ADENOCARCINOMA OF THE ESOPHAGUS AND ESOPHAGOGASTRIC JUNCTION - STUDIES ON PATHOGENESIS, PROGNOSIS, STAGING AND SURGICAL TREATMENT

ACADEMIC DISSERTATION

To be presented with the permission of the Medical Faculty of the University of Helsinki, for public examination in Lecture Hall I of Meilahti Hospital, Haartmaninkatu 4, on June 12th 2015, at 12 noon.

Helsinki 2015
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# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>8-IP</td>
<td>8-Isoprostane</td>
</tr>
<tr>
<td>8-OHdG</td>
<td>8-OH-deoxyguanosine</td>
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<tr>
<td>AC</td>
<td>Adenocarcinoma</td>
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<td>BE</td>
<td>Barrett’s esophagus</td>
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<tr>
<td>CHT</td>
<td>Chemotherapy</td>
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<td>CRT</td>
<td>Chemoradiotherapy</td>
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<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DFS</td>
<td>Disease free survival</td>
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<td>EGJ</td>
<td>Esophagogastric junction</td>
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<tr>
<td>EMR</td>
<td>Endoscopic mucosal resection</td>
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<tr>
<td>EOX</td>
<td>Epirubicin – Oxaliplatin – Cebecitabin</td>
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<tr>
<td>ESD</td>
<td>Endoscopic mucosal resection</td>
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<td>EUS</td>
<td>Endoscopic ultrasound</td>
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<tr>
<td>FDG</td>
<td>18F-fluorodeoxy-D-glucose</td>
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<tr>
<td>FDG-PET</td>
<td>18F-fluorodeoxy-D-glucose positron emission tomography</td>
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<tr>
<td>FDG-PET-CT</td>
<td>18F-fluorodeoxy-D-glucose positron emission tomography with computed tomography</td>
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<tr>
<td>GERD</td>
<td>Gastro-esophageal reflux disease</td>
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<tr>
<td>GSH</td>
<td>Glutathione content, reduced form</td>
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<tr>
<td>GSSG</td>
<td>Glutathione content, oxidized form</td>
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<tr>
<td>HGD</td>
<td>High grade dysplasia</td>
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<tr>
<td>HPI</td>
<td>Helicobacter pylori infection</td>
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<td>HPR</td>
<td>Histopathologic response</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
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<tr>
<td>LES</td>
<td>Lower esophageal sphincter</td>
</tr>
<tr>
<td>LNM</td>
<td>Lymph node metastases</td>
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<tr>
<td>MIE</td>
<td>Minimally invasive Ivor Lewis esophagectomy</td>
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<tr>
<td>OE</td>
<td>Open transthoracic, Ivor Lewis esophagectomy</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
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<tr>
<td>OEGD</td>
<td>Upper gastrointestinal endoscopy</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>OS</td>
<td>Oxidative stress</td>
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<td>PEG</td>
<td>Percutaneous endoscopic gastrostomy</td>
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<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>RFA</td>
<td>Radiofrequency ablation</td>
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<tr>
<td>ROC</td>
<td>Receiver operator characteristics</td>
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<tr>
<td>ROI</td>
<td>Region of interest</td>
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<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
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<tr>
<td>SEAC</td>
<td>Superficial esophageal adenocarcinoma</td>
</tr>
<tr>
<td>SM</td>
<td>Submucosal</td>
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<tr>
<td>STS</td>
<td>Society of thoracic surgeons</td>
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<tr>
<td>SUV</td>
<td>Standardized uptake values</td>
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<tr>
<td>TH</td>
<td>Transhiatal esophagectomy</td>
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<tr>
<td>TTE</td>
<td>Transthoracic esophagectomy</td>
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This thesis is based on following original publications, which are referred to in the text by their Roman numerals.

I Kauppi J, Räsänen J, Sihvo E, Ahotupa M, Arkkila P, Nieminen U, Salo JA. Increased oxidative stress in the proximal stomach of patients with Barrett’s esophagus and adenocarcinoma of the esophagus and esophagogastric junction. (Submitted).


These publications are reprinted with permission of the copyright holders. (In addition, some unpublished material is presented).
Adenocarcinoma (AC) of the esophagus and esophagogastric junction (EGJ) is a disease with poor prognosis and increasing incidence in western countries. Its pathogenesis is associated with oxidative stress (OS) in the esophageal epithelium. Long-term survival is associated with successful radical surgery, early stage of the disease, and successful downstaging with neoadjuvant therapy. As surgery is accompanied with a large number of possible complications, it is essential to identify patients who might not benefit from surgery and on the other hand, could be treated with less invasive options. The aims of this study were 1) to assess the role of OS below EGJ in the pathogenesis of Barrett’s esophagus (BE) and AC, 2) to assess the prognoses and causes of death in early esophageal AC, 3) to determine the value of 18F-fluorodeoxy-D-glucose positron emission tomography with computed tomography (FDG-PET-CT) in quantifying the response to neoadjuvant therapy and 4) to compare the novel mini-invasive technique (MIE) to traditional open esophagectomy (OE) in radical surgery.

To quantify OS, we measured 8-isoprostane (8-IP), glutathione content (GSH), and 8-OH-deoxyglucose (8-OHdG) values from mucosa below EGJ, BE-mucosa, and AC-tumors from 43 patients with BE and/or AC and compared them to samples from corresponding sites of 15 healthy control patients. To determine the long-term prognosis of patients with early esophageal AC, we studied patient records and causes of deaths for 85 patients, treated with radical esophagectomy over a 27-year time span. To evaluate pre-treatment response to neoadjuvant therapy in locally advanced AC, we recorded FDG-PET-CT results before and after induction therapy in sixty-six consecutive patients who were to be operated on for locally advanced AC. Decrement in radioactive glucose uptake values was associated with survival and histological treatment response. We compared MIE to OE, to see, if minimal invasiveness reduces the rate of complications and if they are comparable in terms of oncologic radicality and survival.

Proximal gastric GSH content was lower and 8-IP and 8-OHdG levels higher with statistical significance in the study patients (BE and AC) as compared to healthy controls. In patients with early esophageal AC, overall and long-term (>5–year) survival rates were mostly affected by diseases related to aging. During the first five years after the operations, disease recurrence was the most common cause of death. However, recurrence-free survival was 80% at five years and no new recurrences were detected after that. Microscopic eradication of locally advanced AC was optimally
predicted by a 67% decrease in uptake values before and after induction chemotherapy, with a sensitivity of 79% and specificity of 75%. However, this association was not linear and complete eradication of radioactive glucose uptake, was not always associated with a complete histologic response. However, a decrease in glucose uptake was associated with improved overall and recurrence free survival. MIE and OE were equivalent in terms of 90-day mortality, pneumonia-, leak-, and overall complication rates. Also a minimally invasive technique was associated with significantly shorter overall hospital stay and significantly less blood loss during the operations.

OS levels are also elevated below the EGJ, as lipid peroxidation can be detected (8-IP) and antioxidant defense (GSH) is reduced. Also the levels of 8-OHdG adducts were higher showing that DNA is being damaged by free radicals. This suggests that inflammation of the proximal gastric mucosa induced by gastroduodenal content, has a role in the pathogenesis of BE and esophageal AC. As the prognoses for patients with early esophageal AC were good, recurrence was still the most important cause of death. The risk was highest for patients with lymph node metastases and deep submucosal infiltration. Therefore radical surgery should be preferred with patients with a low risk of surgical complications and submucosal infiltration. In patients with intramucosal AC, endoscopic ablation should be considered. Evaluation of the patients’ responses to induction chemotherapy with FDG-PET-CT was not accurate enough to give indications better than the exclusion of metastatic disease. However, a significant decrease in radioactive glucose uptake was associated with improved survival, independently of histopathologic response. This information can be useful when balancing the risks of surgery against expected benefits. The perioperative and oncological results for MIE were comparable to those of the open approach and MIE seems to shorten hospital stay. However, the MIE technique is demanding and its mastery requires a sufficient number of cases and skilled practitioners.
4 INTRODUCTION

Esophageal carcinoma consisting of adenocarcinomas (AC) and squamous cell carcinomas is the 8th most common cancer worldwide and 6th most common cause of cancer related death (1). The incidence of AC has been rising rapidly in high-income western countries, replacing squamous cell carcinoma as the most common histological subtype (2-7). AC of the esophagus and EGJ, is a disease with poor prognosis, as at the time of diagnosis, 60% of patients can only receive palliative treatment because of underlying illnesses and / or disseminated disease. The expected overall 5-year survival of all patients is 17% (8, 9). It is possible to cure the disease if it is diagnosed at an early stage and if the patients are treated with radical esophagectomy, with experienced centers achieving 40-50% overall 5-year survival rates (1, 8, 9).

The incidence of AC has undergone a dramatic increase over the last 40 years. In the United States, from 1975 to 2004, the age-adjusted incidence of esophageal carcinoma in white men has increased 463%, from 5.76 to 8.34/100000/year (10). In Finland a similar increase has been seen with the incidence in males jumping from 0.28 to 0.77/100000/year between 1976 and 1995 (8) and from 1995-2012 0.8–2.1/100000/year (Figure 3). Obesity, gastro-esophageal reflux disease (GERD) and tobacco smoking are the principal factors associated with an increased risk for AC of the esophagus and EGJ (11, 12) and the rise of its incidence can be attributed to changes in prevalence of those factors (12). At highest risk of esophageal AC, are patients with GERD, who have acquired Barrett’s esophagus (BE) and approximately 60% of patients with AC have this condition (13-16). It is estimated, that 10% of patients with BE, have a genetic predisposition (17) for the condition. The annual risk of esophageal AC in patients with BE is 0.12% and the risk is increased to 5% when metaplasia progresses to low grade dysplasia (18). The role of Helicobacter pylori infection (HPI), the most important risk factor for gastric AC, is unclear in the development of EGJ AC. As some studies have connected HPI with EGJ AC, recent meta-analysis suggests it grants a protective effect against AC in general (19).

Chronic inflammation in the esophageal mucosa caused by GERD, is considered to be the main mechanism behind the development of BE and subsequent dysplasia and AC in the esophagus (14, 20, 21). Chronic inflammation leads to a state of oxidative stress (OS) i.e. accumulation of toxic oxygen free radicals that damage cell membranes, proteins and DNA making a patient susceptible to mutations that may lead to carcinogenesis (22, 23). OS has been shown to strongly associate with
the development AC of the esophagus and EGJ (23-26). On the other hand, an increased intake of antioxidants has been associated with a lesser risk of AC (27). Patients with GERD and without esophagitis seem to have increased OS and deficient antioxidant barrier in their proximal esophageal mucosa, and this remains unchanged even after successful fundoplication (24). In the gastric cardia, inflammation has been associated with HPI, but also with GERD (28) and inflammation of the cardia has been linked with AC of the EGJ (29). The importance of OS in the proximal gastric folds of patients with GERD, BE and AC is largely unknown.

In the last decades, the overall mortality to AC of the esophagus and EGJ has not decreased, but incidence based mortality due to the early stage disease has decreased, which may be largely attributes to BE surveillance programs and treatment at an early stage (30). Radical surgery offers the possibility of curing patients with AC, but it is associated with substantial rates of complications (31) and mortalities (32). International guidelines suggest endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) with radiofrequency ablation (RFA) of residual BE segments, for patients with high grade dysplasia and intramucosal esophageal cancer (pT1a), as it is reported that the incidence of lymph node metastases (LNM) and recurrence are very low (33, 34) and the morbidities associated with radical surgery can thus be avoided. However, as patients with early esophageal AC are mostly older and may not live over the 5-year follow up period, it is not known for how long the risk of disease recurrence persists and what are causes of death in this patient population. This data is necessary to inform optimal selection for therapy.

Neoadjuvant therapy with chemo- or radiochemotherapy has improved results of locally advanced AC (35, 36). Nearly 20-25% of patients may have a complete histopathologic response, which is associated with markedly improved survival (37). As neoadjuvant therapy may also cause complications and delay of surgery, there would be a need to find an imaging modality to select patients who can or cannot benefit from the multimodality approach, or even from resection.

Positron emission tomography (PET) measures the accumulation of a fluorinated glucose analog (18F-fluorodeoxy-D-glucose; FDG) in malignant cells (38). It is more accurate in detecting distant metastases than computed tomography (CT) (39, 40). The accumulation of FDG offers a possibility to grade the activities of tumors during and after treatment with repeated scans and it has been shown to be able to grade treatment response during neoadjuvant chemotherapy (41).

As esophageal resections are associated with a high rate of complications, traditional en-bloc open transthoracic esophagectomy (OE) has been replaced in many experienced centers with the videothoracoscopic and laparoscopic approaches i.e. minimally invasive esophagectomy (MIE) (42-
Randomized data from a single institution suggests these approaches lead to less pulmonary complications, shorter hospital stays and improved short-term quality of life for MIE (46). There is a lack of data concerning oncologic safety for patients with locally advanced AC who are operated on after neoadjuvant therapy.
5 REVIEW OF THE LITERATURE

5.1. Definition of histology and anatomy

AC of the esophagus and EGJ, occurs in the distal third of the esophagus or in the EGJ (47) and it is classified according to the International Union Against Cancer and the American Joint Committee for Cancer (UICC/AJCC) TNM staging system (48). AC is rarely located more proximally than the tracheal bifurcation (9). It is not possible to define EGJ AC histologically, as columnar elements found in those tumors are also present in the normal mucosa of the proximal stomach, distal esophagus and Barrett’s metaplasia (49). The Western endoscopic definition of cardia is the top of the gastric folds, whereas the Japanese define it as the lower limit of the palisade vessels (50-52). The histologic definition of cardia is also unclear, as the squamocolumnar junction and EGJ may not coincide and cardiac type distal esophageal mucosa, or a mixture of fundic, cardiac and intestinalized mucosa may be present in this area (Figure 1) (53, 54). The modern concept is, that a mixture of columnar cell types is found between true squamous or intestinal metaplastic-, and true gastric mucosa, called the squamo-oxyntic gap. It is strongly associated with reflux, and cannot be seen in autopsy studies of patients without reflux (50, 55). To overcome these difficulties of definition for clinical purposes, a clinical topographic classification has been described by Siewert et al. (56) (Figure 1). Tumors reaching EGJ are divided into three classes. Class I tumors are those that have their epicenter within 5 cm of the cardia in the distal esophagus, class II tumors have their epicenter within 1 cm above or 2 cm below the EGJ, and class III subcardial tumors having their centers of mass 2-5 cm from the EGJ. Type I tumors are thought to arise from the esophageal mucosa, type III tumors from the fundic gland mucosa and type II tumors from both.
5.2 Barrett’s esophagus

5.2.1 Definition

Metaplasia is defined as a process where one adult cell type replaces another as a consequence of chronic tissue injury (57). Barrett’s esophagus (BE) is nowadays defined as a condition in which metaplastic columnar mucosa that has a risk of becoming cancerous, replaces esophageal squamous mucosa that has been damaged by gastroesophageal reflux disease GERD (14). Its diagnosis requires biopsy confirmed esophageal intestinal metaplasia with specialized goblet cells in any distance from proximal gastric folds, although some gastroenterologic societies also only accept cardiac columnar mucosa for the diagnosis (14, 58). The prevalence of BE is 5.6% and 4% in the American (14) and Finnish populations (59) respectively.

5.2.2 Pathogenesis

GERD is generally accepted as the cause of BE (14, 60-62). The most important cause for GERD is lower esophageal sphincter (LES) insufficiency, causing more than half of reflux episodes in reflux patients (63-65) Other important ailments affecting reflux and esophageal injury are hiatal hernia,
impaired esophageal emptying, and delayed gastric emptying (66, 67). It has been reported that 90% of patients with BE have mechanically insufficient LES and 93% have increased exposure to gastric contents according to pH monitoring (63). Refluxing contents that damage the esophageal mucosa are acid, pepsin and duodenal contents, such as trypsin, bile acids and bile salts (68-73). In BE, the squamous epithelium is replaced by mucus secreting columnar cells that have better tolerance to acid and bile (73). The metaplastic process can be the result of a direct conversion from differentiated squamous epithelial cells to metaplastic mucosa or a change in the development of the esophageal or intestinal stem cells to BE mucosa (57, 74). It is unclear what cells give rise to metaplasia, but esophageal stem cells, stem cells of the submucosal glands, and stem cells of the gastric cardia have been suggested (75) as candidates. In a rat model, BE develops from circulating stem cells originated in bone marrow (76). A genetic predisposition to the development of BE is known to exist and 10-12% of all patients with BE are considered to have a familial background (17, 77). Therefore, the concept of BE being an acquired condition, is being challenged (77).

5.3 Oxidative stress
An organism’s oxidative metabolism produces reactive oxygen species (ROS) as byproducts, which are generated when oxygen molecules are reduced. A one-electron reduction of oxygen produces superoxide, whereas a two-electron reduction produces hydrogen peroxide (78). ROS are a part of normal oxygen metabolism but when in excess, they are a threat as they can cause oxidative injury to cells by damaging DNA, proteins and cell membranes (79). Free radicals can modify DNA bases and cause the production of DNA adducts, such as 8-OHdG, and these mutations can lead to further mutations that cause the dysfunction of key genes and the initiation of carcinogenesis (79, 80). OS has been suggested to play a key role in GERD related chronic injury esophageal mucosa (81). The expression of inflammatory cytokines in response to damage induced by gastroduodenal reflux, leads to infiltration of inflammatory cells to the esophageal mucosa, and their activity results in the overproduction of ROS (81). Studies of BE and esophageal AC in human tissues (24, 25, 82, 83) and animal models (84) have shown that there are increased OS markers and decreased antioxidative capacity as compared to normal squamous epithelium and duodenal mucosa. Also, consequent DNA damage has been demonstrated in BE and esophageal AC tissues as compared to normal squamous mucosa of the esophagus (80, 83, 85, 86). In other GI-tract malignancies, for example esophageal squamous cell carcinoma (87), and gastric AC, OS plays an essential role. The pathogenesis of peptic ulcer disease and gastric AC are driven by Helicobacter pylori infection associated oxidative stress
Cellular antioxidant mechanisms are essential for protecting esophageal epithelial cells against the ROS generated by GERD. Glutathione S-transferase (GST), glutathione peroxidase (GPx) and superoxide dismutase (SOD) systems play crucial roles in cellular detoxification, protecting macromolecules from attack by reactive electrophiles. Reduced levels of these enzymes, and/or reduced glutathione have been reported in BE and Esophageal ACs, implying that an impaired antioxidative defense may contribute to the carcinogenesis of esophageal AC. (25, 26, 90, 91). Increased antioxidant dietary intake is associated with reduced risk of esophageal AC, which further supports the role of oxidative damage (92, 93). Overall, mutations in genes controlling cellular antioxidant defenses represent a key step in the development of BE and subsequent carcinogenesis (75).

5.4 Epidemiology
The incidence of AC has been rapidly rising in western countries during the last four decades (Figure 2 and 3) and it has replaced squamous cell carcinoma as the most common histological subtype (2-4, 94). This change has coincided with an increase in obesity and GERD, and on the other hand, a reduction in smoking and alcohol consumption (7, 11, 16). Incidence rates have been highest in Great Britain (5-8.7/100000/year), Australia (4.8/100000/year), the Netherlands (4.4/100000/year) and the USA 3.7/100000/year (2). In Finland, the incidence of esophageal AC in males rose from 0.28 to 0.77/100000 between 1976-1995 (95), during the years 1998-2002 it rose to 1.10/100000 (96) and according to the Finnish cancer register, from 1.2 to 2.1/100000 during 2001-12 (Figure 3). Other Nordic countries have had a similarly low incidence, Denmark (2.8/100000/year), Sweden 1.0/100000/year and Norway 0.8/100000/year (2).

Recent reports from the USA (97) suggest that the incidence of esophageal AC is plateauing from an 8.2% annual rate of increase to 1.3% and a Swedish study (6) reports that the incidence in Sweden has remained stable since 2001. Another recent report shows that the incidence in the USA has been growing steadily annually at a rate of 2.2% and it grew in Australia by 1.5% between 1998 and 2008 (98). So the overall incidence still appears be growing, but at a slower pace. The rise in incidence of AC of the EGJ has plateaued earlier than that of AC of the esophagus, having remained at 2/100000/year since 2000 in the US (99). Overall, the worldwide variation in incidence of esophageal AC is much less than that of squamous cell carcinoma. Differences occur in genders and races in the same geographical areas, for example, in the USA esophageal AC is five times more common in whites than blacks, and eight times more common in men than women (100). In Finland
the incidence of AC between 1991 and 1995 was 7-fold higher in men than women (0.77 vs. 0.11/100000/year) (95) as seen in a study by Voutilainen et al. (96). Values in other European countries are: a male to female ratio of 12:1 in France, 2:1 in the Netherlands, 5.5:1 in Denmark and 9.6:1 in Iceland (101). If AC of the EGJ is examined separately, its incidence can be seen to have plateaued earlier than of AC of the esophagus, having remained at 2/100000/year since 2000 in the US, and at the same time, the incidence of true gastric AC has decreased steeply (99). EGJ AC has a similar male to female ratio (4.7:1 in the USA) and black to white ratio (2:1 in the USA) (99). Misclassification of esophageal AC as true gastric AC may have occurred and the effect of such misclassification on the incidence is unknown (2, 99, 102). In Finland, the incidence of EGJ AC has remained the same over the last decades (2.1/100000/year in males and 0.5/100000/year in females) (95, 96). Finnish cancer registry data suggests that during 1995-2012, the incidence of cardiac adenocarcinomas in both men and women has remained stable, between 0.8-1.4/100000/year.

Figure 2. Age-adjusted incidence rates (blue bars) and 5-year survival rates for persons with esophageal adenocarcinoma diagnosed in the United States. Data are from the population based Surveillance, Epidemiology and End Results cancer registries. Reproduced with permission from Rustgi et al., NEJM 2014 (9), copyright Massachusetts Medical Society.
5.5 Risk factors

In most cases esophageal AC originates from a region of the BE in a stepwise process from GERD associated chronic inflammation to metaplasia, dysplasia, and finally AC (13, 14, 20, 21, 103). The annual risk of developing esophageal AC for patients with BE, is 30-fold compared to the general population and the absolute risk is 0.12% per year (18). GERD is known to be a risk factor even in the absence of BE (15) and the severity of symptom scores has been associated with increased risk of AC (104). Factors increasing the risk of BE progression are hiatal hernia, length of BE segment >3 cm, dysplastic lesions and ulceration (105-107). Other significant risk factors are obesity and smoking. Meta-analyses showed a pooled 2.78 (95%CI 1.850-4.164) fold risk for AC in patients with BMI over 30kg/m² (108) and 1.96 (95%CI 1.64-2.34) fold risk for smokers (109). Previous cholecystectomy raises the risk to 1.3 (95%CI 1-1.8) (110). In a recent meta-analysis high fiber nutrition was associated with significantly decreased risk of esophageal AC (OR 0.66; 95%CI 0.44-0.98) (111) but alcohol consumption did not affect the risk (112).
AC of the esophagus and EGJ share the same risk factors, but the risks are lower for EGJ AC (99, 103). There are also reports of EGJ AC arising without BE (113-115). It is thought that EGJ AC has a more heterogeneous origin than esophageal AC with the clinicopathologic features, however, being the same as in BE originated AC (49, 115). HPI may be associated with subcardiac (Siewert type III) AC but its presence is inversely associated with the risk of esophageal AC (19). It has been proposed that the prominent decline in HPI colonization in the last few decades may partly be responsible for the increase seen in the incidence of esophageal AC (116, 117). The association between EGJ AC and HPI is considered to be unclear (116-118). Other protective factors may be the use of anti-inflammatory medication (119), statins (120) and antioxidants (27).

5.6 Clinical presentation and diagnosis
Most esophageal ACs (75%) are located in the distal third of the esophagus and AC of the EGJ is considered to be a continuation of the same process (9). Small tumors may be asymptomatic, while locally advanced tumors cause progressive dysphagia and weight loss. Other common symptoms are heartburn and blood loss (9). Barium swallow has a 95% sensitivity for detecting tumors and is considered a safe and inexpensive method, but upper gastrointestinal endoscopy (OEGD) is the method of choice to confirm the presence of even small tumors and for making possible biopsies with histological diagnosis (121, 122).

5.7 Staging
Once diagnosis of AC is made, the next goal is to evaluate if the patient is a candidate for complete surgical resection. Staging is accomplished in accordance with the latest version of the International Union against Cancer and American Joint Committee for Cancer (UICC/AJCC) TNM staging system (48) (Figure 4 & 4.1). The TNM stage involves the depth of infiltration of the tumor into the esophageal wall (T), the lymph node status (N) and the possible presence of distant metastases (M). The latest version is from 2010 and the most significant changes to the previous system are that all distant metastases are classified as M1 instead of M1a and M1b. A regional lymph node has also been redefined to be any periesophageal node from the cervical to the coeliac areas. Therefore, for example, retroperitoneal and supraclavicular metastatic nodes are considered as stage IV (M1) disease. Also, the N class is stratified according to the amount of regional lymph node metastases and T4 is divided into resectable (T4a) and unresectable T4b.
The workup for staging includes evaluation of the history and general physical condition of the patient, OEGD to determine the location and extent of the tumor, CT of the abdomen and chest, endoscopic ultrasound (EUS) and FDG-PET-CT (123). FDG-PET-CT is always used in assessing patients who are being considered for an operation. However, if CT of the abdomen and chest reveals distant metastases, FDG-PET-CT is not necessary. Minimally invasive staging (laparo-, thoraco- or mediastinoscopy) may also be used in unclear situations (124).

5.7.1 T & N –staging

EUS (Figure 5, panel B) can evaluate the esophageal wall in detail and the accuracy of determining tumor depth (T-stage) is between 73% and 89% and for lymph node status (N-stage) 69%-83% accuracy as compared to histopathological staging from surgical specimens (125, 126). Fine needle sampling with EUS can increase the accuracy of N-stage determination to 90% (127). In the early stages of AC (stage 0, Figures 4 and 4.1), i.e. high-grade dysplasia (HGD, stage 0) and intramucosal tumors (T1a, stage Ia), tumors do not invade through the lamina propria. Submucosal tumors (T1b, Stage Ib) invade the lamina propria layer, i.e. the submucosal layer of the esophageal wall (stage I, Figure 4). The accuracy of EUS in separating stage 0 and Ia from stage Ib, is however inferior to endoscopic mucosal resection (EMR), as only 54% of T1 tumors were staged correctly according to a meta-analysis (128). Therefore EMR is recommend for the more accurate staging of early stage tumors. Tumor stenosis may prohibit the use of EUS and all nodes cannot be reached with a needle. EUS is the most accurate method for determining local disease (stage Ib-IIa, Figures 4 and 4.1) from locally advanced (stages IIb-IIIc, Figures 4 and 4.1) (129, 130). If metastases or an extension to adjacent organs are not present, CT gives more reliable information of the tumor stage (129, 130). The accuracy of PET in the detection of N-status is more variable and its accuracy is between 27%-90% and it is not useful in the evaluation of T-status (131). The use of PET-CT has improved the accuracy of detection of the regional lymph node metastases, but EUS still seems to be a more accurate predictor of nodal status (132).

5.7.2 M-staging

The first goal of staging is to exclude metastastic (stage IV Figures 4 and 4.1) disease, as those patients do not benefit from surgical therapy and further staging is not needed. CT of the abdomen and chest that can detect stage IV disease with an accuracy of 80% (133-136), is readily available and relatively inexpensive and therefore first-line modality. FDG-PET is superior to all other
modalities in the detection of stage IV disease (137-141). Combining PET and CT has further improved the staging accuracy of PET (142-144). Most metastases appear in solid organs, non-regional lymph nodes and bone (131, 145). Distant nodal metastases remain a challenge to both CT and PET, as they lack accuracy when the nodes are less than 10 mm in diameter. PET also has a risk for false positive findings as inflammatory lesions also have increased uptake of FDG (138, 141). However, overall the use of PET-CT results in the detection of more advanced disease in 10-20% of patients, as PET-CT may identify occult distant nodal metastasis especially in supraclavicular and retroperitoneal areas not detectable by CT (9).

5.7.3 Treatment response evaluation
Multimodality therapy i.e. neoadjuvant therapy in conjunction with surgery is increasingly used to improve the treatment results of locally advanced esophageal AC (146). Re-staging after neoadjuvant therapy is necessary to evaluate if a patient is going to benefit from continuing with neoadjuvant and if surgery is still feasible. CT, EUS and OEGD have been shown to be inaccurate in neoadjuvant response evaluation (141, 147, 148). However sequential metabolic imaging by PET and PET-CT has been shown to correlate with neoadjuvant chemotherapy response and survival after surgery, much better than CT or EUS (38, 41, 149, 150), but its accuracy is not high enough to predict histopathologic complete remission of the disease. The present results are contradictory when trying to predict responses to neoadjuvant chemoradiotherapy, mostly because of radiation-induced inflammation (146, 147, 151-153).
Simplified Staging of Esophageal Carcinoma.

Stages 0 through IV are used to classify carcinoma characterized by different degrees of tumor invasion, lymph-node involvement, and metastasis. Stage 0 tumors are intramucosal tumors that do not invade the lamina propria. Stage I tumors invade the lamina propria without lymph-node or distant involvement. Stage II tumors extend to the muscle layer either without (IIA) or with (IIB) lymph-node involvement. Stage III tumors invade through the muscular layer and involve lymph nodes or other adjacent structures. Stage IV tumors spread to distant organs or lymph nodes.

Figure 4. Reproduced with permission from Rustgi et al., NEJM 2014 (9), copyright Massachusetts Medical Society.
5.8 Treatment

The general consensus remains that surgical treatment of esophageal AC is the key for cure and restoration of swallowing function (154-156). In recent years two randomized studies (157, 158) have suggested that overall survival is not improved with the addition of surgery to definitive chemoradiation in esophageal epidermoid carcinoma, although palliation of dysphagia and disease free survival are better in surgery groups. Therefore chemoradiation is frequently offered as a definitive treatment to patients with high surgical risk and epidermoid histology. However, there is no such evidence for AC of the esophagus as prolonged survival with definitive chemoradiation has been reported in only selected patients with esophageal AC (159) and the results do not compare with the best surgical series.

Treatment of esophageal AC is defined according to tumor stage and for the purposes of treatment it can be divided according to the latest classification (48) as early (stages 0-Ia), localized (stages Ib - IIa), locally advanced (stages IIb - IIIc i.e. T3-4 and N0-3 or any T and N1-3) and patients with distant metastasis (stage IV). Patients with T1a and T1b esophageal AC may have 65-85% 5-year survival.
after surgery (160-166) and similar survival rates have been reported after endoscopic mucosal resection (EMR) for early esophageal AC (167). In locally advanced esophageal AC, experienced units (39, 168-171) have reported up to 40-50% 5-year survival after neoadjuvant therapy and surgery, but with surgery only, the results are disappointing with 5-35% 5-year survival (172).

The first determinant of prognosis after surgical resection is the status of the resection margins, and the survival of patients with positive margins is poor, 0-14% at 5 years after operation (173, 174). In patients with completely resected disease, the prognosis is independently associated with the presence of regional lymph node metastases and also their number (173-177). Regional lymph node status is predicted by the depth of tumor infiltration (177, 178). After induction therapy, lymph node metastases and histopathologic regression of the tumor are both independent predictors of survival (179). Patients with complete histopathologic response have been reported achieving similar 5-year survival rates as stage I & II patients, and at best 67% disease-specific 5-year survival in retrospective series (37, 179, 180).

5.8.1 Early stage tumors (stage 0-Ia)

Early esophageal AC is defined as either high-grade dysplasia (HGD) or intramucosal AC (T1a) (48) (Figure 5, panel A). HGD has almost no risk for nodal metastasis, but resected specimen may harbor occult invasive cancer in up to 12% of patients (181). For intramucosal cancer, the risk of nodal disease is 0-2% (182). As the risk of nodal metastasis is very low, endoscopic treatment is generally recommended as a first line therapy for HGD and T1a tumors (33). Different methods include argon beam coagulation, photodynamic therapy, EMR, ESD, radiofrequency ablation (RFA), cryo- and laser therapy. Of these, most commonly EMR is used to remove visible lesions and residual metaplastic mucosa is ablated with RFA (Figure 5, panel C-F) (183). EMR allows for histopathologic diagnosis and the most accurate staging of the possible invasive AC and may lead to further esophagectomy if necessary. A German group compared the results of surgical and endoscopic treatment in 114 patients with early AC (184). Surgery was associated with morbidity, and local recurrence were more likely in the EMR group and frequent follow-ups necessary (184). However, similar long-term results can be achieved with both endoscopic and surgical treatments (167). According to a recent meta-analysis, the risk of recurrence after endoscopic therapy is associated with higher tumor grade, lymphovascular- and microvascular infiltration, piecemeal resection and metachronos in-situ carcinoma (185) and the presence of those risk factors are considered to support surgical treatment over endoscopic. The ESD method is increasingly utilized, as a larger piece of mucosa may resected
in one piece. A review of retrospective analysis suggests a lower rate of cancer recurrence but an increased risk of perforation and bleeding as compared to EMR (34).

5.8.2 Local tumors (stage Ib - IIa)
Tumors extending to the submucosa (T1b) or infiltrating muscularis propria layer, are defined as locally infiltrating tumors (48). The submucosal layer can be divided into three layers classified as SM1 (superficial one-third), SM2 (middle one-third), and SM3 (deep one-third) according to a Japanese classification (186). The risk of nodal metastases increases steeply when the tumor infiltrates the submucosal layers, and is between 27-41% in T1b tumors (160, 173, 178, 187, 188) and in a large series after radical resection up to 50% risk of nodal metastasis is reported in tumors.

Figure 5. Reproduced with permission from Rustgi et al., NEJM 2014 (9), copyright Massachusetts Medical Society.
clinically staged as T2 (173, 177, 178). Good results from endoscopic therapy of T1b tumors with infiltration limited in the superficial one-third (SM1) have been reported (189) but other studies have reported alarmingly high rates of nodal metastases also in the SM1-category (160, 190) and generally surgery is recommended for the T1b-T2 category of tumors (9, 154, 156). Clinical T2 matches the pathological stages with modern methods in fewer than 17-27% of patients, and most likely the patients have higher stages (45-67%) than expected (191, 192). It is unclear, whether the survival benefit of induction therapy to cT2N0 patients outweighs the risk and costs associated with induction treatment and the practice is variable. According to the STS database, between 2002 and 2011 35.9% of patients with clinical T2 received neoadjuvant therapy (192), which is more than earlier reports indicate (193). In a randomized study, neoadjuvant therapy in stage I-II esophageal cancer was associated with adverse events with little or no survival benefit (194) and at present it is generally not recommended.

5.8.3 Locally advanced tumors (stage IIb - III)
Tumors staged as T3-T4a or with detected regional lymph node involvement, constitute locally advanced esophageal AC (48). In a large series of radical resections, adenocarcinomas with pT3 level infiltration are 81-83% likely to have lymph node metastases and in pT4 category 93%-100% have nodal disease (173, 177, 178). Therefore R0 resection with radical, at least two-field lymph node dissection is generally considered the best treatment (154). However, as nearly 60% of patients tend to develop distal or local recurrence within 2 years after surgery alone (169, 172, 173, 178) we have to resort to oncologic induction therapy to improve resectability, recurrence rate and survival. Theoretically chemotherapy should eliminate circulating malignant cells and radiotherapy improves the local control rate. Chemo- (CHT) and chemoradiotherapy (CRT) have been utilized for this purpose and several meta-analyses have been published with the most recent and important being from Gebski and Sjoquist (35, 36). Gebski et al. compared the results of 10 randomized trials of neoadjuvant CRT vs. surgery alone and 8 randomized trials of neoadjuvant chemotherapy vs. surgery alone in patients with locally resectable esophageal AC and epidermoid carcinoma. CHT gave the AC group significant survival benefits (HR for mortality 0.78 (0.64-0.95); p=0.014), whereas patients with epidermoid histology did not benefit. CRT was of benefit for both types of histology and the mortality HR was 0.75 (0.59-0.95; p=0.02) for adenocarcinoma. Sjoquist et al. updated the previously meta-analysis by including all 17 trials from the previous meta-analysis and seven further studies. The HR for all-cause mortality after neoadjuvant CHT in AC group was 0.83 (0.71-0.95);
p=0.01) and after CRT 0.75 (0.59-0.95; p=0.02). The HR for the overall indirect comparison of all-cause mortality for neoadjuvant CRT versus neoadjuvant chemotherapy was 0.88 (0.76-1.01; p=0.07). The latest randomized trial compared the outcome of CRT followed by surgery and surgery alone (168). The median overall survival rate was 49.4 months for the CRT and surgery group compared to 24 months for the surgery only group. Overall survival was significantly better in the CRT group [HR 0.657 (0.495-0.871; p=0.003)]. Overall, the evidence strongly supports the use of neoadjuvant therapy in patients with locally advanced esophageal AC. Meta-analyses suggest better response to CRT than CHT and CRT is utilized more widely. The variations in treatment protocols and practices are wide and therefore definite answers cannot be presently drawn for optimal neoadjuvant regimen. The role of postoperative adjuvant therapy in esophageal AC is unclear. A randomized trial by Cunningham et al. demonstrated a survival benefit of preoperative CHT and surgery as compared to surgery alone (195). Chemotherapy consisted of three preoperative and three postoperative cycles of intravenous epirubicin and cisplatin and a continuous intravenous infusion of fluorouracil for 21 days. There was a significant survival advantage to CHT + surgery group over the surgery only group. All the patients did not complete post-operative cycles of chemotherapy due to complications, side effects and disease progression and it was concluded it is impossible to evaluate the role of post-operative chemotherapy. However, many centers that administer neoadjuvant CHT, also continue postoperative cycles according to this protocol. In another trial, postoperative adjuvant therapy with paclitaxel and cisplatin improved 2-year survival as compared to historical controls suggesting there is some benefit (196). In a randomized trial by Macdonald et al., postoperative CRT improved survival significantly over a surgery only group in patients with AC of the stomach or ge-junction (197) and patients with gastric cancer are frequently offered postoperative CRT. Overall, postoperative therapy is problematic due to the poor condition of patients after resection, complications and the fact that not all patients are eligible for those treatments.

5.8.4 Metastatic disease (stage IV)

Treatment in stage IV disease is palliative as the expected survival despite treatment is less than 6 months (198, 199). The addition of chemo- or radiotherapy may prolong survival and also quality of life for up to 9 months if a response is achieved (200, 201). Palliative oncologic therapy should therefore be offered to patients with good general condition.
In symptomatic malignant obstruction of the esophagus, endoscopic interventions may be used. An easy and effective option is the insertion of self-expanding metallic stents (SEMS) (202). Stents are the most used option because of their rapid and easy placement and rapid relief of obstruction and they seem to produce the best long-term relief of dysphagia as compared to other local therapies such as laser, photodynamic therapy or brachytherapy (203). SEMS are however associated with re-occlusion due to food boluses, stent migration and tumor granulation tissue overgrowth is found in 20-55% of cases, and the technique has 45% morbidity and 9% mortality rates (204). Stent occlusion can be managed in most cases by combining balloon dilatation, endoscopic removal of food boluses, re-stenting and laser therapy (205). In cases with hemorrhaging tumors, radiotherapy may provide a more lasting effect, if tumor bleeding cannot be controlled by laser treatment or stenting (206). In cases where the stent cannot be placed, i.e. because of a difficult location, or the stent does not produce palliation dysphagia due to complications or loss of appetite, a percutaneous endoscopic gastrostomy (PEG) or surgically placed jejunal feeding tube can allow a secure route for enteral nutrition (207).

5.8.5 Operative techniques and complications
The traditional technique to achieve radical esophagectomy is a transthoracic (Figure 6) (208, 209) approach with upper midline laparotomy, right thoracotomy, and intrathoracal anastomosis (Ivor Lewis esophagectomy). Another common transthoracic operation is the McKeown approach, consisting of laparotomy, right thoracotomy and cervicotomy for neck anastomosis (210, 211). Also, the left thoracoabdominal approach may be used (212, 213). The transhiatal approach (214) (Figure 7) includes laparotomy, mediastinal dissection through the diaphragmatic hiatus and cervicotomy for a neck anastomosis. The recommended extent of resection margins is at least 5 cm in the distal stomach and at least 3 cm in the proximal esophagus and frozen section sampling of the margins during the operation is mandatory (173, 215-217). The extent of lymphadenectomy is more controversial. Two-field lymphadenectomy, i.e. dissection of nodes in the abdomen and chest from laparotomy and right thoracotomy, is the most common method (218). Three-field dissection includes cervical nodes along recurrent laryngeal nerves in addition to two-field dissection and it is most common in Japan, where squamous histology predominates (219, 220). In a randomized study between two- and three-field lymphadenectomy by Nishihara et al. (219), three-field dissection was associated with increased rates of complications without significant survival benefits. The thranshiatal approach has been criticized because all the thoracic nodes are not accessed. Meta-
analyzes (221) and also randomized studies (170, 171, 222, 223) have compared the results of different operation methods for esophageal cancer and no significant differences have been shown in overall survival for the various operation methods. Most commonly, reconstruction is done with the gastric tube pull-up and anastomosis is carried out at the carinal level or neck (218). Neck anastomosis is necessary in the transhiatal operation, but in the transthoracic approach either neck- or intrathoracic anastomosis can be done, with the outcomes being similar in both and the additional resection of the esophagus that must be done for cervical anastomosis does not seem to affect the outcome (224, 225). Colonic interposition is a secondary option used if the stomach cannot be used (226).

Surgery for esophageal cancer is complex and the risks for complications and mortality are high. For example, in American units with less than 10 esophagectomies per year, mortality can be as high as 20% and this decreases to less than 10% in units with more than 20 operations per year (32). In the 1950s, mortality was close to 30% and nowadays experienced units reach 2-5% mortality rates (227, 228). The main complications after esophagectomy are anastomotic leak with mediastinitis, respiratory failure and cardiovascular complications (229, 230). In a prospective cohort of the United States Department of Veterans Affairs database, 1777 patients undergoing esophagectomy had a perioperative mortality of 10% and overall morbidity of 50% (31). The most frequent complications were pneumonia (21%) and respiratory failure (16%). Transhiatal (TH) and transthoracic (TTE) operations were randomized in a study by Hulscher et al. (171). There was a nonsignificant trend for improved overall survival in the transthoracic group and less complications in the TH group with shorter median hospital (TH 15 days (4-63) vs TTE 19 days (7-154), p<0.001) and intensive care unit (ICU) stays (transhiatal 2 days (0-38) vs. transthoracic 6 days (0-79), p<0.001). In a later subgroup analysis of the same material (170), patients in the TTE group without involvement of the cardia, had significantly better long-term survival than corresponding patients in the TH group. The rate of respiratory complications was as high as 57% in the TTE group as compared to 27% in the TH group (p=0.001). Mortality (2% TH vs. 4% TTE) and anastomotic leaks (14% TH vs. 16% TTE) rates did not differ significantly.

Minimally invasive esophagectomy (MIE) is a novel method introduced by Cushieri 1992 (231) and further developed and popularized in experienced esophageal centers (232). Its aim is to reduce complications with the thoraco- and laparoscopic approach, while maintaining the radical nature of transthoracic Ivor-Lewis /Mckeown esophagectomy (OE). MIE encompasses a variety of methods ranging from total thoraco-laparoscopic resection and combinations of thoratomy/laparoscopy,
Laparotomy/thoracoscopy, laparoscopic transhiatal to robotic assisted resections (233). Luketich et al. (232) have published a retrospective series of 1000 consecutive totally thoraco-laparoscopic MIE’s, with a median stay in ICU of 2 days (1–3), hospital stay of 8 days (6–14), and 30-day operative mortality of 1.7%. Meta-Analyses of retrospective studies, mostly single center cohorts, demonstrate similar outcome as compared to OE with two-field lymph node dissection. Generally, in MIE patients, hospital stay is shorter, blood loss is less and there are fewer pulmonary complications (43-45, 234). Dantoc et al. (235) analyzed oncologic outcomes in 16 comparative studies (MIE vs. OE), and the rate of R0 resections, the amount of retrieved lymph nodes and short-term survival seem to be equivalent. Biere et al. (46) have published the so far only randomized study comparing MIE to OE, with primary end point respiratory complications. The hospital length of stay was shorter in patients who underwent MIE (11 vs. 14 days), and there were fewer pulmonary infections in the MIE group (9% within 2 weeks of MIE vs. 29% after OE). The rates of leaks (7% OE vs. 12% MIE) and in-hospital mortality (2% for OE and 3% for MIE) did not differ. Luketich et al. (40) published the results of a prospective non-randomized multicenter study evaluating the feasibility of MIE in a multicenter setting. The protocol operation was completed in 95 of 104 patients with 2.1% perioperative mortality, an 11.4% rate of leak, a 5% rate of pneumonia, a 5.7% rate of ARDS level respiratory failure and 61% total rate of complications. Median ICU stay was 2 days and median total hospital stay was 9 days. At the three-year follow up, 58.4% of patients were alive. Overall, the feasibility of MIE in high-volume experienced centers has been successfully demonstrated and short-term oncologic results seem comparable to open esophagectomy.

The selection of optimal treatment requires an exhaustive workup to determine the correct stage and subsequent treatment. The patient's ability to tolerate both neoadjuvant treatment and radical esophagectomy should be evaluated. The experience of the surgical team and also the institution's tradition in esophageal surgery are important determinants of optimal outcome regardless of the approach used. For example, MIE requires that surgical teams have extensive experience in minimally invasive surgery and preferably training in a high volume center before starting a program.
Figure 6. Transthoracic approach to esophagectomy. Reproduced with permission from Kitajima et al. NEJM 2002 (236), copyright Massachusetts Medical Society.
Figure 7. Transhiatal approach to esophagectomy. Reproduced with permission from Kitajima et al. NEJM 2002 (236), copyright Massachusetts Medical Society.
6 AIMS OF THE PRESENT STUDY

I To evaluate the presence of oxidative stress in proximal gastric mucosa, in patients with Barrett’s esophagus and/or esophageal adenocarcinoma.

II To evaluate the long term prognosis and causes of death of patients with early stage esophageal adenocarcinoma.

III To evaluate the accuracy of FDG-PET-CT in predicting survival and response to neoadjuvant chemotherapy in patients with locally advanced esophageal adenocarcinoma.

IV To compare surgical and oncological outcomes of minimally invasive and open esophagectomy in the treatment of locally advanced esophageal adenocarcinoma.
7 PATIENTS AND METHODS

7.1 Patients
Study I included 57 patients treated at Helsinki University Hospital. Nine samples were from patients with only BE, nine from patients with esophageal AC and 24 had both BE and esophageal AC. The control group consisted of 15 patients with healthy esophagi and stomachs as assessed by endoscopic examination. Study patients records were evaluated to obtain their HPI histories.

Study II included 85 patients operated on for superficial esophageal AC during 1984-2011, at the Department of General Thoracic and Esophageal Surgery at Helsinki University Hospital in Finland, at the Department of General and Abdominal Surgery at the University Medical Center, Mainz, Germany, and at the Division of Gastroenterologic Surgery at Tampere University Hospital in Finland. Pathology reports and medical records of the patients were evaluated and pathology samples re-evaluated. Cause-of-death data were acquired from the Finnish and German national death registries.

Study III included 66 patients operated on for locally advanced esophageal AC and treated preoperatively with neoadjuvant chemotherapy, at the department of General Thoracic and Esophageal Surgery at Helsinki University Central Hospital between 2005-2011. The patients were consecutively staged with FDG-PET-CT before and after neoadjuvant chemotherapy in addition to normal staging procedures.

Study IV included 153 patients undergoing surgery for locally advanced esophageal adenocarcinoma between 2003 and 2013. Of these, 74 were minimally invasive esophagectomies and 79 open transthoracic esophagectomies. The types of data assessed were oncologic, intraoperative, and postoperative.

7.2 Methods
7.2.1. Tissue sample collection
In study I, samples were acquired during endoscopy from BE follow-up patients and pre-treatment endoscopy of esophageal AC patients, or from a resected specimen during the operation (11 of esophageal AC samples). During endoscopy the most obvious area of pathology was sampled with biopsy forceps and if present, both tumor and metaplastic mucosa were sampled. Proximal gastric mucosal samples were taken 5 cm below the top of proximal gastric folds to gain gastric mucosal
samples of the cardiac region (56), instead of junctional or esophageal tissue. In the control patients, squamous epithelium samples were taken 5 cm above the gastroesophageal junction and proximal gastric mucosal samples were taken as in study group. All the samples were immediately frozen and stored at -70 Celsius and were later on sent for analysis.

7.2.2. Biochemical analysis of collected samples
Biochemical analyzes were carried out with commercial kits at Turku University Institution of Biochemical Sciences. 8-Isoprostanes were determined by STAT-8-Isoprostane EIA Kit (Cayman Chemical, Ann Arbor, MI, USA). Glutathione reduced form (GSH) and glutathione oxidized form (GSSG) were measured by Glutathione Assay Kit by Cayman Chemical. 8-OH-deoxyguanosine was measured by the OxiSelectTM Oxidative DNA Damage ELISA Kit (8-OHdG) (Cell Biolabs, Inc., San Diego, CA, USA).

7.2.3. Histopathologic analysis
In studies II & III, pathology slides from the original operations were acquired and re-analyzed by an experienced gastropathologist. In study II, the depth of infiltration of the tumor was re-evaluated and re-classified by dividing both the mucosa and submucosa into three layers (m1-3 & sm1-3) (186). In study III, resected specimen slides were evaluated for the presence of viable cancer cells and the response was graded according to the histomorphologic regression grading system of Schneider et al. (179). Tumor bed specimens were classified as grades I to IV, grade I meaning more than 50% living tumor cells in the tumor bed, grade II, 10% to 50% living tumor cells, grade III, less than 10% and grade IV, no living tumor cells. Grades III to IV were classified as histopathologic responders and grade I to II as the non-responder group.

7.2.4 Staging
Staging of patients in studies II-IV included OEGD, an iv-contrasted spiral CT-scan of the thorax, abdomen, and pelvis (3–5 mm slice thickness), EUS, and FDG-PET-CT. PET was done before and after induction therapy.

7.2.5 Positron emission tomography imaging of neoadjuvant therapy response
Patients in study III were scanned with a dedicated whole-body scanner at Helsinki University Central Hospital, and three patients at the Turku PET Centre. We determined their heights and
weights and measured the serum glucose levels of diabetic patients. The dose of FDG was 5 MBq/kg body weight and the scan started one hour after the FDG injection. Standardized uptake values (SUV) were determined with a small fixed-dimension region of interest (ROI), 8 mm in diameter; and the value was determined using the highest activity inside this area. SUV values were calculated accordingly after correction for radioactive decay. The SUV of the primary tumor was determined at the baseline and after therapy. A second PET scan was done within one month after the last cycle of chemotherapy. The maximal SUV of the pretreatment scan was labeled SUV1, and the post-treatment scan SUV2. The change percentage (SUVΔ%) was expressed as \( [(\text{SUV1} - \text{SUV2})/\text{SUV1}] \times 100 \).

### 7.2.6 Neoadjuvant therapy

Patients in studies III and IV were preoperatively treated with neoadjuvant chemotherapy, according to the protocol published by Cunningham et al. (195). In study III, 53 patients received epirubicin-oxaliplatin-cabecitabine (EOX), four received epirubicin-cisplatin-fluorouracil, and nine, a docetaxel-cisplatin-fluorouracil combination. In study IV 78% of the patients in the open esophagectomy group received neoadjuvant therapy, and of these 62% had chemotherapy and 15% radiochemotherapy. In the minimally invasive group, 82% of patients had neoadjuvant therapy and of these, 74% was chemotherapy and 4% chemoradiotherapy. In study IV, since 2007, eligible patients have been treated with epirubicin-oxaliplatin-capecitabine neoadjuvant chemotherapy. Prior to this, selected patients received various types of chemotherapy or chemoradiotherapy. Chemoradiotherapy consisted of platin- and 5-fluorouracil-based therapy over 5–6 weeks, followed by a 45-gy total dose of radiation to the tumor and regional nodes.

### 7.2.7 Surgical methods

In our institution, the routine approach to esophageal AC has been two-field lymphadenectomy done from laparotomy and right posterolateral thoracotomy or laparoscopy and right thoracoscopy. Earlier, in selected cases, transhiatal resection was carried out. Some of patients in study II were operated on in Mainz, Germany, and most resections were transhiatal.

Two-field resection for AC of the distal esophagus and/or gastric cardia, included resection of the proximal stomach with a 10 cm margin to the tumor and the distal esophagus at the level of tracheal carina. The proximal resection margin is checked to be at least 5 cm if possible, and confirmed with a frozen section. Adjacent tissues and lymph nodes are removed en bloc with the specimen, from the superior border of pancreas to the carina. The lymph nodes are resected along the splenic
artery, along the celiac artery, nodes associated with the left gastric artery and nodes in the \textit{parahiatal and -esophageal areas}. The rim of the hiatal muscle, both pulmonary ligaments, mediastinal pleura and thoracic duct are included in the specimen. In minimally invasive esophagectomy, exactly the same resection is done, except that the thoracic duct is usually spared. The thoracic part of the resection is done in the left lateral decubitus position with one-lung ventilation in both the minimally invasive and open approaches. Reconstruction is done with a gastric tube created with a stapling device. Esophagogastric anastomosis was done mainly intrathoracally in both groups, stapled anastomosis with a DST™ EEA™ circular 25-28 mm stapler (Covidien, Mansfield, MA), and hand-sewn anastomosis in two layers with absorbable 4-0 sutures (PDS). In the transhiatal technique, the thoracic cavity was not entered and after abdominal dissection, the esophagus was bluntly removed through a diaphragmatic hiatus and a hand-sewn anastomosis was constructed from a left-sided neck incision.

In study II, there were 5 patients whose tumors were resected endoscopically due to comorbid conditions precluding surgery. Mucosal resection was carried out by lifting the mucosa with a suction cap and rubber band ligature, the lifted mucosa was resected with a diathermy snare (184). Endoscopic procedures were carried out under deep sedation supervised by an anesthesiologist.

7.2.8 Statistical methods

The rarity of esophageal cancer limits possibilities for randomization and prospective trials. Therefore the data used in these studies is retrospective. In all studies, values were expressed as medians with ranges, or means with standard deviations. All \( p \)-values were based on two-tailed tests and significance was set at <0.05. In study I, comparisons of medians and distributions across groups were compared with the Mann Whitney U-test. In study II, III and IV, comparisons of categorical variables were done with the chi-square test, and for continuous variables the Kruskal–Wallis, Mann Whitney U, or independent samples median-test were used. Survival rates were estimated according to Kaplan–Meier. Statistical comparisons of survival between groups of patients were performed with a log-rank test, and multivariate survival analysis by the Cox proportional hazards model. Overall, disease-specific, and recurrence-free survival rates were calculated from the date of operation and in study IV, from the start of neoadjuvant treatment. The endpoint was defined as death from any cause for overall survival, as cancer-related death for disease-specific survival, and local or distal recurrence for recurrence-free survival. In study IV, the diagnostic accuracy of FDG-PET-CT was calculated by the receiver operating characteristics (ROC) test.
8 RESULTS

8.1 Study I
The results are presented in Figure 8. A marker of lipid peroxidation, 8-IP, was present in proximal stomach of patients with esophageal AC and / or BE (study group), and its content was significantly higher than in proximal gastric folds of control patients (p=0.039). Similarly, the amount of a marker for oxidative DNA damage, 8-OHdG, was significantly higher in the proximal gastric folds of the study than the control group (p=0.008). An antioxidant buffer in the form of GSH, was present in a significantly smaller concentration in the proximal stomachs of the study - than the control group (p=0.031). The concentration of GSSG in the proximal stomach of the study and control groups did not differ with any statistical significance. The amounts of 8-IP and 8-OHdG were significantly higher and GSH significantly lower when comparing the study group samples of BE mucosa and tumor, to the control patients- samples above the ge-junction. HPI was present in 8% of the study group and in none of the control patients.
Figure 8. Comparisons of 8-isoprostane (8-IP), 8-OH-deoxyguanosine (8-OHdG), oxidized glutathione (GSH) and the reduced form (GSSG) levels between the study and control groups. Mann Whitney U test.
8.2 Study II

In the histopathological reclassification, the disease was intramucosal in 35 (44%), and submucosal in 44 (56%) of the patients. The rate of lymph node metastases (LNM) was 3% in intramucosal tumors, 9% in submucosal SM1-tumors, 20% in the SM2-3 layer. Of 35 T1a patients, 13 (37%) had an en bloc transthoracic esophagectomy, 15 (43%) transhiatal esophagectomy, 4 (11%) vagal sparing esophagectomy and 3 (9%) EMR. Of the 44 T1b patients, 20 (45%) had an en bloc transthoracic esophagectomy, 21 (47%) had transhiatal, 2 (5%) patients had EMR and one (2%) had a vagal sparing esophagectomy.

The median follow-up was 5 years (range 0–26 years). Overall survival probability was 67% at 5 years and 50% at 10 years (Figure 9a). The disease-specific survival probability was 82% at 5 years and 78% at 10 years (Figure 9b). At 5 years of follow-up, 80% were recurrence free with no new recurrences after 5 years of follow-up.

The in-hospital mortality from postoperative complications was 4 patients (5%). Mortality due to recurrent disease was 15 (18%) patients, 5 (6%) another primary malignancy, and 11 (13%) of non-cancer-related causes. The cause of death for 2 (2%) is unknown.

The overall risk for recurrence of SEAC was 18%. Recurrence risk was 9% for intramucosal and 27% for submucosal SEAC. In univariate and multivariate analyses, regional lymph node metastases were significantly associated with poor survival for overall, disease-specific and recurrence free survival. Disease-specific and recurrence-free survivals were also significantly affected by depth of infiltration in both uni- and multivariate analyses.
8.3 Study III

The change of maximal SUV (SUVΔ%) between sequential PET scans before and after neoadjuvant therapy was significantly (p<0.0001) more prominent in histopathologic responders than in non-responders. A decrease of 67% in maximal SUV was the optimal cut-off value differentiating between histopathologic responders and non-responders, giving a sensitivity of 79% and specificity of 75%. If a lower cut-off of 35% was used, a sensitivity of 100% and specificity of 33% were reached. Total loss of uptake in second scan, did not equal complete histopathologic response.

Median follow-up was 16 months (range 4–72). Overall survival was 59% and disease-free survival 50% at three years after the start of neoadjuvant therapy. For the univariate Cox regression proportional hazards regression test (Figure 10), the SUVΔ% of 67% and histopathologic response were both associated with improved recurrence free time. When SUVΔ% was used as a continuous variable, it is an independent predictor of both overall and disease-free survival in the Cox multivariate model. In 8 patients there was no regression in maximal SUV of the primary tumor, or the second scan showed increased activity. In these patients AC recurrence was detected within one year after beginning the treatment.
8.4 Study IV

Comparing surgical outcomes between OE and MIE, the overall complication rate was also similar (60% for OE and 50% for MIE, p=0.181). The rates of the most important complications - anastomotic leak, conduit necrosis, pneumonia, respiratory failure and re-operations did not differ with any significance. Blood loss during surgery was significantly less for MIE (OE 800 (110–4,000) ml vs. MIE 300 (50–3,000) ml, p<0.0001). ICU stay did not differ, but the median for overall length of hospital stay was less for MIE (14 (9–63) days with OE and 13 (6–87) days with MIE, p=0.040).

The median for follow-up after surgery was 28 (0–116) months. In the OE group, 61% of the patients were followed for under, and 39% for over three years, with 31% for over 5 years. In the MIE group, 75% of patients were followed for under, and 24% for over three years. Only 4% have reached the 5-year follow up in the MIE group. There were no significant differences in overall 3- (OE 49% vs. MIE 64%) or 5-year (OE 41% vs. MIE 56%) survival rates (p=0.321). Recurrence-free survival for 3 years was 53% for OE and 57% for MIE (p=0.911). The rate of R1 resection in the OE group was 2 versus 1% in the MIE group (p=0.522). The median for harvested nodes was less in the MIE group, 20 (4–49) than in the OE group, 22 (8–58), (p=0.021). Overall, male gender and pathological stage over 2B remained significant for overall survival in the multivariate COX model, and therefore these
variables are independent predictors. The multivariate model showed that type of operation did not affect survival.
9 DISCUSSION

9.1 Pathogenesis
In study I, we were able to show OS, oxidative DNA damage and antioxidative capacity reduction in the proximal stomachs, in the BE mucosa and the AC tissue of the study group as compared to the healthy controls. The most common cause of cardiac and proximal stomach mucosa inflammation is known to be HPI, but its presence is known to reduce the risk of esophageal AC (29, 49, 117, 118, 237). Similarly, in our study, only 8% of study patients had a previous history of HPI. A group of patients with carditis, which is not associated with HPI, but is strongly correlated with GERD and erosive esophagitis, is known to exist (28). In our study group, patients also had BE and esophageal AC, which are known to be GERD related. Therefore, it may be that inflammation and OS in the cardiac region are also connected to GERD related esophagitis. Another cause of gastric inflammation is duodenogastric reflux, which is known to cause gastritis in patients with partial gastrectomy (238). Overall it is likely that gastroduodenal contents cause injury not only to the esophageal mucosa, but they may also directly injure the proximal stomachs mucosa causing chronic inflammation and OS.

OS is a result of imbalance of oxygen metabolism as a result of chronic inflammation and it has been suggested to be associated with pathogenesis of esophageal AC (23-26) and other gastrointestinal tract malignancies (87-89). Our results further strengthen the role of gastroduodenal content related inflammation and oxidative damage behind pathogenetic processes ultimately leading to esophageal AC. This also may further clarify the pathogenesis of AC within the cardiac region.

9.2 Prognosis
In study II, the most frequent cause of death was recurrent cancer within 5 years of follow-up and after that, causes of death related to aging dominated. No new recurrence was detected after five years of follow-up, which is in line with the literature (239-241). Overall survival was 67% at 5 years and 50% at 10 years, which is comparable to previously published series (160, 161, 163, 165, 166, 242, 243). The presence of regional lymph node metastases was independently associated with overall, disease-specific and recurrence-free survival in the multivariate Cox model. In the same analysis, the depth of tumor infiltration was independently associated with recurrence and disease...
specific survival. These are also in line with what has been previously published for lymph node metastases (173, 175-177) and depth of tumor infiltration (177, 178).

In study III, the overall survival of patients with locally advanced disease and the multimodality approach, was 57% at three years after surgery and 50% of the patients were disease free at three years. In study IV, three-year survival was 49% for the OE and 64% for MIE groups and at five years, survival was 41% for the open- and 56% for the minimally invasive approach. The survival of patients with locally advanced AC of the esophagus is reported to be 15-35% at 5 years after surgical therapy (9, 172) and the best series report survival to be up to 50% after multimodality therapy (39, 168-171), which compares well with our results. In study III, metabolic response (decrease of metabolic activity between PET scans before and after neoadjuvant chemotherapy) was the strongest prognosticator of recurrence and overall survival. A histopathologic response and a pathologic stage $<2B$ (48) predicted recurrence in the univariate model. In the literature, histopathologic response and lymph node metastases are the strongest predictors of survival after multimodality treatment (37, 179, 180). In our study, the small number of patients may limit the accuracy of statistics and most studies using PET in response evaluation have been done after chemoradiotherapy, thus they are not directly comparable due to post radiation inflammation disturbing the second PET scan (146, 147, 151-153). However, after neoadjuvant chemotherapy, the results are similar to ours regarding prediction of survival after treatment (38, 41, 149, 150).

9.3 Staging

Neoadjuvant therapy has improved the prognosis of patients with locally advanced esophageal AC (35, 36). Patients with complete eradication of malignant cells from the surgical specimen after neoadjuvant chemo- or chemoradiotherapy may have excellent 5-year survival rates (37, 179, 180). In study III, we evaluated the accuracy of FDG-PET-CT in the prediction of histopathologic regression of esophageal AC. A decrease of 67% of metabolic activity between PET scans before and after neoadjuvant chemotherapy predicted histopathologic regression with a sensitivity of 79% and specificity of 75%. With a lower cut-off of 35%, a sensitivity of 100% and specificity of 33% was reached, this result is similar to those previously published (41, 149, 150, 244). Overall, accuracy of FDG-PET-CT in predicting response and survival seems insufficient to justify withdrawal from surgery based on degree of treatment response only. If primary tumor metabolic activity did not decrease, or increased after neoadjuvant therapy, the prognosis was poor – disease recurrence was detected
within one year of beginning treatment. This information could be useful in decision-making, especially in patients with borderline general condition for radical esophagectomy.

9.4 Treatment

9.4.1 Stage 0-Ia

Surgical treatment of esophageal cancer is associated with substantial morbidity and also mortality, especially in lower volume centers (31, 32). In superficial esophageal AC, treatment has shifted from radical resection to endoscopic ablation. Recent guidelines suggest endoscopic ablation for patients with HGD and intramucosal (pT1a), when lesion size is <20 mm, the lesion is well or moderately differentiated and no lymphovascular infiltration is present (33, 245, 246). In study II we evaluated prognosis and risk for recurrence in early esophageal AC (pT1a and pT1b) after surgical resection. Overall survival was mainly affected by causes related to aging in the long-term (>5 year) follow-up and 80% patients were recurrence free at 5 years. The risk for recurrence in patients with T1a AC was 9%, which was higher than previously published 0-3% (190, 239, 240, 247). This could be explained by staging bias, as lymph node metastases may have been missed. For example, in transhiatal esophagectomy, no formal lymph node dissection is done intrathoracally. Also, the staging for early esophageal AC requires the skills of specialist pathologists because differentiating between T1a and T1b may be difficult. In a meta-analysis, long-term survival in the treatment of early esophageal cancer and high-grade dysplasia does not seem to differ (167). Also, RFA in addition to EMR afford us simple and reproducible means for the eradication of associated BE mucosa (242). Therefore, especially in patients with HGD, the aim should be for endoscopic eradication to avoid substantial morbidity and risk for mortality associated with esophagectomy. The individualized approach should be emphasized in intramucosal cancer. If significant risk factors for recurrence are present the aim should be for surgery in eligible patients and in patients with high risk for surgery, the aim should be for endoscopic ablation.

9.4.2 Stage Ib-III

In patients with submucosal AC, the overall risk of lymph node metastases was 20% in sm2-3 and overall risk for recurrence 27%, results in accordance with previously published results (160, 173, 178, 187, 188, 242). With higher risks for metastasis and recurrence, radical surgery is recommended generally (9, 33, 248). A German group (189) reported favorable long-term survival after mucosal resection of submucosal esophageal AC, in a group with sm1 level infiltration, well to
moderate differentiation and no lymphovascular infiltration. If low risk patients can be reliably identified by pathologists, endoscopic ablation may be a viable alternative for patients, even for those in the superficial pT1b category, at high risk of not undergoing successful surgery.

MIE has been developed to decrease the rate of pulmonary complications after traditional OE (231, 232). In study IV, we compared the perioperative and oncologic results of OE and MIE following esophageal resection, for locally advanced esophageal AC after neoadjuvant chemotherapy. One-month mortality rates and also three-month mortality rates were both low, as compared to series from high volume centers (31, 42, 46, 170) and they did not differ from each other with any significance. The anastomotic leak rates and rates of respiratory complications did not differ and the overall rates of complications were similar. Statistical difference was seen in intraoperative bleeding and total hospital stay in favor of the minimally invasive approach. Less pulmonary complications, less operative bleeding, a shorter hospital time for MIE, and similar rates of anastomotic leaks between the OE and MIE approaches are reported in meta-analyses (43-45, 234) and a recent randomized trial (46). These results are in line with ours. In our study, the rate of R0 resections was the same and short-term (three-year) survival did not differ with any significance. The number of retrieved lymph nodes was higher for open esophagectomy, but for MIE, the median of retrieved nodes was 20, a result similar to reports from meta-analyses (234, 235). The incidence of late complications did not differ between the OE and MIE approaches.

Overall, MIE appears to be comparable to traditional OE when comparing postoperative results and it achieves the same oncologic radicality with comparable short-term survival rates. Our series also includes the learning curve for a new, very demanding technique, and our results should be expected to be even better in future. Surgery and treatment for esophageal cancer overall, is complex and requires an experienced multidisciplinary team. Treatment options range from endoscopic therapies to different surgical resections. The surgical team should be able to handle all methods and tailor treatments to match their patients’ reserves.
10 CONCLUSIONS

1. In proximal gastric mucosa of patients with Barrett’s esophagus and esophageal adenocarcinoma, elevated oxidative stress, increased oxidative DNA damage and depleted antioxidative buffer concentrations can be measured.

2. In early esophageal adenocarcinoma, half of the patients were alive 10 year after the operation. Cancer recurrence was the most common cause of death during the 5-year follow-up, and after that, diseases related to aging.

3. The accuracy of FDG-PET-CT was not good enough to guide clinical decision-making, based on this modality alone. An over 67% decrease in the metabolic activity of the primary tumor was associated with a 4-fold decrease in the risk death due to esophageal adenocarcinoma.

4. As compared to open esophagectomy, minimally invasive esophagectomy shortens overall stay in hospital and is associated with less blood loss during the operation. The rates of complications or re-operations do not differ with any significance. The oncologic results are also comparable, as the rates of complete resection and 3-year survival are similar.

Tämän tutkimuksen tavoitteena oli 1) selvittää oksidatiivisen stressin merkitystä mahalaukun alkuosassa Barrett’n ruokatorven ja ruokatorven adenokarsinooman synnyssä, 2) arvioida varhaisvaiheen ruokatorven adenokarsinooman pitkääikaisennusteta ja potilaiden kuolinsyitä, 3) arvioida kuinka 18F-fluorodeoksi-D-glukoosi-positroniemissiotomografia liitetynä tietokonetomografiaan (FDG-PET-CT) ennustaa kemoterapijan vastetta ruokatorven adenokarsinooman hoidossa ja 4) verrata mini-invasiivisen radikaalileikauksen tuloksia avoimeen ruokatorven syövän leikkaukseen.

paikallisesti levinnytä ruokatorven adenokarsinoomaa. Tutkimuksessa verrattiin leikkausen jälkeistä kolesterolisuutta, komplikaatioita, leikkauskseen onkologista radikaliteettia sekä ennustetta.

lyhentävän hoitoaikaa. Se on kuitenkin teknisesti vaativampi ja edellyttää riittävää potilasmäärää ja kokemusta jotta etu avokirurgiaan nähden saavutetaan.
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