageal malignancy or benign disease. We compared the factors affecting major stent-related adverse events, defined as stent failure.

Results
SEMS insertion did not negatively affect the overall survival (OS), progression-free survival (PFS) or complication rates. Stenting produced a low complication rate in this patient group. Patients with preoperative SEMS insertion, did however have longer operation times.

Sarcopenia is not a prognostic factor in EC patients undergoing NAT, it did not affect OS, RFS or complication rates. However, loss of skeletal muscle mass, measured in this study by Skeletal muscle index (SMI) had a significant effect: patients who lost more skeletal muscle than median had a worse OS.
In advanced EC patients receiving a SEMS, sarcopenia, defined by predefined SMI values, was not a prognostic marker for OS. A low SMI on the other hand correlated well with worse outcome. SMI change below the median was also correlated with worse OS.

Esophageal stent failure is most common in non-malignant indications. Stenting of the middle third of the esophagus also carries a high risk of adverse events, as do shorter stents.

Conclusions
Using stents before surgery for EC seems to be safe regarding oncological outcomes and complications. Surgeons should however be aware that the following operation may be more challenging, reflected in our study by the prolonged operative time.

Muscle mass loss during NAT for EC is a marker of poor prognosis and should be taken into account when evaluating the patients treatment plan. Nutritional evaluation should be done routinely in these patients.

Advanced EC produces a challenge in the patients nutrition from an obstructing and a metabolic point of view, accelerated loss of muscle mass and initial low muscle mass serve as markers for worse prognosis in patients with advanced EC receiving a palliative stent, which should be considered when applying palliative treatments. A palliative stent insertion rarely reverses muscle mass loss or sarcopenia.

Stenting of the esophagus in benign esophageal disease should be approached with caution, as the failure rate is high. Inserting a stent higher in the esophagus is also more risky. Shorter stents also have a higher chance of failure. Stenting of EC and other malignancies is safer, but not without adverse events.
4 INTRODUCTION

There are two main types of EC: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC is the predominant type worldwide (e.g. in Asia, Africa, and South America), accounting for 90% of the cases. The incidence of EAC has increased and surpassed the incidence of ESCC in many western countries. The 5-year survival for EC has historically been poor, and although improvements have been made, the prognosis is still grim. (Cen et al. 2012; Rustgi and El-Serag 2014)

EC commonly causes dysphagia (up to 75% of patients) and weight loss (up to 57% of patients). (Daly et al. 2000) Worse outcomes have been reported in association with over 10% weight loss in esophageal surgery. (Fein et al. 1985; van der Schaaf et al. 2014) Placing a SEMS or a removable stent has been reported to be an effective and safe way of palliating the patients’ dysphagia before NAT. (Park et al. 2015; Pellen et al. 2012; Siddiqui et al. 2012)

5 REVIEW OF THE LITERATURE

5.1. GROSS ANATOMY OF THE ESOPHAGUS

The esophagus is the conduit that serves as a dynamic muscular tube, pushing food forward, between the oropharynx and stomach. It is approximately 18 to 26 cm in length, measured from the upper sphincter to lower sphincter. The esophagus descends anteriorly to the vertebral column through the superior and posterior mediastinum. At the level of diaphragm hiatus the esophagus descends through the gastroesophageal junction (GEJ) to end at the cardia of the stomach. (Kuo and Urma 2006)

The esophagus has three topographical regions: cervical, thoracic and abdominal. The cervical esophagus is 4 to 5 cm long and lies between the

![Figure 1](image.png)

Figure 1 the anatomy of the esophagus. Reproduced with permission from Elsevier
pharyngoesophageal junction to the suprasternal notch. The cervical esophagus is bordered anteriorly by the trachea, posteriorly by the vertebral column, and laterally by the carotid sheaths and the thyroid gland. From the suprasternal notch to the diaphragmatic hiatus, lies the thoracic esophagus. It is located posterior to the trachea, the tracheal bifurcation, and the left main stem bronchus. Esophagus goes through the loop of the aortic arch, and the T4 level it is posterior and to the right of the aortic arch, whereas at the level T8 the esophagus lies anterior to the aorta, until the diaphragmatic hiatus. The approximately 1 cm long abdominal esophagus locates between the diaphragmatic hiatus and the orifice of the cardia of the stomach. The abdominal esophagus lies in the esophageal groove on the posterior surface of the left lobe of the liver. The anatomy of the esophagus and its relation to surrounding structures is portrayed in Figure 1.(Kuo and Urma 2006; Liebermann-Meffert 2001)

The esophageal wall has four layers: mucosa, submucosa, muscularis propria, and adventitia. The esophagus has no serosa, unlike the rest of the gastrointestinal tract.(Kuo and Urma 2006) Muscle in the 54-62% of the esophagus is exclusively smooth muscle and the proximal 4.1-5.6% is striated muscle, remaining parts are mixed muscle types.(Meyer et al. 1986)

The esophagus has a rich blood supply: the inferior and superior thyroid artery supply the cervical esophagus, bronchial arteries and aortic esophageal arteries supply the thoracic esophagus and the left gastric artery, left splenic artery and branch of left phrenic artery supply the lower parts of the esophagus.(Kuo and Urma 2006; Liebermann-Meffert 2001; Liebermann-Meffert et al. 1987) The venous blood supply also has a segmental nature. From the submucosal plexus blood drains into the superior vena cava. Upper parts of the esophagus drain through the thyroid and jugular veins. The venous drainage of mid-esophagus goes to the left gastric vein, a part of a portal vein and splenic veins. Proximal and distal esophageal venous drainage goes into the azygos and hemiazygos systems. There are porto-caval connections in the distal esophageal venous plexus.(Kuo and Urma 2006; Liebermann-Meffert 2001)

Lymphatic drainage in the esophagus flows in longitudinally arranged channels and plexuses, although some connections to the surface exist. Lymphatic vessels have numerous valves, that direct lymphatic flow. Under healthy conditions, lymph drainage below the carina flows into the cisterna chyli by lower mediastinal, celiac and left gastric lymphatic routes. Above the carina, lymph flows cranially into the thoracic duct or subclavian lymph trunk. Lymph vessel or node blockage by e.g. tumor invasion can produce retrograde flow of lymph.(Liebermann-Meffert 2001)
5.2. EPIDEMIOLOGY OF ESOPHAGEAL CANCER

The incidence of EAC has been steadily rising in many western countries for many decades. (Blot et al. 1991; Hur et al. 2013) In the 1970’s and 1980’s, in the United States, the increase in incidence of EAC and gastric cardiac cancer among men ranged from 4% to 10% per year, making the incidence of these cancers the fastest increasing of any cancers. At the same time, the incidence of ESCC remained stable. (Blot et al. 1991) Between 1976-95 in Finland, the total incidence of esophageal carcinoma decreased slightly, but the age-adjusted incidence of EAC in men rose almost 300%. (Sihvo et al. 2009) Current age-adjusted incidence (2011-2015) is at 5.49 per 100,000 for

Figure 2 Age-standardized rates of esophageal cancer between 1960 and 2015 in Finland (top left) and the Nordic countries (top right) and Age-specific rates of esophageal cancer in Finland (bottom left) and in the Nordic countries (bottom right)
both sexes, 8.84 per 100,000 for men and 2.71 per 100,000 for women (Finnish Cancer Registry, 2018). A visual presentation of age-standardized and age-specific incidence in Finland and Nordic countries is shown in Figure 2. Incidence of EAC has steadily risen in the US, although the rate has slowed in the late 1990’s. (Hur et al. 2013) Between 1980 and 2011 in northern Europe, EAC rates rose markedly and surpassed ESCC in men. ESCC remains predominant in several European countries and in women. (Castro et al. 2014)

There is great variation in incidence rates between countries in EC, even up to 21-fold differences. Highest incidence is found in Eastern Asia and Eastern and Southern Africa and the lowest rate in Western Africa. (Torre et al. 2015)

The estimated cumulative risk of developing EC between birth and age 74 is 0.8% in more developed countries and 1.2% in less developed countries, whereas the estimated mortality is 0.6% in more developed countries and 1.0% in less developed countries. (Torre et al. 2015) In Finland the risk of developing EC between birth and age 80 is 0.46% for both sexes, 0.64% for men and 0.28% for women, the respective mortality risks in Finland are 0.28% for both sexes, 0.41% for men and 0.14% for women. (Finnish Cancer Registry, 2018) In EU, the mortality has been falling and between 2000-2004 and 2005-2009 the rate decreased by 7% in men and 3% in women, regardless if age group. (Castro et al. 2014)

5.3. RISK FACTORS FOR DEVELOPMENT OF ESOPHAGEAL CANCER

5.3.1 Modifiable risk factors
Gastroesophageal reflux disease (GERD) is a well-known risk factor for EAC. A meta-analysis reports 4.92 odds ratio (95% CI = 3.90–6.22) for EAC with weekly GERD symptoms. Daily symptoms of GERD increased the odds to 7.40 (95% CI = 4.94-11.1). Duration of symptoms was also associated with increased risk, although heterogeneous results. (Rubenstein and Taylor 2010) Another review also demonstrated positive association between reflux symptoms and EAC risk, with symptom severity and duration increasing the risk further. They also concluded that although a positive association exists, the total risk for EAC is still low, given the ubiquity of GERD symptoms and the rarity of EAC. (Shaheen and Ransohoff 2002) A Swedish population-based case-control study examining the relationship of GERD symptoms, did not find association with GERD and ESCC. (Lagergren et al. 1999) In addition to GERD, the presence of hiatal hernia, esophagitis or esophageal ulcer and dysphagia have been found to associate with increased risk for EAC. (Chow et
Barrett’s esophagus (BE) is a condition in which the stratified squamous epithelium of the distal esophagus is replaced by metaplastic columnar epithelium. Pathogenesis of BE is related to chronic acid reflux. (Spechler 2013) GERD is proven to be a risk factor for BE. (Winberg et al. 2012) Other risk factors include cigarette smoking, obesity and male sex. (Cook et al. 2012; Engeland, Tretli, and Bjorge 2004; Lagergren 2011) BE is thought to be a precursor lesion to EAC and the annual risk of EC is 0.1 to 0.3% for non-dysplastic BE and 6% with high grade dysplasia. (Bhat et al. 2011; Desai et al. 2012; Spechler 2013) Another study found that the risk for developing high-grade dysplasia or EAC was ≤ 1% for non-dysplastic BE and 18-40% for those with low-grade dysplasia and at least one risk factor. The risk factors associated with developing high-grade dysplasia or EAC, in this study, were longer length of BE, esophagitis and longer known duration of BE (≥ 10 years). (Sikkema et al. 2011) The amount of oxidative stress-related DNA damage has been found to be similar in the esophageal mucosa of patients with BE, high-grade dysplasia and EAC. (Rasanen et al. 2007)

Another risk factor for EAC is obesity, with first reports of an association published in the 1990’s. In a Norwegian prospective cohort study with more than 2 million subjects an association with high Body mass index (BMI) and EAC was found. The risk was more pronounced with higher BMI’s. The same study reported and opposite relation for ESCC, with obesity being protective for ESCC. (Engeland, Tretli, and Bjorge 2004) A case-control study done in Australia compared patients with EAC or GEJ adenocarcinomas (N= 793) with control participants (n=1580). They found that EAC risk increased concomitantly with body mass index (BMI) (p <0.001). BMI ≥ 40 kg/m² produced the highest risk compared to individuals with a healthy BMI (OR=6.1, 95% CI = 2.7-13.6) (Whiteman et al. 2008)

Caustic injury, especially lye ingestion, is a known risk factor for ESCC development, with a risk of 1000-3000 times greater than the standard population. (Kiviranta 1952) Caustic ingestion most commonly occurs during ages 2-3 by accidental ingestion, development of esophageal cancer has been reported to have a latent period between 1-4 decades years, although there are reports of cancer formation within 1 year of caustic injury. (Appelqvist and Salmo 1980; Hopkins and Postlethwait 1981; Jain et al. 2010)

 Achalasia, an idiopathic esophageal motility disorder in which there is absence of relaxation of the LES and aperistalsis of the esophagus is a risk factor for both EAC and ESCC development, although the risk of ESCC is markedly higher. (Torres-Aguilera and Remes Troche 2018) Overall
risk for developing EC with achalasia is between 0.4% and 9.2% with an annual incidence of 0.34 and a hazard ratio of 28 compared to the age-matched general population. (Leeuwenburgh et al. 2010; Torres-Aguilera and Remes Troche 2018)

Cigarette smoking is a risk factor for both EAC and ESCC, although the risk is more pronounced with ESCC. (Cook et al. 2010) OR for the association between ESCC and tobacco has been reported to be 16.9 with 80 or more pack-years compared to nonsmokers, and 3.4 for EAC. (Vaughan et al. 1995) A recent meta-analysis cites that tobacco use is associated with 20-30% increased risk for ESCC compared with nonuse. (Prabhu, Obi, and Rubenstein 2014)

Alcohol use has also been associated with increased risk for ESCC and EAC, with similar effect sizes compared to tobacco being cited. (Prabhu, Obi, and Rubenstein 2014) People with 21 or more alcoholic drinks per week have OR of 9.5 for ESCC and 1.8 for EAC, compared to those who drink less than 7 drinks per week. (Vaughan et al. 1995)

Tobacco and alcohol have been found to have synergistic effect for development of EC, especially ESCC. OR’s for the concomitant exposure vary wildly in the literature: 3.28-107, and even up to 149.2 in black males. (Castellsague et al. 1999; Napier, Scheerer, and Misra 2014; Prabhu, Obi, and Rubenstein 2014)

H. pylori infection seems to be protective against EAC. A meta-analysis reported the risk of EAC to be decreased by 41% in persons with H. pylori infection. (Xie et al. 2013) It is thought that H. pylori infection may ultimately reduce acid production by causing gastric atrophy, which in turn reduces the effect of acidic reflux on the distal esophagus and reduces the formation of BE. (Fischbach et al. 2014; Rubenstein et al. 2014) No significant association between H. pylori and ESCC has been found. (Xie et al. 2013)

5.3.2. Non-modifiable risk factors

Three major predisposition genes were found in a genome-wide combined linkage-association analysis of 21 concordant-affected sibling pairs with BE/EAC and 11 discordant pairs of siblings. The genes identified were MSR1 (macrophage scavenger receptor 1), ASCC1 (activating signal co-integrator 1 complex subunit 1), and CTHRC1 (collagen triple-helix repeat-containing 1). Germline mutations in these genes were identified in 11.2% patients in this study. (Orloff et al. 2011) Another genome-wide association study, compared EAC cases and BE cases (N = 5565) with 10 120 controls. They identified associations between CRTC1 (encoding CREB-regulated transcription coactivator), BARX1 (BARX homeobox 1) and FOXP1 (Forkhead Box P1). (Levine et al. 2013) A whole-exome sequencing analysis of 149 EAC tumor-normal pairs identified several genes with
significant associations to EAC such as TP53 (tumor protein 53), CDKN2A(cyclin-dependent kinase Inhibitor 2A), SMAD4 (SMAD Family Member 4), ARID1A(AT-rich interactive domain-containing protein 1A), Pik3CA(PI3-Kinase Catalytic Subunit Alpha), SPG20 (Spastic Paraplegia 20), TLR4 (Toll-like receptor 4), ELMO1(Engulfment And Cell Motility 1) and DOCK2(Dedicator Of Cytokinesis 2). The authors suggested, based on these findings the activation of RAC1 pathway as a key concept in EAC.(Dulak et al. 2013)

5.4. DIAGNOSIS

5.4.1. Clinical presentation
The two types of ECs produce similar clinical pictures, despite different risk factors. Common symptoms of EC include progressive dysphagia, weight loss, and reflux symptoms unresponsive to medical treatment. Signs of blood loss might also be present. Hoarseness, cough, pneumonia and laryngeal nerve paralysis are symptoms that are less frequently encountered. Chest pain and epigastric pain are also possible. (Rustgi and El-Serag 2014) Some sources claim that ESCC has the more classical clinical picture of dysphagia and weight loss and EAC is most commonly found behind new-onset dysphagia in the setting of chronic GERD. (Pennathur et al. 2013) Endoscopic appearance is also similar, although EAC is typically (approx. 75% of cases) found in the distal esophagus, whereas ESCC is frequently found in the middle to proximal esophagus.(Rustgi and El-Serag 2014) The incidence of asymptomatic EC has also risen with increased employment of surveillance strategies. (Daly et al. 2000; Pennathur et al. 2013; Portale et al. 2006; Rustgi and El-Serag 2014)

5.4.2. Staging principles
The most commonly used staging system used is the TNM classification, which takes into account the invasion depth of the tumor, the presence and amount of local lymph node metastases (LNM) and the presence or absence of distant metastatic disease.(Pennathur et al. 2013; Rice, Blackstone, and Rusch 2010) The system is presented in Figure 3 and the stage grouping in Table 1. Separate staging for Clinical (cTNM), pathologic (pTNM), and postneoadjuvant (ypTNM) have been introduced in the 8th edition of the American Joint Committee on Cancer (AJCC) staging of epithelial cancers of the esophagus and GEJ.(Rice, Patil, and Blackstone 2017)
Figure 3 Esophageal cancer staging by TNM categories. Categories of the T stage are as follows; Tis: high-grade dysplasia (HGD). T1 has invaded into lamina propria, muscularis mucosae, or submucosa and its subcategories are T1a (invades the lamina propria or muscularis mucosae) and T1b (invades the submucosa); in T2 cancer, the muscularis propria is invaded; T3 is cancer that breaches the adventitia; T4 stage denotes local invasion to adjacent structures and is subcategorized as T4a (invasion into local structures such as the pleura, pericardium, azygos vein, diaphragm, or peritoneum) and T4b (invasion into the major adjacent structures, such as the aorta, vertebral body, or trachea). N divided into N0 (no regional LNM), N1 (one to two regional LNM), N2 (three to six regional LNM), and N3 (seven or more regional LNM). M is categorized as M0 (no distant metastasis) and M1 (distant metastasis). Reproduced with permission from Elsevier.
**5.4.3. Endoscopy**

Esophagogastroduodenoscopy is required in the diagnosis of EC in order to obtain biopsy samples to determine the histology and for this reason, it has been the preferred diagnostic tool. It allows the physician to assess the location and size of the tumor, the degree of obstruction caused by the tumor, the adherence of the tumor to the muscular layer of the esophagus and whether involvement of the gastric cardia is visible. (Pennathur et al. 2013)

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Grade</th>
<th>Tumor Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis (HGD)</td>
<td>N0</td>
<td>M0</td>
<td>I, X</td>
<td>NA</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>NA</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>1–2, X</td>
<td>NA</td>
</tr>
<tr>
<td>IIA</td>
<td>T2-3</td>
<td>N0</td>
<td>M0</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>IIB</td>
<td>T1–2</td>
<td>N1-2</td>
<td>M0</td>
<td>Any</td>
<td>NA</td>
</tr>
<tr>
<td>IIIA</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>NA</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
<td>Any</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N1-2</td>
<td>M0</td>
<td>Any</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Any</td>
<td>M0</td>
<td>Any</td>
<td>NA</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any</td>
<td>N3</td>
<td>M0</td>
<td>Any</td>
<td>NA</td>
</tr>
<tr>
<td>IV</td>
<td>Any</td>
<td>Any</td>
<td>M1</td>
<td>Any</td>
<td>NA</td>
</tr>
</tbody>
</table>

Tis = intraepithelial neoplasia, HGD = high-grade dysplasia, NA = Not applicable

**Table 1 AJCC 8th edition staging**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Grade</th>
<th>Tumor Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis (HGD)</td>
<td>N0</td>
<td>M0</td>
<td>I, X</td>
<td>NA</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>NA</td>
</tr>
<tr>
<td>IB</td>
<td>T2–3</td>
<td>N0</td>
<td>M0</td>
<td>1–3</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N1-2</td>
<td>M0</td>
<td>Any</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Any</td>
<td>M0</td>
<td>Any</td>
<td>NA</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any</td>
<td>N3</td>
<td>M0</td>
<td>Any</td>
<td>NA</td>
</tr>
<tr>
<td>IV</td>
<td>Any</td>
<td>Any</td>
<td>M1</td>
<td>Any</td>
<td>NA</td>
</tr>
</tbody>
</table>

Tis = intraepithelial neoplasia, HGD = high-grade dysplasia, NA = Not applicable
5.4.4. Imaging

Barium swallow studies are classically used in the primary evaluation and diagnosis of EC with good sensitivity in identifying the primary tumor.(Levine et al. 1997) Nowadays, it is rarely done, since better alternatives are available.

CT imaging has sensitivity of 0.42 and specificity of 0.93 for abdominal LNM in EC and sensitivity of 63-87% and specificity of 14-43% for locoregional lymph nodes.(Meltzer et al. 2000; van Vliet et al. 2008) Sensitivity and specificity for distant metastases are 0.52 and 0.91.(van Vliet et al. 2008) A systematic review concluded the maximum joint value for sensitivity and specificity for CT to be 54% for assessment of response to neoadjuvant therapy.(Westerterp et al. 2005)

Endoscopic ultrasound (EUS) has increased the sensitivity and specificity of local assessment of EC, it has been deemed the most sensitive method for detection regional LNM in a recent meta-analysis, with sensitivity of 80% and specificity of 70%, and a sensitivity of 85% and a specificity of 95% for celiac node involvement(van Vliet et al. 2008). The pooled sensitivity of EUS in detecting T1-disease is 81.6% and 99.4%, for T4 the sensitivity is 92.4% and the specificity 97.4%.(Puli et al. 2008) The sensitivity of EUS to diagnose N stage was improved from 70-90% without fine needle aspiration (FNA) to 96.7% with FNA.(Grimm et al. 1993; Puli et al. 2008; Rosch et al. 1992) Studies report that EUS guides the treatment modalities in 29-34.8% of patients.(Hulshoff et al. 2017; Pfau et al. 2007) The tumor infiltration depth assessment accuracy of EUS was 85.7% in EC.(Grimm et al. 1993) The inability to pass the endoscope by malignant strictures, that may occur in up to 45% of cases, may decrease the performance of EUS.(Kelly et al. 2001) Overall, most studies conclude that EUS has an important role in staging of EC and its strengths are in the detection of tumor invasion depth and local LNM. (Grimm et al. 1993; Kelly et al. 2001; Pfau et al. 2007; Puli et al. 2008; Rosch et al. 1992; van Vliet et al. 2008)

18F-fluorodeoxy-D-glucose positron emission tomography with computed tomography (FDG PET CT) has been studied and widely used in detection of distant metastases in EC staging. FDG PET CT was found to be less sensitive than CT for locoregional lymph node tumor involvement diagnosis in some studies (35-41% vs. 63-87%) and to perform better in some studies (accuracy of 76% with PET CT vs 45% with CT).(Flanagan et al. 1997; Meltzer et al. 2000; Rasanen et al. 2003) A systematic analysis concluded the pooled sensitivity and specificity to be 51% and 84% for locoregional metastases.(van Westreenen et al. 2004) PET CT was, however more specific in detecting distant metastases (approximately 90-93% vs. 14-43%) and with a sensitivity of 71-74%.(Meltzer et al. 2000; Rasanen et al. 2003; van Vliet et al. 2008) The pooled sensitivity and specificity for detecting metastases is 67% and 97%, respectively.(van Westreenen
et al. 2004) PET CT has been reported to detect metastatic disease undetected by standard CT in 15% of patients. (Downey et al. 2003) PET CT has a sensitivity of 50% and specificity 92.9% for detecting residual tumor after neoadjuvant CRT, whereas the joint sensitivity and specificity to evaluate response in this scenario has been estimated to be 85%. (Song et al. 2004; Westerterp et al. 2005) A decrease of ≥60% in standardized uptake value has also been shown to correlate with later disease-free and OS, offering valuable prognostic information after induction therapy. (Downey et al. 2003) FDG PET CT has been claimed to be the most accurate noninvasive test to predict long-term survival after neoadjuvant CRT before surgical resection, with a standardized uptake value (SUV) value limit of ≥4 (HR = 3.5). (Swisher et al. 2004) SUV change of >67% during neoadjuvant treatments has been associated with better histopathological response and OS. (Kauppi et al. 2012) It also is a good prognostic study in the setting of metastatic disease. (Sihvo et al. 2004) PET has been studied as a way to predict pathological complete response (defined as no visible tumor and a SUV < 2.5) after neoadjuvant CRT, and was deemed to outperform conventional response measurements. (Schmidt et al. 2015; Song et al. 2004)

5.4.5 Histologic subtypes of esophageal cancer

Esophageal cancer has two main histologic types: adenocarcinoma and squamous cell carcinoma. EAC has moderate or well differentiated cells, which are usually mucin producing. Foci of squamous or endocrine differentiation are not uncommon. HGD and Barrett’s metaplasia are commonly adjacent. Signet cells, Paneth cells, and papillary structures are less common. (Smith et al. 1984) ESCC displays keratinization and intercellular bridging is common. Differentiation is usually moderate or well-differentiated. Angiolymphatic invasion and distant tumor clusters may be present. Foci of glandular or small cell differentiation are possible. Desmoplastic reaction is common when adventitial penetration is present. (Syrjanen 1982) Small-cell carcinoma is a rarer diagnosis with aggressive nature and poor prognosis. It comprises 0.8-2.4% of all esophageal malignancies. (Beyer et al. 1991; Medgyesy et al. 2000) Its histologic classification follows the typical histologic classification of small-cell cancers with cells that are small-sized, a round-to-fusiform shape, scant cytoplasm, fine granular nuclear chromatin and inconspicuous/absent nucleoli. (Travis 2012)
5.5. TREATMENT

Treatment of esophageal cancer is based on careful assessment of the local stage and possible distant metastases of the tumor, and the treatment plan and decisions are individualized based on patient comorbidities and patient preferences.

5.5.1. Mucosal tumors

Tumors that do not infiltrate beyond the muscularis mucosae (T-stage 1a) can be treated successfully with endoscopic mucosal resection with or without ablation. (Rustgi and El-Serag 2014) No randomized trials exist. (Bennett et al. 2012) A retrospective study compared 99 patients, who underwent endoscopic mucosal resection to 643 patients treated with surgery, all the patients had early EC. There was no statistical significance in EC-specific mortality between the two groups (Relative hazard = 0.89, 95% CI = 0.51–1.56, p = 0.68). (Das et al. 2008) In a prospective trial, patients with low risk EC (mucosal lesion of diameter ≤ 20 mm, histological grade G1-G2 and/or high-grade dysplasia) were compared to high risk patients. The mean number of endoscopic sessions was 1.3 ± 0.6 in low-risk group and 2.8 ± 2.0 in high-risk group (P < 0.0005). Complete local remission was achieved more often (97% vs. 59%) and earlier (p = 0.008) in the low-risk group vs. the high-risk group. (Ell et al. 2000) In another study, the success rate for complete local control was 99% and required a mean treatment time of 1.9 months (range, 1–18 months) and a mean of 1.47 (range 1-3) resections. (Ell et al. 2007) During a follow-up of period of approximately 11-12 months the recurrence was 11-14%. (Ell et al. 2000; Ell et al. 2007) The need for additional treatments was reported to be 65.7% in a prospective trial, and the success rate 92.8%. Recurrence of high-grade dysplasia was encountered in 19.2. At the end of follow-up 93% of endoscopically treated patients were in local remission. (Peters et al. 2005) A register study compared the long-term survival of two groups of patients with T1 EAC, treated with either endoscopic methods (n = 306) or surgery (n = 1312), and found the long-term survival to be higher in the surgery group (70% vs. 58%, p = 0.003). After adjustment for patient and tumor factors, the OS times and EC-specific survival times did not differ(HR = 1.21; 95% CI = 0.92-1.58 and HR = 0.74; 95% CI = 0.49-1.11, respectively). (Ngamruengphong, Wolfsen, and Wallace 2013) A 5-year survival rate as high as 98% has been reported in early EAC. (Ell et al. 2007) A prospective randomized study compared 100 endoscopic resections done with either “suck-and-ligate” device without submucosa injection...
or cap technique with prior submucosal injection. They found no difference between the methods in regards to efficacy and safety. (May et al. 2003)

A multicenter randomized clinical trial done in Europe, found that patients with BE and low grade dysplasia showed less neoplastic progression to high-grade dysplasia and/or EAC when treated with radiofrequency ablation (RFA) with or without endoscopic resection, compared to surveillance endoscopies only. They found that after 5 years of follow up, 90% were in remission, with all of the recurrences treated endoscopically. (Phoa et al. 2013) A retrospective registry study reported a 88% complete response rate for high-grade dysplasia when treated with RFA and EMR. (Haidry et al. 2015) A multicenter registry study reported EAC incidence to be 2% and EAC mortality to be 0.2% in patients who underwent RFA for BE with or without dysplasia. (Wolf et al. 2015)

Endoscopic submucosal dissection (ESD) is an endoscopic resection technique, in which the resection is carried out by a special needle knife and it enables the en-bloc resection of larger mucosal tumors than the conventional EMR technique. (Oyama et al. 2005; Probst et al. 2015) It is performed with a standard, single accessory-channel endoscope. ESD is typically performed in a stepwise manner including marking the lesion and creating a fluid cushion, incision and submucosal dissection with simultaneous hemostasis. (Ning, Abdelfatah, and Othman 2017) It was originally developed for the treatment of gastric intramucosal lesions in Japan. (Miyamoto et al. 2002) A high en-bloc resection rate (95.0%-100%) and R0-resection rate (83.7%-97%) are associated with the procedure. (Ishihara et al. 2008; Oyama et al. 2005; Probst et al. 2015) However, ESD is time-consuming and has a steep learning curve, which may limit its use in western countries, where gastric and esophageal neoplasms are more seldom encountered compared to Asia. (Chaves et al. 2010; Ning, Abdelfatah, and Othman 2017; Probst et al. 2015) The most common complication after ESD for EC are perforation (incidence of 2.6–10%) and intra-procedural bleeding. (incidence of 0.7–5.2%). (Isomoto et al. 2013; Ning, Abdelfatah, and Othman 2017) Esophageal stenosis following semi-circular or circular ESD is a common late complication with reported rates between 0-17%. (Ishihara et al. 2008; Isomoto et al. 2013; Takahashi et al. 2010)

A meta-analysis comparing ESD and EMR found that ESD produces higher en-bloc (97.1% vs. 49.3%, p < 0.001) and R0 resection rates (92.3% vs. 52.7%, p < 0.001). The same meta-analysis concluded that ESD produced longer operative times (weighed mean difference of 44.7 minutes, p < 0.001) and more perforations (OR = 2.19, 95% CI = 1.08-4.47, p = 0.03) but no difference between esophageal stenosis and intra-procedural bleeding was observed. Recurrence rate was found to be lower with ESD (0.3% vs. 11.5%, p < 0.001). This effect was however only apparent
when the lesions were larger than 20 mm in size in subgroup analysis (OR = 0.05, 95% CI = 0.01-0.28, p < 0.001), which accounted for the whole effect of the pooled analysis.

5.5.2. Locally advanced tumors

Locally advanced esophageal cancer (LAEC) is defined by T-stage of 3 or higher, the presence of locoregional nodal disease, or both, without distant metastases.(Pennathur et al. 2013)

5.5.2.1. Surgery

The treatment approach to LAEC is multimodal, with surgery being a key component in curation.(Pennathur et al. 2013; Urschel, Vasan, and Blewett 2002) There are controversies regarding the optimal technique for EC surgery, and no prospective randomized trials exist.

Ivor Lewis published in 1946 a way of operating on mid- and lower ECs through right thoracotomy and laparotomy. The technique involves mobilizing the stomach and fundus and pulling it through an enlarged hiatus to form a tension-free anastomosis.(Lewis 1946) In 1985, McKeown described a three-incision esophagectomy, with thoracotomy, laparotomy, cervicotomy and a cervical esophageal anastomosis.(McKeown 1985) A left transthoracic approach can also be used for GEJ tumors.(Muller et al. 1990) Surgery without thoracotomy (transhiatal esophagectomy) is also used.(Orringer, Marshall, and Iannettoni 1999) Most surgeons still use these techniques, McKeown esophagectomy is mainly used for high thoracic or cervical ECs and a modified Ivor Lewis esophagectomy for EC located nearer the GEJ.(Hagen et al. 2001; Hulscher et al. 2001; Muller et al. 1990; Orringer, Marshall, and Iannettoni 1999; Pennathur and Luketich 2008; Visbal et al. 2001) Although comparative studies exist, no single operation type has emerged as superior and the choice of surgical technique depends on surgeon preference, the institutional culture, location and extent of the disease and the patient’s comorbidities.(Hagen et al. 2001; Hulscher et al. 2001; Muller et al. 1990; Orringer, Marshall, and Iannettoni 1999; Pennathur and Luketich 2008; Visbal et al. 2001) A randomized controlled study by Hulscher et al. compared transhiatal and transthoracic esophagectomies. They found a higher perioperative morbidity rate with transthoracic esophagectomies and a statistically non-significant trend towards better 5-year survival (39% vs 29%) favoring transthoracic esophagectomy.(Hulscher et al. 2002) A classic series of 1002 consecutive patients described the surgical technique for EAC based on the location of the tumor in relation to the GEJ and introduced a new topographical classification for EAC. Esophagectomy was the treatment of choice for adenocarcinoma of the distal esophagus (Siewert type I) and extended gastrectomy for tumors true carcinoma of the cardia (Siewert type II) and subcardial gastric cancer
infiltrating the distal esophagus (Siewert type III). (Siewert et al. 2000) The importance of microscopically complete resection (R0) as a prognostic variable has been shown in numerous studies. (Barbour et al. 2007; Dexter et al. 2001; Law et al. 1998; Siewert et al. 2000) A macroscopic resection margin of 5 cm distally has been recommended to optimize the amount of R0 resections. (Casson et al. 2000)

Modern esophageal surgery techniques have been developed according to the principles of minimally invasive surgery. Initial reports of the feasibility of thoracoscopic esophageal surgery for EC emerged in the late 1990’s. (Akaishi et al. 1997; Higashino et al. 1997; Law et al. 1997) Results from larger cohorts in the early 2000’s described similar oncological outcomes, shorter hospital stays and faster quality of life improvement postoperatively in comparison to traditional open surgery. (Luketich et al. 2003; Luketich et al. 2000; Nguyen et al. 2000) Recent large reports have estimated the 30-day mortality to be 1.7-2.1%, the median intensive care unit stay is 2 days and the median length of hospital stay is 8-9 days. (Kauppi et al. 2015; Luketich et al. 2012; Luketich et al. 2015) Biere et al. orchestrated a multicenter, open label, randomized trial at five centers and three countries comparing transthoracic minimally invasive esophagectomy (MIE) to traditional open transthoracic esophagectomy. Primary outcome was pulmonary infection within 2 weeks of surgery. Incidence of pulmonary infection in the open esophagectomy group was 29% and in the MIE group 9% (RR 0.30; 95% CI 0.12-0.76; p = 0.005). (Biere et al. 2012) Later publications from the same trial data with additional follow up showed that the 3-year survival between the groups were similar (41.2% vs 42.9%; p = 0633), MIE group had better pain scores at 1 year, and that the mid-term quality of life was improved with MIE. (Maas et al. 2015; Straatman et al. 2017)

The role of extended lymphadenectomy in EC surgery remains somewhat controversial. Three-field dissection of lymph nodes (abdominal, thoracic and neck lymph nodes) is mainly practiced in Japan, where SCC is prevalent. (Pennathur et al. 2013) In Japanese studies, better 5-year survival and quality of life has been associated with three-field lymphadenectomy in comparison to standard two-field (thoracoabdominal) lymphadenectomy (55.0% vs. 38.3%; p = 0.0013). (Akiyama et al. 1994; Fujita et al. 1995) However, the rate of complications, especially recurrent nerve palsy and the need for tracheostomy have been reported to be significantly higher in the extended lymphadenectomy group in a randomized trial, this trial did not show statistically significantly better survival with three-field lymphadenectomy. (Nishihira, Hirayama, and Mori 1998) Three-field dissection has some support in the western countries, and most of its proponents base their argument on the high incidence of cervical lymph node involvement and a possible survival benefit. (Altorki et al. 2002; Lerut et al. 2004) Improved survival with more extensive lymph node retrieval has been reported, although this effect might result from the stage migration from more
accurate staging rather than a therapeutic effect of the lymphadenectomy. (Altorki et al. 2008; Peyre et al. 2008; Talsma et al. 2014) An optimal threshold of minimum of 18-23 lymph nodes collected during surgery has been postulated. (Greenstein et al. 2008; Peyre et al. 2008; Rizk et al. 2006) Later studies have proposed that the ratio of metastatic vs. collected lymph nodes is a more robust independent prognostic variable. (Hsu et al. 2009; Mariette et al. 2008)

5.5.2.2. Definitive chemoradiation & radiation therapy

Definitive radiation therapy has been suggested as a feasible treatment option for superficial ESCC in patients who have high surgical risk. In superficial ESCC the 5-year survival rates are reported to be 38.7% with a 2-year local control rate of 83.0%. (Okawa et al. 1995).

Definitive CRT has been shown to be superior to radiotherapy alone in a randomized trial with 2-year survival rates of 38% vs 10% (p < 0.001). In this study 5000 cGy of radiation therapy and four courses of fluorouracil (1000 mg per square meter of body-surface area daily for four days) and cisplatin (75 mg per square meter on the first day) were compared to 6400 cGy of radiation therapy alone. The rate of severe- and life-threatening complications were 44% and 22% in the CRT group and 25% and 3% in the radiotherapy group (p value not reported). (Herskovic et al. 1992) Persistent disease after treatment occurs in 26% in 5-years after treatment. (Cooper et al. 1999) In some retrospective studies, surgery in addition to definitive CRT has not improved survival of the patients. (de Pree et al. 1995; Ohtsu et al. 1999) Retrospective studies have shown that definitive CRT and additional salvage surgery (surgery for residual disease after definitive CRT) has yielded similar results to planned neoadjuvant CRT and esophagectomy. (Nakamura et al. 2004) Salvage surgery has been shown to improve survival in the setting of locoregional recurrence after definitive CRT. (Chao et al. 2009)

5.5.2.3. Neoadjuvant therapies

NAT is defined as the preoperative induction therapy by either radiotherapy, chemotherapy or a combination of both. NAT is designed to, in theory, eradicate micrometastatic disease and to facilitate radical surgical resection by cancer downstaging, thus improving the survival of EC patients. (Geh et al. 2006; Geh, Crellin, and Glynne-Jones 2001; Lehnert 1999)

A randomized trial compared surgery in combination with preoperative fluorouracil and cisplatin and surgery alone. OS was found to be better in the group that received preoperative chemotherapy (HR 0.79; CI 95% = 0.67-0.93; p = 0.004). The group receiving preoperative
Chemotherapy also had more microscopically complete resections (60% vs. 54%, p < 0.0001). (Bancewicz et al. 2002) The benefit was maintained even in extended follow-up (HR 0.84; 95% CI, 0.72 to 0.98; p = 0.03). (Allum et al. 2009) The MAGIC trial produced similar results in favor of neoadjuvant chemotherapy (NCT) with 5-year survival of 36.3% in the neoadjuvant therapy group vs. 23.0% in the surgery only group (HR 0.74; 95% CI 0.59-0.93; p = 0.0008). (Cunningham et al. 2006) This finding has been confirmed in other non-randomized studies and with other combinations of chemotherapeutic agents. (Pennathur et al. 2008) Some studies have failed to show a benefit in NCT. (Kelsen et al. 1998)

Neoadjuvant chemoradiation (NCRT) has also been used widely in the treatment of EC. The CROSS trial was a randomized controlled trial, that showed improvement in the R0 resection rate (92% in the neoadjuvant group vs. 69% in the surgery only group; p < 0.001) and median OS, which was 49.4 months in the neoadjuvant group vs. 24.0 months in the surgery only group (HR 0.66; 95% CI = 0.495-0.871; p = 0.003). (van Hagen et al. 2012) Long-term follow up of the same patients confirmed the results with median OS of 48·6 months in the neoadjuvant group and 24·0 months in the surgery only group (HR 0.68; 95% CI = 0·53-0·88; p = 0.003). (Shapiro et al. 2015) Another study also showed benefit in neoadjuvant chemoradiation, although this study has been criticized of its low 3-year survival rate and lack of CT staging. (Pennathur et al. 2013; Walsh et al. 1996) Many randomized trials have showed no benefit in NCRT. (Bosset et al. 1997; Burmeister et al. 2005; Leprise et al. 1994; Urba et al. 2001) NCRT has not shown benefit in regards to R0 resection rate or survival, but rather increased the postoperative mortality (11.1% vs. 3.4%; p = 0.049) in stage I and II disease. (Mariette et al. 2014)

A comparison of neoadjuvant chemotherapy vs. NCRT showed an increased chance of pathological complete response with NCRT (17.2% vs. 6.4%; p < 0.001) and an improved R0 rate (94.4% vs. 88.5%; p < 0.001), however no association with long-term survival was found. (Samson et al. 2016) A meta-analysis concluded that there is a clear benefit in NCRT or neoadjuvant chemotherapy, but a clear advantage between the two cannot be established. (Sjoquist et al. 2011) Another meta-analysis concluded that NCRT is the optimal strategy, based on a subgroup analysis. (Pasquali et al. 2017) No randomized controlled trials directly comparing NCRT and NCT exist yet.

5.5.2.4. Adjuvant treatment

Chemotherapy after resection is a mainstay of multimodal treatment in patients with nodal disease and its benefit has been assessed in several randomized trials, especially in ESCC. (Ando et al.
2003; Ando et al. 1997; Armanios et al. 2004) In a Japanese randomized trial postoperative cisplatin plus 5-FU was compared with surgery only in stage I or II EC, showing no OS benefit, but a significant benefit in disease free survival, especially in patients with node positivity. (Ando et al. 2003) A similar study produced results that did not favor adjuvant therapy.(Ando et al. 1997) In an another Japanese trial comparison of the aforementioned agents in neoadjuvant vs. postoperative setting concluded that the neoadjuvant administration was superior with 5-year OS of 60% vs. 38% (p = 0.013). (Igaki et al. 2008)

5.5.3. Advanced tumors

5.5.3.1 Palliative chemotherapy

Palliative chemotherapy is commonly used in the setting metastatic, unresectable or recurrent disease. (Rustgi and El-Serag 2014) Response rates of 35-45% and a few months of prolonged survival are reported with cisplatin or oxaliplatin combined with either fluorouracil or capecitabine, especially among patients with ESCC. (Rustgi and El-Serag 2014) Docetaxel as a single agent therapy has been studied and a median survival time of 8.1 months was reported, but many toxicities were associated with the treatment. (Muro et al. 2004) Addition of docetaxel to other chemotherapeutic agents improved time to progression (32% risk reduction; p < 0.001). (Van Cutsem et al. 2006) Combination of weekly irinotecan and cisplatin produced major objective response in 57% of patients, with similar response rates for EAC and ESCC. Dysphagia improved in 90% of patients following treatment. (Ilson et al. 1999) In a two by two non-inferiority randomized trial, 1002 patients received triplet therapy with epirubicin and cisplatin plus either fluorouracil or capecitabine or triplet therapy with epirubicin and oxaliplatin plus either fluorouracil or capecitabine. This trial reported similar efficacies with capecitabine and oxaliplatin compared to fluorouracil and cisplatin. Oxaliplatin had fewer toxicities than cisplatin. (Cunningham et al. 2008)

5.5.3.2. Palliative procedures

Many palliative procedures are used in the setting of advanced EC. Many of these operations are done endoscopically and include brachytherapy, stent insertion and photodynamic therapy. (Christie, Patel, and Landreneau 2005) SEMS are a widely used method for treatment of dysphagia in the non-operable setting, and they have been shown to offer good relief of symptoms with a safe complication rate. (Christie et al. 2001; DePalma et al. 1996; Knyrim et al. 1993) A randomized trial compared SEMS to plastic stents and found the rate of migration of plastic stents to be higher, in
other regards the treatments were concluded as effective. (Conio et al. 2007) SEMS have been also used as a palliative procedure as an adjunct to (NAT) as a bridge to surgery in the setting of tumor stenosis, in this setting conflicting reports on the effect of stents on oncological outcomes exist. (Jarvinen et al. 2017; Mariette et al. 2015) Stents in EC are discussed more in-depth in paragraph 5.5.4. A randomized multi-center trial compared brachytherapy and SEMS insertion in treatment of dysphagia and found SEMS to produce faster symptom relief, but brachytherapy gave longer lasting results with fewer complications. (Homs et al. 2004) Photodynamic therapy (PDT) is used in the setting of tumor obstruction or bleeding and produces a short lasting benefit on dysphagia in 85% of cases. (Litle et al. 2003) PDT has been compared to thermal ablation with laser and was revealed to be comparable in efficacy with less acute perforations. (Lightdale et al. 1995) Esophageal stents embedded with radioactive iodine beads have been investigated in the palliative setting and have been found to improve survival (OR = 7.5, 95% CI = 2.2- 25.5, p = 0.001) compared to conventional stenting. The relief of dysphagia was better with radioactive stents and the complication rates did not differ significantly. (Chen, Shen, and Liu 2017)

Intraluminal brachytherapy, in which a high dose of radiation is delivered to the tumor by using an intraluminal applicator, inserted during endoscopy, has been proposed as an alternative option for esophageal stent placement in palliation of dysphagia in EC. It provides dysphagia-free survival rates of 67.2% (95%CI = 56.1–76.7%) at 3 months and 29.4% (95%CI = 21.6–38.7%) at 12 months. Rate of severe complications has been reported to be 22.6% with a 12% incidence of stenosis and 8.3% rate of fistula formation. (Fuccio et al. 2017; Lettmaier and Strnad 2014)

5.5.3.3. Targeted therapies

With the advent of immuno-oncology and biologic antitumor agents, there has been numerous studies of these agents in the setting of EC. Bevacizumab, a humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A, has been promising in addition to normal adjuvant chemotherapies in GEJ cancer, although a trial reported 3 spontaneous gastrointestinal perforations in phase II setting. (El-Rayes et al. 2009; Shah et al. 2011; Shah et al. 2006) In a phase III trial for advanced gastric and GEJ cancer, bevacizumab did not show an OS benefit, but a benefit in progression-free survival. (Ohtsu et al. 2011) Bevacizumab, on the other hand, did not show benefit in the neoadjuvant setting as an adjunct to the normal NAT. (Bendell et al. 2012; Ku et al. 2016) Cetuximab, a humanized monoclonal antibody inhibiting epidermal growth factor receptor, has been of no benefit in addition to normal chemotherapeutic regimens in adjuvant therapy of gastric or GEJ cancer. (Lordick et al. 2013) Trastuzumab, a monoclonal
antibody towards human epidermal growth factor receptor 2 (HER2), has shown promise in HER2-positive GEJ or Gastric cancer and produced a median survival benefit, 13.8 months vs. 11.1 months, in addition to chemotherapy (HR 0.74; 95% CI 0.60-0.91; p = 0.0046). (Bang et al. 2010) Panitumumab, which is another epidermal growth factor receptor inhibitor, failed to display a survival benefit in phase III trials when combined with epirubicin, oxaliplatin, and capecitabine in the adjuvant setting in esophageal and GEJ cancer. (Waddell et al. 2013) Many more Phase I and Phase II trials exist for numerous modern anticancer agents, such as cytotoxic T lymphocyte-associated antigen 4 inhibitors (e.g. ipilimumab), programmed cell death protein 1 inhibitors (e.g. nivolumab and pembrolizumab) and programmed death-ligand 1 inhibitors (e.g. avelumab and durvalumab).
5.5.4. Stents in esophageal cancer

Before the usage of SEMS became widely accepted as a means of palliation of esophageal obstruction, rigid plastic prostheses were used. (Parker and Peura 1991) These often required dilatation up to 48-54 French to allow insertion and thus carried with them a high risk of complications. (Fugger et al. 1990) In 1993 a RCT by Knyrim et al. provided evidence that SEMS were superior to previously used prostheses regarding overall complication rate (0 complications vs. 9 complications in 42 patients in the RCT). (Knyrim et al. 1993)

There are many types of esophageal stents in current use, as shown in Figure 4. Most of them are either SEMS or self-expanding plastic stents (SEPS). Metallic stents are mostly made of Nitinol, which is an alloy of nickel and titanium. Nitinol stents have good conformability to anatomical angulations, whereas plastic stents are easier to remove. (De Palma et al. 1996; Sharma, Kozarek, and Practice Parameters Committee of American College of 2010) SEMS are either fully covered, partially covered or uncovered.

Malignant obstruction caused by EC is the most common indication for insertion of an esophageal stent. (Didden et al. 2013; Knyrim et al. 1993) They offer a short operative time, with great efficiency and safety. (Dai et al. 2014; Homs, Kuipers, and Siersema 2005) An image of a deployed stent is shown in Figure 5. Covered stents seem to fare better than uncovered stents with regards to recurrent dysphagia and symptom control due to tumor ingrowth, but have a higher migration rate. (Saranovic et al. 2005; Vakil et al. 2001) Uncovered stents allow for embedding of the stent into the esophageal tissue lowering the risk of migration, whereas covered stents prevent tumor ingrowth and mucosal hyperplasia. Current comparative studies compare partially covered SEMS vs. uncovered SEMS, there are no randomized clinical trials comparing fully covered stents to other stent types. Covered
Stents are recommended for treatment of esophageal malignant obstruction. (Sharma, Kozarek, and Practice Parameters Committee of American College of 2010) Reintervention rate was reported to be 27% in the uncovered group vs 0% in the covered group in one study (p = 0.002). (Vakil et al. 2001)

There are 3 RCT’s comparing SEMS by different manufacturers for treatment of dysphagia caused by EC, but no statistical differences between relief of dysphagia, complications or other endpoints have been documented. (May, Hahn, and Ell 1996; Sabharwal et al. 2003; Siersema et al. 2001)

Figure 5 A malignant esophageal stricture (upper), and a view of malignant esophageal stricture after deployment of an Ultraflex esophageal stent (lower)

SEMS insertion carries a risk of complications. Overall complication rate varies between 23% and 66%. (Acunas et al. 1996; Burstow et al. 2009; Kim et al. 2015; Stewart et al. 2013; Verschuur et al. 2007) The rate of delayed complications reported for palliative SEMS insertion in the literature varies between 32.0% and 64.6%. (Ramirez et al. 1997; Wang et al. 2001) Most common complications include tumor ingrowth (5-36%), stent migration (2%-7%), chest pain (12-36%) , mediastinal or tracheobronchial fistulae (3-5%), bleeding (5-16%) or perforation (0-6%). (Acunas et al. 1996; Stewart et al. 2013; Verschuur et al. 2006; Verschuur et al. 2007) In unresectable malignant esophageal obstruction, the repeat intervention rate has been reported to be between 17% and 51%. (Acunas et al. 1996; Burstow et al. 2009; Stewart et al. 2013) Risk factors for stent-related adverse events include pre- or post-insertion chemoradiation therapy, advanced stage of the tumor and/or tumor invasion of the aorta, whereas longer stent lengths and larger stent diameters have been associated with reduced rate of complications. (Baron 2001; Bick et al. 2013; Fuccio et al. 2016)
5.6. PROGNOSIS OF ESOPHAGEAL CANCER

Table 2: Esophageal cancer survival in Finland

<table>
<thead>
<tr>
<th>Sex</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>40.6%</td>
<td>23.6%</td>
<td>18.3%</td>
<td>15.1%</td>
<td>14.2%</td>
</tr>
<tr>
<td>Male</td>
<td>39.3%</td>
<td>23.3%</td>
<td>17.1%</td>
<td>13.9%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Female</td>
<td>41.0%</td>
<td>22.6%</td>
<td>19.5%</td>
<td>16.8%</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

The yearly survival rate for EC in Finland is presented in Table 2 (Finnish Cancer Registry, 2018), and a graphical relative age-adjusted survival rate is presented in Figure 6 (Finnish Cancer Registry, 2018). EC has a low overall 5-year survival (14.1%) compared to the nationwide median 5-year survival for all cancers (68%) (Finnish Cancer Registry, 2018).

![Figure 6](https://example.com/figure6.png)

**Figure 6** Relative age-standardised survival ratios for male and female EC patients in Finland (Finnish cancer registry 2016)
5.7. NUTRITIONAL DEFICITS AND SARCOPENIA IN ESOPHAGEAL CANCER

5.7.1. Definitions

Sarcopenia is defined as a progressive and generalized loss of skeletal muscle mass and muscle strength, associated with a risk of physical disability, poor quality of life, death and other adverse outcomes. (Chen et al. 2014; Cruz-Jentoft et al. 2010; Fielding et al. 2011)

Cancer cachexia is defined by an validated international consensus as “a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment”. Abnormal metabolism, systemic inflammation and reduced food intake are relevant in its pathophysiology, resulting in negative protein and energy balance. (Blum et al. 2014; Fearon et al. 2011)

Cachexia and sarcopenia are distinct entities, however they might be difficult to distinguish in clinical practice. Most sarcopenic patients do not have cachexia, whereas most cachexic patients are sarcopenic. An acute, rapid loss of skeletal muscle and weight is usually observed in cachexia. In noncachectic sarcopenia, a more gradual loss of muscle is observed. (Rolland et al. 2011)

5.7.2. Prevalence

The rate of malnutrition in EC is among the highest of all cancer types with reported incidence up to 78.9%. (Riccardi and Allen 1999) An analysis of the nutritional status of 1000 cancer patients revealed that EC had the highest mean weight loss percentage of 15.9% (range = -16.2-40.1%) and the highest nutritional risk score of 3.0 (range = 0.0-6.0) compared to patients with other malignancies. The nutritional risk score in this study evaluated the patients on nutritional status (0 = normal nutritional status, 1 = 5% weight loss in 3 months, 2 = 5% weight loss in 2 months, 3 = 5% weight loss in 1 month) and the severity of the disease (0 = normal dietary requirements; 1 = mildly elevated requirement e.g. hip fracture, chronic diseases with acute complications such as cirrhosis or chronic kidney disease; 2 = major abdominal surgery, stroke, hematologic malignancies, severe pneumonia; 3 = ICU patients, major head injury, bone marrow transplant). The scores were then combined. (Bozzetti and Grp 2009)

5.7.2. Mechanism

There are multiple mechanisms that are related to the muscle wasting syndromes in cancer. They stem from a disrupted balance between energy intake and expenditure, and although alterations in
energy intake is often associated with EC, increased resting energy expenditure plays a pivotal role. (Argiles et al. 2014)

Mitochondrial dysfunction is one of the mechanisms behind increased energy expenditure and in many cases the activation of uncoupling proteins disrupts the mitochondrial ATP synthesis, and thus wastes energy in the cell. (Collins et al. 2002) Overexpression of peroxisome-proliferator-activated receptor-γ co-activator 1α (PGC1α) is linked to mitochondrial uncoupling and in addition causes increased respiration and energy expenditure. (Miura et al. 2006) Activity of sarcoplasmic reticulum Ca2+ pumps is increased in the setting of cancer, further consuming ATP and creating a Ca2+ overload in the cytosol. (Fontes-Oliveira et al. 2013)

Muscle wasting in cancer cachexia is driven by many mechanisms. (Argiles et al. 2014) The most important pathway seems to be the protein degradation by the ubiquitin-dependent proteasome pathway. (Argiles and Lopez-Soriano 1996) Many pro-inflammatory cytokines such as tumor necrosis alfa or interleukin 1 play a role in muscle wasting through the nuclear factor-κB pathway and the p38 MAPK pathway. (Argiles et al. 2014) Transforming growth factor-β-family ligand myostatin acts through the SMAD complex, p38 and Janus kinase MAPKs, increasing protein degradation. (Argiles et al. 2012)

The wasting of adipose tissue is thought to be mediated through three mechanisms: increase in lipolytic activity by activation of hormone-sensitive lipase, inhibited lipid uptake by decrease in the activity of lipoprotein lipase and decreased esterification and lipid deposition by reduced de novo lipogenesis in adipose tissue. (Argiles et al. 2014)

5.7.3. Diagnosis

Many instrumental methods have been studied in the diagnosis of sarcopenia, including magnetic resonance imaging (MRI), bone dual-energy x-ray absorptiometry (DXA), bio-impedance analysis, and CT imaging. (Baumgartner et al. 1999; Janssen, Heymsfield, and Ross 2002; Malafarina et al. 2012). Sarcopenia can be measured using CT or MRI imaging by delineating the abdominal wall muscles (transversus abdominus, external and internal obliques, rectus abdominus), the psoas muscles and the paraspinal muscles (erector spinae, quadratus lumborum) at the level of L3 vertebra and summing the cross-sectional area. The combined cross-sectional (cm2) area is then normalized for stature as is conventional for the calculation of BMI to form the L3 skeletal muscle index (cm2/m2). (Pahor, Manini, and Cesari 2009; Prado et al. 2008)
DXA is based on a three-compartment model: fat mass, lean mass, and body mineral content. In DXA the x-ray transmission in crossing tissues is measured at two different energy levels. The energy carried by radiation is absorbed or scattered by anatomical structures, depending on the energy intensity and the thickness and density of the human tissues. Low-density tissues absorb less photons, allowing them to pass through and be measured, than high-density tissues such as bone. Although CT and MRI are considered to be gold standard in body composition measurement, the pros of DXA include less radiation exposure, less compliance requirement for the patient and less expensive measurements. (Guglielmi et al. 2016) BIA is a non-invasive measurement tool which calculates the total body electrical resistance. Skeletal muscle is the dominant conductor of the human body due to its electrolyte-rich nature and it being the largest tissue in the body and since the volume of a conductor is related to its electrical resistance, BIA can be used to indirectly measure the skeletal muscle volume of the body. It has been compared to MRI with a good success rate and its benefits are low cost and reliable results in most subjects. However in the assessment of athletes, the elderly and chronically ill patients it may not perform as well. (Janssen et al. 2000)

The European Working Group on Sarcopenia in Older People (EWGSOP) and Asian Working Group for Sarcopenia (AWGS) recommend using the presence of both, the presence of low muscle function (or low muscle strength) and low muscle mass in diagnosis of sarcopenia. (Cruz-Jentoft et al. 2010) AWGS recommends the following cutoff values: muscle mass of 7.0 kg/m2 for men and 5.4 kg/m2 for women by using DEXA and 7.0 kg/m2 for men and 5.7 kg/m2 for women by using bioelectrical impedance analysis; handgrip strength (<26 kg for men and <18 kg for women), and a gait speed of (<0.8 m/s). (Chen et al. 2014) EWGSOP has proposed the following values: 7.26 kg/m2 for men and 5.5 kg/m2 for men in DEXA, BIA values of 8.87 kg/m2 for men and 6.42 kg/m2 for women, handgrip strength of <30 kg for men and <20 kg for women and gait speed of < 1 m/s. (Cruz-Jentoft et al. 2010)

Diagnosis of cancer cachexia is based on the following criteria: >5% of weight loss over past 6 months, or BMI <20 and weight loss of >2%, or appendicular skeletal muscle index consistent with sarcopenia and a weight loss >2%. (Fearon et al. 2011)

5.7.4. Effect on oncological and surgical outcomes

Sarcopenia has been reported to affect outcomes in many types of cancers. (Balentine et al. 2010; Go et al. 2016; Harimoto et al. 2013; Miyamoto et al. 2015; Prado et al. 2008; Voron et al. 2015)
Following hepatectomy for hepatocellular cancer, sarcopenia was found to be an independent poor prognostic factor for both OS (HR 0.90, 95% CI = 0.84-0.96, p = 0.002) and RFS (HR = 0.97, 95% CI = 0.95-1.00, p = 0.016). (Harimoto et al. 2013; Voron et al. 2015) A negative effect on OS (HR = 2.27, 95% CI = 1.15-4.49, p = 0.019) and RFS (HR = 2.18, 95% CI = 1.20-3.94, p = 0.010) was also observed after curative resection for stage I-III colorectal cancer. (Miyamoto et al. 2015) Sarcopenia was also linked to worse 5-year OS (39% vs 70%, p = 0.003) and cancer-specific survival (49% vs 72%, p = 0.003) in patients with bladder cancer undergoing radical cystectomy. (Psutka et al. 2014) It has been associated with poor prognosis also in advanced non-small cell lung cancer, advanced pancreatic cancer and advanced urothelial carcinoma (Balentine et al. 2010; Fukushima et al. 2015; Go et al. 2016)

In EC sarcopenia has been associated with worsened OS (HR = 1.69-2.70) after esophagectomy in EC with varying prevalence in the study population (28.4%-65%). (Kudou et al. 2017; Tamandl et al. 2016) It has also been associated with worse OS (HR = 1.72, 95% CI = 1.049-2.83, p = 0.032) in patients undergoing NAT for EC. (Paireder et al. 2017) 5-year RFS has also been shown to be worsened by sarcopenia (78.7 vs 51.7%, p = 0.005). (Kudou et al. 2017) On the other hand, sarcopenia has had no effect on OS in several other studies. (Elliott et al. 2017; Grotenhuis et al. 2016; Harada et al. 2016; Reisinger et al. 2015) Harada et al. found a significant impact on survival in patients without lymph node involvement (log rank p = 0.035), however the prognostic effect of sarcopenia did not hold in multivariate analysis in this study. (Harada et al. 2016) A study found sarcopenia to clinically significantly worsen the 5-year OS (26.5% vs 56.0%, p < 0.001) and 5-year disease-specific survival (32.5% vs 65.7%, p < 0.001) in patients older than 65 years of age. There was no statistical difference in patients under the age of 65 in this study. (Nakashima et al. 2017) Sarcopenia has been linked to increased postoperative pulmonary complications (OR 2.96-5.82), with no increase in other types of complications in these studies. (Ida et al. 2015; Makiura et al. 2016; Nishigori et al. 2016) Some studies also report a higher risk of anastomotic leakage in sarcopenic patients, which was confirmed in multivariate in one study (OR = 2.30, 95% CI = 1.06-5.12, p = 0.034). (Harada et al. 2016; Nakashima et al. 2017) Loss of skeletal muscle has been linked to a risk of positive resection margin. (Yip et al. 2014) Decrease in skeletal muscle mass during neoadjuvant therapy has been linked to grade 4 and febrile neutropenia during treatments. (Miyata et al. 2017) Loss of skeletal muscle mass during neoadjuvant therapy has also been associated with worse survival in EC. (Reisinger et al. 2015)
6 AIMS OF THE PRESENT STUDY

I To evaluate the effect of preoperative stenting on overall survival and progression-free survival in EC patients who underwent surgery

II To compare survival between sarcopenic and non-sarcopenic EC patients undergoing surgery.

III To compare survival between sarcopenic and non-sarcopenic EC patients who received a stent for palliation of malignant obstruction

IV To identify the factors affecting esophageal stent failure in treatment of esophageal malignancy, non-esophageal malignancy and benign esophageal disease.
7 PATIENTS AND METHODS

7.1. Patients
Study I included a patient cohort of 174 with EC of clinical T-stage ≥ 2, who underwent curative surgery between January 2006 and January 2014 at the Helsinki University Central Hospital (HUCH). The study populations’ median age was 63 (IQR = 56-71) years. 135 (77.6%) patients had EAC, 38 (21.8%) patients had ESCC and 1 (0.6%) patient had a tumor that was poorly differentiated.

Study II comprised of 115 patients with EC who underwent esophagectomy and neoadjuvant therapy between 2010 and 2014 at HUCH. Median age of the patient population was 63 (±8) years. The histology of the tumor was adenocarcinoma in 88 (76.5%) patients and ESCC in 27 (23.5%) patients. Location of the tumor was the upper third of the esophagus in 3 (2.6%), middle third in 17 (14.8%) and lower third / GEJ in 95 (82.6%).

Study III consisted of 238 patients with stent inserted between 2005 and 2013 for palliative treatment of malignant esophageal obstruction caused by EC. Median age of the patient population was 66 (IQR = 59-72). ESCC was found in 110 (46.2%) patients, EAC in 108 (45.4%) of the patients and other histology in 20 (8.4%) patients. The tumors were located in the proximal third of the esophagus in 22 (9.2%) patients, in the middle third of the esophagus in 114 (47.9%) and in the distal third / GEJ in 102 (42.9%) patients.

Study IV included 469 patients receiving esophageal stents between January 2005 and December 2013 at HUCH. EC was the primary diagnosis in 331 (70.6%) patients, non-esophageal malignancy in 79 (16.8%) patients and in 59 (12.6%) the primary diagnosis indicating the stent insertion was a benign esophageal disorder. Median age of the study population was 67 (IQR = 61-76). Median ages were 68 (IQR = 61-77), 67 (IQR = 63-75) and 64 (IQR = 58-72) for the primary diagnosis groups, respectively.

7.2. Methods
7.2.1. Staging
In Study I, Gastroscopy and biopsies of the esophagus and stomach determined the extent and histopathology of the disease. Endoscopic ultrasound (EUS) was done, whenever technically possible, to assess for local LNM and depth of invasion. A FDG PET CT served to evaluate the
presence of mediastinal and distal metastases. A total of 135 patients had a histopathologic
diagnosis of EAC and 39 had ESCC.

7.2.2 Definition of sarcopenia

Study II and III followed the same definition of sarcopenia. A single image from CT studies
obtained from the patients was selected at the level of third lumbar vertebra. Both transverse
processes had to be visible on the image for it to be acceptable. The selected image was imported
into Osirix® Version 3.3 (32-bit Pixmeo, Sarl, Switzerland). A semi-automated region of interest
selection tool was used to select abdominal muscles (rectus abdominis, external oblique, internal
oblique, psoas muscles, quadratus lumborum, paraspinal muscles and transverse abdominal
muscle). Hounsfield units (HU) between -29 and 150 were used as a threshold for the tool. Manual
correction of the selection was done, if needed, by the propulsion and brush tools. Figure 7 shows a
visual demonstration of the semi-automatic delineation. Cross-sectional total muscle area (TMA)
was calculated and SMI formed by dividing the TMA value with the square of the patients height in
meters. We used a previously established SMI thresholds as a basis on our definition of sarcopenia:
SMI of ≤39 cm²/m² for women and ≤55 cm²/m² for men.(Fearon et al. 2011)

Figure 7 a patient without sarcopenia (on the left) and with sarcopenia (on the right) delineated by the semi-automated
process with Osirix® Version 3.3 (32-bit Pixmeo, Sarl, Switzerland). The reduced muscle mass can be appreciated in
the reduced thickness of the rectus abdominis muscles (top of the picture).

7.2.3. Neoadjuvant therapy

Patients with cT3-T4 tumors or cN+ disease underwent NAT. For EAC epirubicin–oxaliplatin–
capcitabine (EOX) neoadjuvant chemotherapy as per MAGIC (Medical Research Council
Adjuvant Gastric Infusional Chemotherapy) protocol was used.(Cunningham et al. 2006) NAT of
choice for ESCC was neoadjuvant CRT with of 2 cycles of platin- and 5-fluorouracil-based therapy
over 5–6 weeks followed by a 45-gy total dose, in 1.8 gray daily fractions, of radiation to the tumor and regional nodes.

In study I, a total of 91 patients underwent neoadjuvant chemotherapy, 42 patients neoadjuvant radiochemotherapy, and one patient neoadjuvant radiotherapy. Study II included only patients who underwent NAT (N = 118), 28 receiving neoadjuvant chemoradiation therapy and 87 receiving neoadjuvant chemotherapy.

7.2.4. Stent insertion
Preoperative stenting served as a bridge therapy to surgery in 30 patients, with evidence of obstructive tumor growth, in study I. In study II, 30 patients received a stent before surgery in addition to their neoadjuvant therapy.

In study III & IV, all of the patients included in the studies (N = 238 & N = 469, respectively) received a stent for treatment of malignant obstruction caused by EC (Study III & IV), non-esophageal malignant obstruction (Study IV) or obstruction caused by benign esophageal disease (Study IV).

In studies I, II, III and IV the stents were inserted under fluoroscopic and endoscopic guidance over guidewires and with propofol sedation. The size and location of the stent was decided based on the tumor location, as well as the length and severity of the stricture. Stent position was confirmed endoscopically and with a post-insertion barium swallow study. In study IV, stent removal for benign indication was planned at 4 weeks after stent insertion.

7.2.5. Nutritional evaluation and treatment
In studies I and II, all of the patients were evaluated by nutritionists, using NLS 2002 screening tool for the risk of malnutrition and their nutritional status was optimized before and after surgery according to the nutritionists’ recommendations.

7.2.6. Surgical therapy
Surgical techniques in Study I & II included MIE (50% of patients in study I & 68% of patients in study II), hybrid MIE (7% & 7%), Ivor-Lewis & McKeown open esophagectomy (36% & 22%), transhiatal esophagectomy(5% & 3%), and thoracoabdominal esophagectomy (2% & 0%).
7.2.7. Adjuvant therapy
In study III, 33 (13.7%) patients received either chemotherapy (N = 7, 2.9%) radiation (N = 8, 3.4%) therapy or chemoradiation (N = 18, 7.6%) before the insertion of a SEMS, whereas these treatments were received after SEMS insertion by 155 (65.1%) patients (N = 53, 22.3%; N= 61, 25.6%; N = 41, 17.2%; respectively).

7.2.8. Follow-up
In Study I, all patients were followed until death or January 2016, yielding a follow-up period of at least 24 months and a median follow-up time of 33 months.

In study II, the patients were followed until death or January 2017, which produced a minimum follow-up of 24 months. Meeting at an outpatient clinic 1 month after surgery was arranged to evaluate for recovery from surgery. Every 6 months a gastroscopy was done up to 2 years post-surgery and then annually for up to 5 years. CT scans were taken at 6 months and 18 months after surgery and annually up to 5 years.

In study III, all of the patients were followed up until death (median follow-up = 146 days, IQR = 73-226 days. No consistent follow-up regimen was in place for the patients in this study.

In study IV patients were followed up until death or January 2017. Median follow-up was 169 days (IQR = 70-380 days). Follow-up schemes varied based on the type of disease that was treated, and thus there was no consistent follow-up schedule for the study group as a whole.

7.2.9. Statistical methods
In all studies, values are presented as means with standard deviation or medians with range (study I) or interquartile range (study II & III & IV). Normality for variables was tested using the Shapiro-Wilks test. Student’s t-test was used for normally distributed continuous variables and Mann-Whitney’s U-test nor non-normally distributed continuous variables. Pearson’s $\chi^2$ test was used for testing between categorical variables. For survival analyses, Kaplan-Meier survival curves and log rank test were used. For multivariate survival analyses Cox’s multivariate regression analysis was used, with backwards elimination (P value limit of 0.2). All p-values were based on two-tailed tests and the limit for statistical significance was set at <0.05.

In study I Patients with preoperative SEMS insertion were propensity matched 1:1 to a control group who underwent surgery without SEMS insertion. Calculation of propensity scores was done by binary logistic regression. Preoperative SEMS insertion status functioned as the dependent variable; and gender, age, weight loss 3 months before surgery, Eastern Cooperative
Oncology Group (ECOG) performance score, tumor histology, smoking history, cancer stage, cancer location and operation type served as the covariates for the matching. Propensity scores were matched by 5→1 digit matching using an algorithm. Matching was done until all 30 patients in the SEMS insertion group were matched.

The statistical analyses in study I were performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. In studies II, III & IV statistical analysis was performed using R Project (R Core Team, 2016, R Foundation for Statistical Computing, Vienna, Austria, URL: https://www.R-project.org/).

7.2.10. Study endpoints
Study I, II & III used the primary endpoint of OS. Secondary endpoints for Study I were overall recurrence (OR), operative time and rate of postoperative complication. Secondary endpoints for study II were RFS and complication rate. The secondary endpoints for study III were the need for an alternative enteral feeding route (Percutaneous endoscopic gastrostomy or jejunal feeding tube) and complication rate of stent insertion.

For Study IV, we defined a primary endpoint of stent failure as stent-caused major complication, migration of the stent (when stenting was used as a destination therapy), tumor overgrowth requiring re-stenting, or non-planned urgent removal of a stent for any reason. This endpoint served as a means to evaluate any variables that lead to major stent-related harm or inconvenience to the patient. Secondary study endpoints were OS and complication rate.
8 RESULTS

8.1. Study I
Median OS of the study population was 32.5 months (range 0-118 months). Median survival in the SEMS insertion group was 28.5 months (0-116 months) and in the control group, 34 months (4-118 months). Figure 8 shows the Kaplan-Meier analysis of the OS between the SEMS insertion and control groups. In OS rates between the SEMS insertion and control groups, no significant difference existed ($p = 0.882$ using Log-Rank test). Median PFS or recurrence rates between the groups showed no difference ($p=0.764$ and $p = 0.752$, respectively). No statistically significant differences emerged in any of the post-surgical complication groups or subgroups. Mean operative times were higher in the SEMS insertion group, 436 min vs. 375 min ($p=0.017$). The stent group had few complications related to stent insertion, one patient had to undergo an emergency open esophagectomy related to stent perforation and suffered an in-hospital death with an extended ICU stay.

Figure 8
![Kaplan-Meier survival functions of the study groups in Study I](image)

$p = 0.88$
8.2. Study II

Sarcopenia was prevalent in 80% (N = 92) of this study’s patients. Sarcopenic patients were older and taller, weighed less, and smoked less than their non-sarcopenic counterparts. The demographic differences between the patients are displayed in Table 3. There were no statistical differences between Clavien-Dindo complication scores or complication rates between the sarcopenia groups in this study.

Table 3 Baseline characteristics of the patient populations in Study II

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Pre-operative sarcopenia</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>115</td>
<td>23</td>
<td>92</td>
</tr>
<tr>
<td>Age, years (mean [SD])</td>
<td>63 [9]</td>
<td>59 [8]</td>
<td>64 [9]</td>
</tr>
<tr>
<td>Height, cm (median [IQR])</td>
<td>174 [166,179]</td>
<td>171 [160,174]</td>
<td>175 [167,180]</td>
</tr>
<tr>
<td>Preop. weight, kg (mean [SD])</td>
<td>74 [16]</td>
<td>82 [18]</td>
<td>73 [15]</td>
</tr>
<tr>
<td>CCI (median [IQR])</td>
<td>5 [4,6]</td>
<td>5 [4,6]</td>
<td>5 [5,6]</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>Female</td>
<td>29 (25.2)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>86 (74.8)</td>
<td>14 (60.9)</td>
</tr>
<tr>
<td>ECOG (%)</td>
<td>0</td>
<td>40 (35.1)</td>
<td>11 (47.8)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>69 (60.5)</td>
<td>10 (43.5)</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>32 (27.8)</td>
<td>11 (47.8)</td>
<td>21 (22.8)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>40 (34.8)</td>
<td>3 (13.0)</td>
<td>37 (40.2)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>43 (37.4)</td>
<td>9 (39.1)</td>
<td>34 (37.0)</td>
</tr>
<tr>
<td>T-stage (%)</td>
<td>1</td>
<td>2 (1.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10 (8.9)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>86 (76.8)</td>
<td>17 (73.9)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>14 (12.5)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>N-stage (%)</td>
<td>0</td>
<td>33 (29.5)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>74 (66.1)</td>
<td>15 (65.2)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4 (3.6)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Cancer type (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>88 (76.5)</td>
<td>21 (91.3)</td>
<td>67 (72.8)</td>
</tr>
<tr>
<td>Squamous Cell</td>
<td>27 (23.5)</td>
<td>2 (8.7)</td>
<td>25 (27.2)</td>
</tr>
<tr>
<td>Tumor location (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower third</td>
<td>95 (82.6)</td>
<td>20 (87.0)</td>
<td>75 (81.5)</td>
</tr>
<tr>
<td>Middle third</td>
<td>17 (14.8)</td>
<td>3 (13.0)</td>
<td>14 (15.2)</td>
</tr>
<tr>
<td>Upper third</td>
<td>3 (2.6)</td>
<td>0 (0.0)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Neoadjuvant treatment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemoradiation</td>
<td>28 (24.3)</td>
<td>2 (8.7)</td>
<td>26 (28.3)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>87 (75.7)</td>
<td>21 (91.3)</td>
<td>66 (71.7)</td>
</tr>
<tr>
<td>Operation type (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIE†</td>
<td>78 (67.8)</td>
<td>18 (78.3)</td>
<td>60 (65.2)</td>
</tr>
<tr>
<td>Thoracotony</td>
<td>26 (22.6)</td>
<td>2 (8.7)</td>
<td>24 (26.1)</td>
</tr>
<tr>
<td>Hybrid-Laparoscopy</td>
<td>5 (4.3)</td>
<td>1 (4.3)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>Hybrid-VATS‡</td>
<td>3 (2.6)</td>
<td>1 (4.3)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Transhiatal</td>
<td>3 (2.6)</td>
<td>1 (4.3)</td>
<td>2 (2.2)</td>
</tr>
</tbody>
</table>

† Minimally invasive esophagectomy
‡ Video-assisted thoracoscopic surgery
Median OS was 900 days for the whole patient population. No statistical difference between 2-year OS or RFS could be established between the patients with or without preoperative sarcopenia (respective logrank p = 0.74 & p = 0.64). Based on the amount of change between preneoadjuvant and preoperative SMI (SMI), two groups were formed. Median percentual change of SMI (-2.98%) served as the cut-off point. Patients with more pronounced SMI loss (SMI below than the median) had worse OS (logrank p = 0.022), but no statistical difference in RFS was observed (logrank p = 0.11), the Kaplan-Meier survivals are shown in Figure 9. In a multivariate Cox regression analysis, the patients with more positive SMI change group had better survival per level of SMI(p = 0.049; HR: 0.544; HR 95% CI: 0.297-0.997). Other covariates in the model (T- & N-stage or CCI) did not reach significance. There was 11.75 events per variable (47 events, 4 variables).

Study II also established that the prevalence of sarcopenia persists after esophagectomy: before NAT 91 (79.1%) patients had sarcopenia, 92 (80%) were sarcopenic pre-operatively, 82 of 99
(82.8%) were sarcopenic in 6 month follow-up and 18 months post-operatively, 67 of 78 (85.9%) suffered from sarcopenia.

8.3. Study III

Of the study’s population of 238 patients, 83.6% (N = 199) had sarcopenia. Sarcopenic and non-sarcopenic patients did not differ statistically significantly in age, gender, weight loss, the Charlson Comorbidity Index (CCI), cancer histology, tumor location, T-stage, N-stage, M-stage or rate of pre- or post-stent oncological treatments. Most patients had a stent inserted for destination therapy (N = 196, 82.4%). The stage of the disease was beyond curative therapy in 47.9% (N = 114) of the patients, 30.3% (N = 72) of the patients’ general condition was too poor to proceed to curative therapies and 4.2% (N = 10) of the patients refused curative therapy. Stenting was done a median of 19 (IQR = 7-39) days after cancer diagnosis, and in 12.6% of patients (N = 30) there was more than a 180 day delay between the diagnosis of cancer and stent insertion. There were no significant differences in location-, size- or type of inserted stent between the groups. Complication rate was 31.1% (N = 74), with no fatal complications in the study population.

Follow up CT scan was available for analysis in 49.6% (N = 118) patients, with median time between scans of 91 days (IQR = 61-113). Sarcopenia was prevalent in 108 (91.5%) of patients. 75.4% (N = 89) of patients had sarcopenia in both CT scans, 16.1% (N = 19) of patients developed sarcopenia between the CT scans, in 5.1% the sarcopenia was reversed between scans and only 3.4% patients had no sarcopenia in either CT imaging study.

Median OS was 146 (IQR = 73-226) days from stent insertion. There was no significant difference in OS between sarcopenic and non-sarcopenic patients (median 146 vs. 152 days, logrank p = 0.61). Patients who had a second CT imaging study available were divided into two groups (N = 59) using the median SMI change (-11.6%) between CT imaging studies as a cut-off. These groups had a statistically different OS in Kaplan-Meier analysis (logrank p = 0.018) as shown by Figure 10.
Figure 10 Kaplan-Meier survival analysis of the groups formed by using the median Skeletal muscle index (SMI) change (-11.6%) as a cut-off. Group 1 had SMI change more positive than the median, whereas Group 2 had a more negative change.

Cox proportional hazards model using the backwards-eliminating method was done with gender, age, body mass index, weight loss, CCI, cancer histology, location and TNM-status, previous treatments, post-stent insertion treatments, “destination therapy” status and SMI as the initial variables. The final model is depicted in Table 4. Events per predictor variable ratio was 39. CCI score was correlated with worse OS (hazard ratio [HR] 1.13, 95% confidence interval [CI] 1.06–1.20; \( p = 0.001 \)) whereas both SMI (HR 0.98, 95% CI 0.97–0.99; \( p = 0.033 \)) and patient age (HR 0.98, 95% CI 0.96–0.99; \( p = 0.001 \)) had an inverse correlation with OS. Post-stent insertion treatment was associated with lower risk of death (HR 0.56, 95% CI 0.41–0.76; \( p = 0.001 \)).

<table>
<thead>
<tr>
<th>factor</th>
<th>HR</th>
<th>95% CI</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.98</td>
<td>0.96–0.99</td>
<td>0.001</td>
</tr>
<tr>
<td>CCI†</td>
<td>1.13</td>
<td>1.06–1.20</td>
<td>0.001</td>
</tr>
<tr>
<td>Skeletal muscle index</td>
<td>0.98</td>
<td>0.97–0.99</td>
<td>0.033</td>
</tr>
<tr>
<td>Clinical N-Stage</td>
<td>0.87</td>
<td>0.74–1.04</td>
<td>0.122</td>
</tr>
<tr>
<td>Non-curative intent</td>
<td>0.75</td>
<td>0.51–1.08</td>
<td>0.123</td>
</tr>
<tr>
<td>Treatment after stent</td>
<td>0.56</td>
<td>0.41–0.76</td>
<td>0.001</td>
</tr>
</tbody>
</table>
8.4. Study IV

The most used stent type in this study was partially covered SEMS (N = 391, 83.4%), with 49 (10.4%) fully covered SEMS and 29 SEPS (6.2%). Patients were admitted for a median of 2 (IQR = 1-5) days. A second stenting was done in 139 (29.6%) patients. No immediate deaths due to stent insertion were reported. No immediate perforations related to stenting were observed in this study. Amount of complications related to stenting was 115 (24.5%), with 18 (3.8%) patients suffering multiple complications. Migration of the stent was the most common complication (N = 53, 11.3%), with esophago-bronchial/tracheal fistula being the second most common (N = 29, 6.2%). Patients with EC had the most complications (N = 91, 27.5%), benign esophageal disease patients had 13 (22%) complications and the group with non-esophageal malignancies had the least complications with 13.9% (N = 11) complication rate (p = 0.037). Type of stent (Partially covered SEMS, self-expanding plastic stent, or fully covered SEMS) did not have an effect on the complication rate (p = 0.937). Stents that were inserted as a permanent palliation had less complications (N = 51, 18.1%) than stents that were inserted as a temporary treatment (N = 64, 34.0%), with statistical significance (p = 0.001). More serious complications (Fistula or perforation) occurred earlier in the stent treatment course (194 days vs. 111 days, p = 0.006).

![Kaplan-Meier survival curves](image)

**Figure 11** Overall Kaplan-Meier survivals between the diagnosis groups in Study IV
The study populations’ median OS was 169 (IQR = 70-380) days from stent insertion. The median survivals differed statistically significantly (logrank p = 0.001) between the patients with EC (174 days; IQR = 81-319), non-esophageal malignancy (66 days; IQR = 26-145) and benign esophageal disease (1190 days; IQR = 425-1678), the Kaplan-Meier figures are shown in Figure 11.

6-month stent failure rate was 38.2% (N = 179) with a median time to stent failure of 75 (IQR = 24-161) days. Time to stent failure was 100 (IQR = 31-180) days for EC patients, 46 (IQR = 18-98) days for patients non-esophageal malignancy and for patients with benign esophageal disease, 32 (IQR = 18-70) days (logrank p = 0.01). The cumulative hazard ratio are shown in Figure 12.

Figure 12

Table 5 Cox proportional hazards models for stent failure

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign vs. malignant</td>
<td>3.93</td>
<td>2.60-5.92</td>
<td>0.001</td>
</tr>
<tr>
<td>12-15 cm vs &lt; 12 cm</td>
<td>0.17</td>
<td>1.00-1.97</td>
<td>0.048</td>
</tr>
<tr>
<td>&gt;15 cm vs &lt; 12 cm</td>
<td>0.28</td>
<td>0.48-1.43</td>
<td>0.51</td>
</tr>
<tr>
<td>Mid vs. lower</td>
<td>1.66</td>
<td>1.16-2.37</td>
<td>0.005</td>
</tr>
<tr>
<td>Upper vs. lower</td>
<td>2.21</td>
<td>0.95-5.14</td>
<td>0.065</td>
</tr>
</tbody>
</table>

Figure 12 Cumulative hazard ratios of stent failure by diagnosis group in Study IV

Table 5 Cox proportional hazards models for stent failure
Table 5 shows the multivariate Cox proportional hazards analysis of variables affecting stent failure. Variables included in the initial model were age, gender, primary diagnosis (benign or malignant disease), iatrogenic injury, location (lower, mid or upper esophagus) and type of stent (plastic vs. metallic) and length of stent. With backwards elimination, the final model depicted in Table 5 was produced. Event-per-variable ratio was 38.8 (number of events 155). Stent failure risk was higher in benign disease (HR = 3.93, 95% CI = 2.60-5.92, p < 0.0001). Stents of length between 12-15cm were associated with lower risk of stent failure compared to stents under 12 cm (HR = 0.17, 95% CI = 1.00-1.97, p = 0.048). Mid-esophagus was a higher risk location for stenting compared to lower esophagus (p = 0.033, 95% CI = 1.16-2.37, HR = 1.7).
9 DISCUSSION

9.1. Esophageal stenting as a bridge to surgery in resectable esophageal cancer

Insertion of a preoperative esophageal stent was not associated with worse oncological outcomes (2-year OS or 2-year RFS) in cT\(\geq 2\) EC in study I. The rates of intraoperative, early postoperative and late complications were non-different between the patients receiving the stent and the patients that were not stented.

The limitations of study I include, among others, its retrospective design and small study groups. This predisposes the study to selection bias and both Type I and Type II errors. Only patients undergoing surgery were included so the effect of stenting on the progression of tumors to unresectable status could not be evaluated in this study. The usage of propensity matching was a statistical tool to overcome the effect of selection bias by simulating randomization process post-hoc. (Lonjon et al. 2014).

Previous studies investigating the use of SEMS as a bridge to surgery during NAT report a prompt relief of dysphagia, maintenance of body weight and reasonable complication rates. (Bower et al. 2009; Brown et al. 2011; Siddiqui et al. 2012) Stents maintained better albumin levels and had less chemotherapy interruptions vs. feeding tubes or oral nutrition only. (Bower et al. 2009) In these studies, many patients progressed during the NAT and thus the rate of proceeding to curative surgery was variable (14.5%-69%). (Bower et al. 2009; Brown et al. 2011; Siddiqui et al. 2012). These studies included patients that did not progress to curative resection and only 1 of the studies had any control group (Bower et al. 2009), so direct comparison to study I is not feasible.

A previous study, also using propensity matching, found that stenting was associated with worse outcomes. (Mariette et al. 2015) This study matched 38 patients with SEMS inserted as a bridge to surgery with 152 patient control group. Unlike our study, this study also included T1 EC patients. The stent group had a lower R0 resection rate (71.0% vs 85.5%), a lower median time to recurrence (6.5 vs. 9.0 months), higher 3-year locoregional recurrence rate (62% vs 34%), and a worse 3-year OS (25% vs 44%). They reported that SEMS insertion remained an independent significant predictor of poor prognosis (HR = 1.6) after adjusting for pretherapeutic confounding factors (which are not outlined in the article). (Mariette et al. 2015)

Study I failed to show a poor prognostic effect with preoperative esophageal stenting, whereas Mariette et al showed a clearly reduced OS and increased locoregional recurrence rate. Both studies explored similar end-points through slightly different variables (i.e. 2-year OS vs. 3-
year OS and 2-year RFS vs. median time to recurrence), which could explain some of the differences. Study I did not include EC cancer patients with T1-tumors, since dysphagia is rarely associated with T1-tumors and T1-tumors have esophagus-sparing treatment options such as endoscopic mucosal resection and radiofrequency ablation. Ell et al. 2000; May et al. 2000; Pouw et al. 2010) In the study by Mariette et al. most SEMS were inserted in rural hospitals without consulting the tertiary cancer center, whereas in study I the SEMS were inserted in a single tertiary center by experienced esophageal surgeons. (Mariette et al. 2015) These differences between the studies can be used to explain some of the differences in outcomes between the studies. To the best knowledge of the author, no prospective and/or randomized studies on the subject have been done and such the current literature is contradictory.

9.2. Skeletal muscle mass and sarcopenia as a predictor of poor prognosis in esophageal cancer patients receiving neoadjuvant treatment

Study II showed a decrease in 2-year OS when patients had a more negative muscle mass change, compared to the median value of -2.98%, during NAT for EC. Sarcopenia, defined by SMI cut-offs established by an international consensus, did not show prognostic significance. Fearon et al. 2011; Prado et al. 2008)

This finding is, to the authors’ knowledge, first in the published literature in this population. This effect, however, has been established in ESCC patients undergoing NAT and surgery in a study by Liu et al. Liu et al. 2016) This study used psoas muscle index (PMI) as the surrogate measurement for total body muscle mass and showed a reduced OS in the patients whose PMI was lower between the initial measurement (pre-treatment) and post-neoadjuvant therapy. This effect held its significance in Cox multivariate analysis including gender, histological response to NAT, pathological N-grade and PMI decrease. Bower et al. 2009) Reisinger et al. showed in EC patients undergoing NAT that no association between skeletal muscle mass and mortality exists. Reisinger et al. 2015) In stage III-IV tumors the amount of SMI decrease during NAT was greater in the population that died within 30 days of surgery. In stage I-II tumors, this effect was non-significant. Changes during NAT in fat mass, fat-free mass, subcutaneous fat to muscle ratio and visceral to subcutaneous adipose tissue ratio measured using the same CT assessment method have been associated with positive circumferential resection margin in EC, but in this particular study no effect on OS was seen. Yip et al. 2014)
Many previous studies report sarcopenia as an independent poor prognostic factor in EC patients undergoing surgery.(Koudou et al. 2017; Paireder et al. 2017; Tamanl et al. 2016) Paireder et al. showed sarcopenia to be an independent risk-factor for worse OS (HR = 1.72) in EC undergoing esophagectomy following NAT .(Paireder et al. 2017) Tamanl et al. had the same finding (HR = 1.87) in EC patients undergoing resection.(Tamanl et al. 2016). In a study including patients with EC and upper gastric cancer, Koudou et al. found sarcopenia to be a poor prognostic factor for OS in multivariate analysis (HR = 2.70). Sarcopenia has also been associated with higher risk of pulmonary complications in post-esophagectomy setting for EC.(Elliott et al. 2017; Nishigori et al. 2016) Lean psoas area, used as a surrogate for total body muscle mass, has also been associated with OS and disease-free survival in patients not receiving NAT and undergoing transhiatal esophagectomy for EC.(Sheetz et al. 2013)

Some studies however, report no such association between sarcopenia and oncological outcomes.(Elliott et al. 2017; Grotenhuis et al. 2016) Elliott et al. found no evidence of sarcopenia affecting post-operative OS or disease-specific survival.(Elliott et al. 2017) In a study by Grotenhuis et al. long-term OS or disease-free survival rates did not differ between sarcopenic and non-sarcopenic patients.(Grotenhuis et al. 2016) Similar findings were observed in a study by Awad et al. where sarcopenia did not affect OS of the patient population undergoing NAT and esophagectomy for EC.(Awad et al. 2012)

Study II also found that progression of sarcopenia and BMI loss continues after esophagectomy. A previous study has had similar results.(Elliott et al. 2017) Malnutrition has been found to be prevalent even years after esophagectomy.(Martin et al. 2007) The effect of this body composition change on the patients outcomes is unknown.

The limitations of Study II include the retrospective nature of the study, exposing it to selection bias and systemic errors. Statistical power is of concern with a study of this size and thus type I and type II errors are of concern, especially regarding rarer events such as specific complications.

9.3. Skeletal muscle mass loss & sarcopenia in advanced esophageal cancer treated with palliative stent insertion

Study III showed an association, in multivariate Cox regression analysis, with lower SMI and worse OS in advanced EC patients receiving a SEMS for palliation of dysphagia. Sarcopenia, by using the aforementioned thresholds (SMI of ≤39 cm²/m² for women and ≤55 cm²/m² for men)
was not a prognostic factor. Sarcopenia was very prevalent in this study population (83.6%) and it
was not associated with the TNM-staging of the cancer. Sarcopenic patients, in comparison to their
non-sarcopenic controls, had significantly more alternative feeding routes, such as PEG or jejunal
feeding tube, inserted. In addition, using the median of percentual change of SMI (ΔSMI) of -11.6%
produced clearly differentiated survival curves in Kaplan-Meier analysis.

Prior studies have linked poor nutrition, assessed by weight, BMI and serum albumin, to
poorer survival in advanced EC patients treated with SEMS. (Gray et al. 2011; Lecleire et al. 2006)
To the authors knowledge, no prior link between SMI and poor survival in patients with advanced
EC treated with stent insertion has been established.

Study III has several limitations, such as the retrospective nature of the study and the
heterogeneous nature of the follow up of the patients due to their advanced disease and mostly
palliative treatment attempts. Frequency of follow-up CT scans was low and the timing was
variable. Sarcopenia was very prevalent in this population and due to this, the size of the population
without sarcopenia was small. This study evaluated only patients with SEMS inserted and the
results can’t be extrapolated to advanced EC patients without SEMS insertion. It also can’t be
established whether improving the patients SMI leads to better outcomes.

9.4. Stent failure in malignant and benign esophageal disease

In Study IV, non-malignant disease, mid-esophageal stents and shorter stent lengths were associated
with higher risk of stent failure. The overall stent failure rate in this study was 34.3%

The rate of complications related to stenting in our study was comparable with previously
published literature (23-56%), as was the rate of re-stenting (17-47%). (Burstow et al. 2009; Kim et
al. 2015; Stewart et al. 2013; Verschuur et al. 2007) Stent migration was the most common
complication in our study with esophageal fistula formation being the second most common. EC
patients and patients with nonmalignant disease had similar complication rates, but non-esophageal
malignancy patients had a markedly lower complication rate, this difference was statistically
significant and most likely explained by the rarity of late complications in the non-esophageal
malignancy group due the extremely low OS of this group.

Multivariate analysis revealed stent location in the middle third of the esophagus to be
associated with greater risk of failure, stent location within the upper third of the esophagus showed
a similar trend, but without statistical significance, probably due to the low amount of patients with
stents inserted into the upper third. Previous studies have recognized distal esophageal stenting to
be an risk factor for stent migration, with the study by Verschuur et al. showing that this risk can be negated by inserting larger diameter stents, but with increase in other stent related complications. (Homann et al. 2008; Verschuur et al. 2007) One possible explanation for the higher rate of failure in the middle third of the esophagus is that there is more room for the operator to work with in the stenting of the distal esophagus. In the mid esophagus, the airway is more adjacent, enabling the formation of trachea- or bronchioesophageal fistula.

In the same analysis, stents between 12-15 cm of length had lower risk of failure compared to stents shorter than 12 cm. Stents longer than 15 cm had no protective effect. A prior study has found that the risk of adverse stent-related events diminishes by every 10 mm of stent length increase. (Fuccio et al. 2016)

Non-malignant esophageal disease showed the greatest risk of stent failure in Kaplan-Meier analysis and was an independent risk factor in multivariate Cox analysis. This effect likely due to the lowest mortality rate in this group as stent failure becomes increasingly common when stents are left in place for longer times. (Freeman et al. 2015) The nature of benign esophageal disease might also be non-progressive and thus stent migration might be a sign of healing, indeed, stent migration rates have been reported to be up to 81.8% in benign strictures treated with plastic stents. (Hohn et al. 2008)

Limitations of study IV consist of the heterogeneity of the patient population and retrospective nature of the study. This increases the risk of selection bias and makes the interpretation of the results more difficult. Many of the patients had such poor overall condition that the reporting and noticing of minor complications is more challenging.
10 SUMMARY

EC is a major contributor to cancer-related mortality and morbidity worldwide, with a low 14.1% 5-year survival rate in Finland. This thesis studied the effect of body composition on the prognosis of EC and elucidated the role and risks related to esophageal stent insertion, a commonly used treatment method against the nutritional problems related to EC.

Usage of SEMS as a bridge to surgery was not associated with worse survival, oncological outcomes or complications. It serves as a safe and effective treatment strategy, when used by specialized centers, in selected EC patients undergoing surgery.

Although the traditionally defined limits of sarcopenia did not correlate with outcomes in the EC patients receiving NAT, pronounced skeletal muscle loss in CT imaging during NAT for EC is associated with worse survival. Skeletal muscle standardized to the patients height, the SMI, was also an independent prognostic factor in multivariate analysis.

SMI also proved valuable in evaluating the prognosis of EC patients with advanced disease treated with the insertion of a palliative esophageal stent. In this patient population, SMI was an independent prognostic factor and its accentuated loss in follow-up predicted poor OS.

When using esophageal stents as a treatment method, we identified that the middle third of the esophagus carries the highest risk for stent-related adverse events. Benign indications for stenting were also more risky, as were shorter stent lengths.
11 CONCLUSIONS

I Pre-operative insertion of self-expanding metallic stent in locally advanced esophageal cancer (cT $\geq$ 2) does not have a negative effect on survival, oncological outcomes, or complication rates. This practice seems to be safe when performed in a tertiary center.

II Loss of skeletal muscle mass during neoadjuvant treatment is associated with worse outcomes in surgically treated esophageal cancer. Sarcopenia is extremely prevalent in this population, but does not offer prognostic significance.

II In patients with advanced esophageal cancer, treated with a self-expanding metallic stent, low skeletal muscle mass and loss of skeletal muscle mass during follow-up indicate a poorer prognosis.

IV There is a significant risk of complications related to esophageal stenting, which is highest with benign esophageal diseases as the indication, furthermore, mid-esophageal stenting and shorter stents were associated with higher stent failure rates.
Ruokatorven syöpä on huonon ennusteen omaava syöpä, jossa pitkäaikaiselviystyminen länsimaissa on alle 15%. Ravitsemushäiriöt, lihassamman kato ja nielemisvaikeudet ovat ruokatorvisyöpään usein liittyviä ilmiöitä.

Tämän tutkimuksen tavoitteena oli selvittää 1) ruokatorven syövän leikkaushoitoa edeltävän ruokatorven metalliverkkostenttauksen turvallisuutta ja vaikutusta potilaan ennusteen, 2) lihaskadon ja lihassamman vähyyden vaikutusta leikkausta edeltävän (neoadjuvantti) solunsalpaaja- ja säde-yhdistelmän syöpäjäteen ruokatorvisyöpäpotilaisten ennusteen, 3) lihaskadon ja lihassamman vähyyden vaikutusta oireita helpottavan ( palliatiivisen) stenttauksen syöpäjäteen ruokatorvisyöpäpotilaisten ennusteen. Tämän lisäksi tutkimme myös 4) stenttihoitonsa epäonnistumiseen vaikuttavia tekijöitä, ruokatorvisyövän, muun syövän tai ei-syöpäperäisen taudin vuoksi stentattujen potilaisten hoidossa.


Stentin asettaminen ennen ruokatorvisyöpäleikkausta ei vaikuttanut kokonaisselviyttymiseen, syöpäpäaseen selviyttymiseen tai komplikaatioiden määrään. Itse

13 ACKNOWLEDGEMENTS

This study was carried out in the Division of General Thoracic and Esophageal Surgery of the Department of Cardiothoracic Surgery of the Helsinki University Central Hospital between 2014 and 2018. I wish to express my deepest gratitude to the following people who made this work possible:

To professor Karl Lemström, M.D., Ph.D and professor emeritus Ari Harjula, M.D. Ph.D. for providing the possibility to conduct this research.

To professor Markku Voutilainen M.D., Ph.D and docent Juha Saarnio M.D., Ph.D for their invaluable comments and insight which have improved this thesis immensely.

To my supervisor docent Jari Räsänen, M.D. Ph.D. for his excellent guidance, advice and critique as well as dedication. His knowledge in the field of esophageal surgery has been an inspiration and a great help all these years.

To my other supervisor Dr. Ilkka Ilonen, M.D. Ph.D., for his extreme dedication, helpfulness, ideas and overall care for this project and my success. You have been an outstanding mentor during these years.

Professor Martti Färkkilä, M.D. Ph.D. and docent Leena Kylänpää, M.D. Ph.D. for their evaluation of my progress during these years and valuable comments.

Professor h.c. Jarmo Salo, M.D. Ph.D. for his extensive experience and wisdom regarding the field of thoracic surgery.

To Dr. Juha Kauppi, M.D. Ph.D. for his support and comments on the methodologies of my projects.

To Dr. Kaisa Nelskylä, M.D: Ph.D. and Dr. Emmi Ylikoski M.D. Ph.D. for their tremendous help in anesthesiologic point of views regarding my first manuscript.
Carol Norris, Ph.D., and Stephen Stalter, MA, for reviewing the language of my articles.

To my colleagues at Päijät-Häme Central hospital, to my former colleagues at Kymenlaakso Central Hospital.

To my parents: my father Markku and my mother Anu. Your upbringing, love and support and genes has made all this possible.

My brother Miikka, for being a dear friend and providing great alternative views to things.

To my friends from Porvoo: Tomi, Atte, Lauri, Erik. For taking my mind of medicine and my career for every once and in a while.

My friends from later in life: Arttu, Marko, Sakari, Sofia, and Enni. You have all showed me something to strive for as a person and as a doctor.

To all the others I am forgetting to mention.

And finally, to my love Crista, without your never-ending love and support all of this wouldn’t have been possible. I am forever grateful and in awe of your ability to see the light in the end of the tunnel even when I fail to do so.

This thesis was supported financially by financially supported by the Research Foundation (EVO) of the Helsinki University Central Hospital, and the Orion Research Foundation sr.


Dulak AM et al. (2013) Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity Nat Genet 45:478-U437 doi:10.1038/ng.2591

El-Rayes BF et al. (2009) A phase II study of bevacizumab, docetaxel, and oxaliplatin in gastric and GEJ cancer Journal of Clinical Oncology 27


Fearon K et al. (2011) Definition and classification of cancer cachexia: an international consensus Lancet Oncology 12:489-495 doi:10.1016/S1470-2045(10)70218-7


Igaki H et al. (2008) A randomized trial of postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus neoadjuvant chemotherapy for clinical stage II/III squamous cell carcinoma of the thoracic esophagus (JCOG 9907) Journal of Clinical Oncology 26

Ilson DH et al. (1999) Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer Journal of Clinical Oncology 17:3270-3275


Kiviranta UK (1952) Corrosion carcinoma of the esophagus; 381 cases of corrosion and nine cases of corrosion carcinoma Acta Otolaryngol 42:89-95

Ku GY et al. (2016) Phase II study of bevacizumab and preoperative chemoradiation for esophageal adenocarcinoma J Gastrointest Oncol 7:828-837 doi:10.21037/jgo.2016.08.09

Kudou K et al. (2017) Prognostic Significance of Sarcopenia in Patients with Esophagogastroduodenal Junction Cancer or Upper Gastric Cancer Ann Surg Oncol 24:1804-1810 doi:10.1245/s10434-017-5811-9


Levine DM et al. (2013) A genome-wide association study identifies new susceptibility loci for esophageal adenocarcinoma and Barrett’s esophagus Nat Genet 45:1487-U1119 doi:10.1038/ng.2796


71


Rasanen JV et al. (2003) Prospective analysis of accuracy of positron emission tomography, computed tomography, and endoscopic ultrasonography in staging of adenocarcinoma of the esophagus and the esophagogastric junction Ann Surg Oncol 10:954-960


Sheetz KH et al. (2013) Decreased core muscle size is associated with worse patient survival following esophagectomy for cancer Dis Esophagus 26:716-722 doi:10.1111/dote.12020


Song SY et al. (2004) Usefulness of whole body FDG-PET for the prediction of pathologic response after neoadjuvant chemoradiotherapy in locally advanced resectable esophageal cancer. Journal of Clinical Oncology 22:332s-332s


75


Whiteman DC et al. (2008) Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus Gut 57:173-180 doi:10.1136/gut.2007.131375


ORIGINAL PUBLICATIONS