ADENOCARCINOMA OF THE ESOPHAGUS AND ESOPHAGOGASTRIC JUNCTION

STUDIES ON EPIDEMIOLOGY, PATHOGENESIS AND TREATMENT

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Academic Dissertation

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1 ABBREVIATIONS

COX	cyclooxygenase
CT	computed tomography
EG	esophagogastric
EN4	endothelium-specific antibody (anti-CD31)
EUR	euro
EUS	endoscopic ultrasonography
FCR	Finnish Cancer Registry
FGF	fibroblast growth factor
GERD	gastroesophageal reflux disease
GSH	glutathione
HGD	high-grade dysplasia
HRP	horse-radish peroxidase
ICDO	International Classification of Diseases for Oncology
LES	lower esophageal sphincter
M	mucosa
MMP	matrix metalloproteinase
MP	myeloperoxidase
Nd:YAG	neodymium: yttrium-aluminum-garnet
NOS	nitric oxide synthase
PAL-E	endothelium-specific antibody (recognizes an undefined endothelium-specific antigen)
PBS	phosphate-buffered saline
PET	positron emission tomography
SD	standard deviation
SEM	standard error of mean
SEMS	self-expanding metallic stent
SM	submucosa
SMA	smooth muscle cell actin
SOD	superoxide dismutase
TGF	transforming growth factor
TLC	thin-layer chromatography
TNM	tumor node metastase
UICC	Union International Contre le Cancer
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

2 LIST OF ORIGINAL PUBLICATIONS

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

I Sihvo Eero I.T., Salminen Jukka T., Rämö O. Juhani and Salo Jarmo A. The epidemiology of oesophageal adenocarcinoma: Has the Cancer of Gastric Cardia an Influence on the Rising Incidence of Oesophageal Adenocarcinoma? Scand J Gastroenterol 2000; 10:1082-1086.

II Sihvo Eero I.T., Salminen Jukka T., Rantanen Tuomo K., Rämö O. Juhani, Ahotupa Markku, Färkkilä Martti, Auvinen Merja I., Salo Jarmo A. Oxidative Stress has a Role in Malignant Transformation in Barrett's Esophagus. Int J Cancer (in press).

III Auvinen M.I., Sihvo E.I.T., Ruohtula T., Salminen J.T., Koivistoinen A., Siivola P., Rönnholm R., Rämö O.J., Bergman M., Salo J.A. Incipient angiogenesis in Barrett's epithelium, and lymphangiogenesis in Barrett's adenocarcinoma. J Clin Oncol 2002;20:2971-9.

IV Sihvo E.I.T., Luostarinen M.E., Rämö O.J. and Salo J.A. Fate of the patients with adenocarcinoma of the esophagus and esophagogastric junction: a population-based analysis with special reference to different treatment modalities. (Submitted).

V Sihvo Eero I.T., Pentikäinen Tuomo J., Luostarinen Markku E., Rämö O. Juhani and Salo Jarmo A. Inoperable adenocarcinoma of the oesophagogastric junction: A comparative clinical study of laser coagulation versus self-expanding metallic stents with special reference to cost analysis. Eur J Surg Oncol (in press).

3 ABSTRACT

Background

One of the most lethal malignancies, with less than 5% of patients surviving in the long term, has been adenocarcinoma near the esophagogastric (EG) junction. Esophageal adenocarcinoma is a complication of gastroesophageal reflux disease (GERD) and arises from Barrett's mucosa. Although the esophagitis-metaplasia-dysplasia-adenocarcinoma sequence in Barrett's mucosa is well recognized, the pathomechanism in this malignant transformations is not well defined.

The aim of the present study was to evaluate 1) changes in the incidence of adenocarcinoma of the esophagus and gastric cardia in Finland, 2) the role of oxidative stress and radical scavenger capacity in the pathogenesis and malignant transformation of Barrett's esophagus, 3) the extent of angiogenesis and lymphangiogenesis in Barrett's esophagus and related malignancies, 4) the fate of patients with adenocarcinoma near the EG junction, and to compare 5) the results of different types of therapeutic procedures in the treatment of these adenocarcinomas.

Patients and methods

The Finnish Cancer Registry provided the primary data for Studies I and IV. In Study I, the trends in adenocarcinoma of the esophagus and gastric cardia were evaluated in Finland during the 20-year period of 1976 to 1995; in Study IV, the outcome of all 402 patients treated between 1990 and 1998 in two Finnish health-care districts with a population of 1 750 000 was analyzed.

In Study II, parameters of oxidative metabolism (myeloperoxidase, MP; glutathione, GSH; superoxide dismutase, SOD), and DNA adducts were measured to discover the role of oxidative stress and radical scavenger capacity in the pathogenesis and malignant transformation of Barrett's esophagus. Mucosal specimens were taken from 52 patients in six groups: symptomatic GERD without and with endoscopic esophagitis, Barrett's metaplastic epithelium without dysplasia, Barrett's epithelium with dysplasia, adenocarcinoma in the esophagus/esophagogastric junction, and control group.

For Study III, an immunohistochemical whole-mount section technique was set up to show expression of well-established angiogenic

molecules during development of Barrett's adenocarcinoma. Mucosa samples were collected from 15 surgically resected dysplasia and carcinoma patients.

In Study V, the relative lifetime costs and clinical results of the Nd:YAG laser were compared to those of self-expanding metallic stents (SEMS) as alternative forms of primary palliation of dysphagia for adenocarcinoma near the EG junction. In this retrospective analysis, 32 patients had been treated with laser therapy and 20 with SEMS.

Results

The incidence of esophageal adenocarcinoma increased significantly in Finland only in men (almost 300%). In neither sex did the incidence of the cancer of gastric cardia change. The combined incidence rate of these adenocarcinomas in men increased steadily, but this increase was not as dramatic as in esophageal adenocarcinoma.

The esophagitis-metaplasia-dysplasia-adenocarcinoma sequence of Barrett's esophagus revealed simultaneous formation of DNA adducts, increased oxidative stress (increased MP activity), and decreased antioxidant capacity (decreased GSH content). This sequence was also characterized by on increasing percentage of immature blood vessels. Barrett's esophagus was already strongly neovascularized. This metaplastic epithelium expressed high levels of vascular endothelial growth factor A and its receptor. Matrix metalloproteinases were also expressed along the lining of the new blood vessels. In addition, we showed 3-dimensional evidence that the rich new vascular bed is already highly abnormal in non-malignant Barrett's epithelium and in adenocarcinoma; the structure of lymphatics was loose in dysplasia and cancer. Furthermore, adenocarcinoma overexpressed lymphangiogenic growth factor and its receptor.

Overall, prognosis of these patients was still poor, with only 12.5% surviving more than 5 years. Surgical resection offered the best chance for a cure with a 5-year survival rate of 29.0%. Less than one percent of the patients treated with other methods were alive at 5 years. On the other hand, half the adenocarcinoma patients who were eligible for major surgery with 2-field lymphadenectomy had a chance to survive in the long term (50% 5-year survival). Laser therapy palliated dysphagia effectively with lower morbidity and mortality rates than did the use of self-expanding metallic stents, and without increased costs or hospital stays.

Conclusion

Though the increase in incidence of esophageal adenocarcinoma in Finnish men has seemed highly significant, the combined incidence of cancers of the EG junction shows only a slight increase, comparable to that of other cancers which are increasing.

Simultaneous formation of DNA adducts, increased oxidative stress, and decreased antioxidant capacity indicates the important role of oxidative stress in the pathogenesis and malignant transformation of Barrett's epithelium. In early stages of this process, the angioarchitecture is already abnormal. High expression of vascular endothelial growth factor and its receptor, and of matrix metalloproteinases suggests their important role in angiogenesis in Barrett's epithelium and related adenocarcinoma. In addition, tumor lymphangiogenesis may be an important phenomenon for the frequent lymph node metastasis formation found in esophageal adenocarcinoma.

Although overall prognosis for adenocarcinoma near the EG junction is poor, a substantial percentage of patients eligible for major surgery achieve long-term survival. In palliation, laser therapy relieves dysphagia of these patients effectively without increased costs or hospital stays and with lower morbidity and mortality rates than for self-expanding metallic stents.

4 INTRODUCTION

In several countries, the incidence of adenocarcinoma in the esophagus and gastric cardia, especially in men, has increased (Powell and McConkey 1990, Blot et al. 1991, Hansson et al. 1993, Hansen et al. 1997, Lord et al. 1998). The rate of increase in the USA has surpassed that of any other cancer type (Blot et al. 1991). The reason for this increase is unknown. Problems in the classification and coding of the primary site create difficulties in the analysis of the occurrence of cancers located near the esophagogastric junction. In addition, the definition of gastric cardia in the literature is inconsistent (Appelman 1998, Spechler 2001). The gradual transfer of the name "cancer of gastric cardia" to "esophageal adenocarcinoma" in coding may therefore explain these rising incidence rates for esophageal adenocarcinoma (Hansen et al. 1997).

A strong epidemiological association exists between esophageal adenocarcinoma and gastroesophageal reflux disease (Lagergren et al. 1999a). A complication of gastroesophageal reflux disease is Barrett's esophagus, the most important risk factor for esophageal adenocarcinoma. Though the high risk for esophageal adenocarcinoma associated with this specialized intestinal metaplasia has recently been questioned, the risk may be up 30 to 125 times as great as in the general population (Cameron et al. 1985, Hameeteman et al. 1989). The presence of dysplasia, especially high-grade dysplasia (HGD), length, large hiatal hernia, and the presence of Barrett's ulcer are features which have predicted the development of adenocarcinoma in Barrett's epithelium (Iftikhar et al. 1992, Dees et al. 1996, Weston et al. 1999). Although the major factor contributing to this metaplasia seems to be the synergistic action of acid, pepsin, and duodenogastoesophaeal reflux, and a direct morphological sequence from metaplasia via dysplasia to adenocarcinoma is recognizable, the exact pathomechanism of this malignant transformation is unknown (Hameeteman et al. 1989, Vaezi and Richter 1996, Öberg et al. 2000).

Cancer in several organs has been linked to chronic inflammation and oxygen free radicals (Shimoda et al. 1994, Holzinger et al. 1999). Recently, antioxidants have been inversely associated with risk for esophageal adenocarcinoma (Terry et al. 2000). In esophagitis and

Barrett's epithelium, because growing evidence exists that oxidative stress is involved in the pathogenesis of mucosal damage (Olyaee et al. 1995, Wetcher et al. 1995, Oh et al. 2001), the malignant transformation of Barrett's esophagus may thus be related to free radicals and oxidative stress.

Precancerous tissue on its way to becoming cancerous is required to have angiogenic capacity. This angiogenesis is often activated, as seen also in Barrett's esophagus, during the early stages in tumor development (Hanahan and Folkman 1996, Couvelard et al. 2000). In Barrett's epithelium, the morphology of this neovascularization is not characterized, nor is any possible role evident for lymphangiogenesis in the early lymphatic spread of these tumors.

Adenocarcinoma near the esophagogastric junction is one of the most lethal malignancies known. In two population-based studies before the 1980's, the overall 5-year survival was 2.7% for lesions at the esophagus and 3.7% at the esophagogastric junction (Allum et al. 1986, Matthews and Walker 1990). Though in recent surgical series the 5-year survival rate has been over 30%, these are highly selected and do not reflect the overall pattern of this disease at population level (Siewert et al. 2000, Collard 2001, Hagen et al. 2001). In this era of continuous development in treatment modalities, a detailed picture of the nature and behavior of this tumor under modern staging and treatment modalities is lacking.

Endoscopic treatment modalities such as stents or laser therapy play an important role in palliation of these patients, but continuous debate in the literature confirms that none of the palliative methods to treat esophageal cancer is entirely optimal. Obstructive carcinomas of the EG junction are especially difficult to palliate. Despite the different needs for repeated therapy and different one-off costs between palliative treatment modalities, the economic implications of the treatment of dysphagia due to malignant disease, especially adenocarcinoma near the EG junction, have received little attention. In this era of increasing interest in the health resources consumed, selection of treatment should take into account the cost of therapy.

5 REVIEW OF THE LITERATURE

5.1 Gross anatomy and lymphatic spread of adenocarcinoma in the distal esophagus and esophagogastric junction

Esophageal adenocarcinoma is seldom located above the tracheal bifurcation, 24 to 26 cm from the incisor teeth (Hagen and DeMeester 2000). Below this level, the esophagus lies between the pericardium, aorta, and vertebral column. Laterally it is covered by the hilar structures of the lungs, mediastinal pleura, and pulmonary ligaments. In the lower mediastinum the esophagus passes beside the azygos vein and thoracic duct, and together with the vagal nerves it reaches the diaphragmatic hiatus. The length of the abdominal esophagus is variable, generally a few centimeters, meaning that the esophagogastic junction lies just below the diaphragm (Skandalakis and Ellis 2000). The abdominal esophagus and EG junction are located retroperitoneally on top of the aorta and left diaphragmatic crus. The peritoneum and left lobe of the liver cover them anteriorly.

Though reflecting the person's height, 38 to 40 cm from the incisors lies the squamo-columnar junction. Below this junction, cardiac mucosa, based on recent studies, rarely extends more than a few millimeters (Kilgore et al. 2000, Chandrasoma et al. 2000); even in normal people, the presence of cardiac mucosa, with its tubular glands lined almost exclusively with mucin-secreting cells (Owen 1986, Spechler 2001), has been questioned, as well (Chandrasoma et al. 2000, DeMeester 2001).

The lymphatics of the esophagus originate from the deepest part of the mucosa (Liebermann-Meffert 2001). In the submucosa they form plexuses and longitudinal collecting channels. Though the lymph flow in these channels is directed by valves, the direction of flow, especially in cancer with obstructions of the lymphatics, is unpredictable (Liebermann-Meffert 2001). Tumor cells may travel a considerable distance before reaching the lymph nodes. Figure 1 outlines the lymphatic drainage of the EG junctional area.

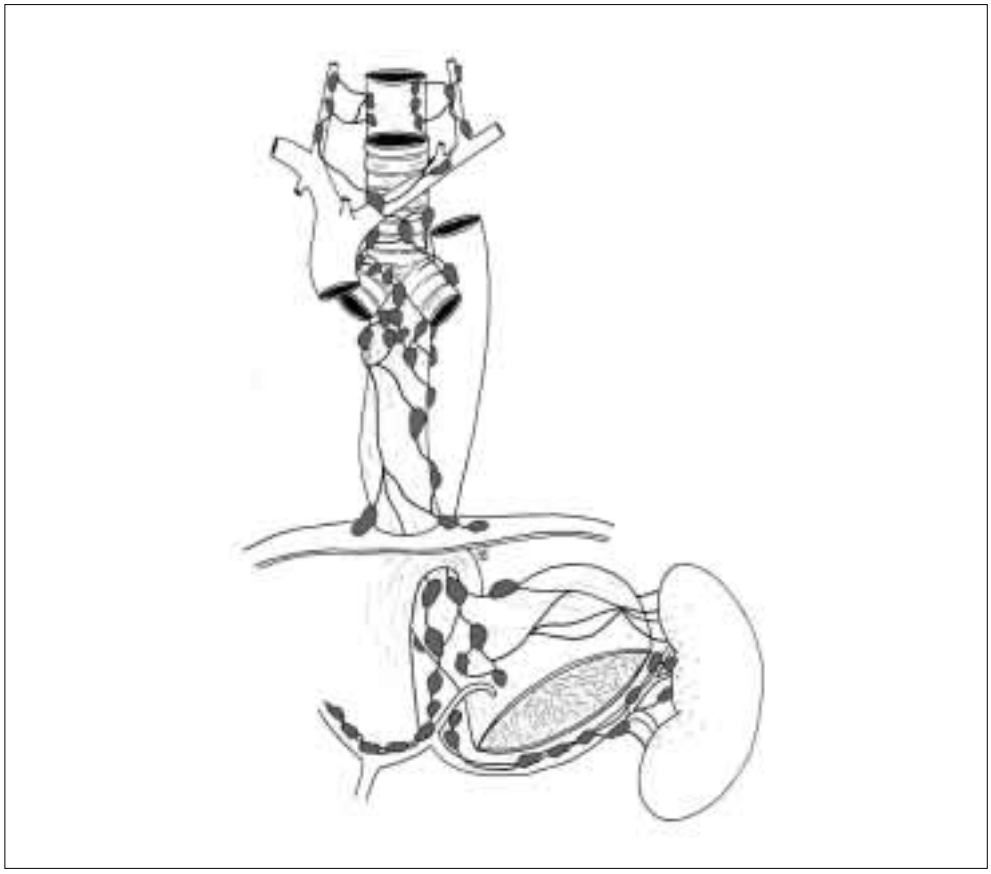

FIGURE 1 Lymphatic drainage of the EG junctional area

Adenocarcinoma near the EG junction spreads early into lymphatic tissue. One-fifth of the patients with disease limited to the submucosa and over 80% of transmural tumors have nodal metastases (Rice et al. 1998, Stein et al. 2000a, Hagen et al. 2001). Most frequently, these metastases are located in the paratumoral lymph nodes (Nigro et al. 1999a, Van de Ven et al. 1999). Regardless of their location, these tumors frequently have lymphatic metastases on either side of the diaphragm (Nigro et al. 1999a, Van de Ven et al. 1999). Up to 35% of patients having adenocarcinoma at the distal esophagus and 20% of those with cancer at the EG junction may have cervical nodal metastases, sometimes even without thoracic nodal involvement (Altorki and Skinner 1997, Van de Ven et al. 1999). In most cases, these are probably patients with advanced disease showing a wide lymphatic spread (Sons and Borchard 1986).

5.2 Classification of adenocarcinoma near the esophagogastric junction

The classification of adenocarcinoma near the EG junction is still controversial, mainly because the definition of gastric cardia in the literature is inconsistent (Appelman 1998, Spechler 2001). The International Union Against Cancer (UICC) even classifies cancer of the cardia as a subgroup of gastric cancer without a specific definition (International Classification of Diseases for Oncology [ICDO] site code C16.0) (UICC 1997). Data reported in the literature about cancer of gastric cardia and esophageal adenocarcinoma are thus not always comparable.

In order to overcome the difficulties in classification of these cancers, Siewert et al (1987) proposed an anatomical-topographical classification based upon the location of the tumor center 5 cm proximal or distal to the lower esophageal sphincter (Figure 2). Type I adenocarcinoma includes the tumors of the distal esophagus. The center or more than two-thirds of the tumor is located more than 1 cm above the EG junction (a). A Type II tumor is located between 1 cm above and 2 cm below the EG junction (b). Carcinoma of Type III represents a carcinoma of the proximal stomach, and the main tumor center is located between 2 and 5 cm below the EG junction (c). Although this classification has been accepted in a recent consensus conference organized by the International Gastric Cancer Association and the International Society for Diseases of the Esophagus, it is not based on histology (Siewert and Bumm 1997).

5.3 Epidemiology

Adenocarcinoma located either in the distal esophagus or gastric cardia mainly occurs in patients over 50 years of age. The mean age at diagnosis has been around 67 (Dolan et al. 1999). The incidence is several times more common in males and higher among whites than blacks (Yang and Davis 1988, Blot et al. 1991).

In several countries, the incidence of adenocarcinoma in the esophagus, especially in men, has increased (Table 1) (Powell and McConkey 1990, Blot et al. 1991, Hansson et al. 1993, Hansen et al. 1997, Lord et al. 1998). Before the mid-1970's, adenocarcinoma

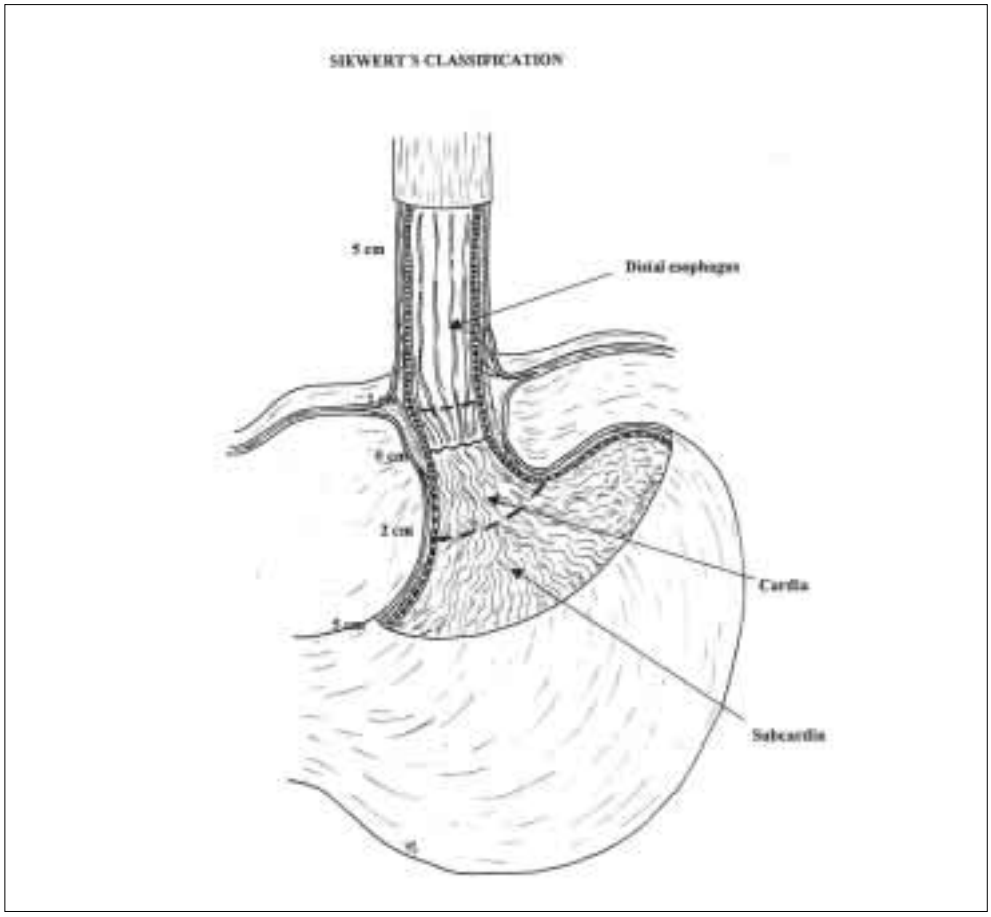

FIGURE 2 Classification of adenocarcinomas near the EG junction by Siewert

accounted for less than 5% of all esophageal cancers (Turnbull and Goodner 1968, Webb and Busuttil 1978), but by the 1990's this number had increased to more than 25% in men in various countries (Blot et al. 1991, Hansson et al. 1993, Hansen et al. 1997, Lord et al. 1998). In the USA, the rate of increase has surpassed that of any other cancer type (Blot et al. 1991). At the same time, the incidence of cancer of the gastric cardia in both sexes and the incidence of esophageal adenocarcinoma in women have remained relatively stable in several other countries (Levi et al. 1990, Levi 1991, Blot et al. 1991, Hansson et al. 1993, McKinney et al. 1995, Armstrong and Borman 1996, Hansen et al. 1997, Lord et al. 1998). In some countries, cancer of the gastric cardia and esophageal adenocarcinoma in women are also on the increase (Blot et al. 1991, Dolan et al. 1999). The combined

TABLE 1 Change in incidence of esophageal and gastric cardial adenocarcinoma

Author and year	Location	Data – collection period	Esophageal adeno-carcinoma*		Cancer of gastric cardia*		Esophagus and cardia combined*	
			Male	Female	Male	Female	Male	Female
Hansen et al. 1997	Norway	1958–1962 1988–1992	0.1 0.8	0.0 0.1	3.5 3.1	1.3 0.9	3.6 3.9	1.3 1.0
Powell and McConkey 1990	United Kingdom	1962–1966 1977–1981	0.2 0.9	0.1 0.3	1.1 3.0	0.4 1.0	1.3 3.9	0.5 1.3
Blot et al. 1991	USA	1976 1987	0.9 1.9	0.15 0.2	2.4 3.4	0.4 0.6	3.3 5.3	0.55 0.8
Levi et al. 1990 and Levi 1991	Switzerland	1976–1981 1982–1987	0.4 1.6	0.2 0.1	6.5 5.3	1.1 0.8	6.9 6.9	1.3 0.9
Armstrong and Borman 1996	New Zealand	1978–1982 1988–1992	1.8 2.3	0.3 0.5	2.2 1.9	0.5 0.4	4.0 4.2	0.8 0.9
Lord et al. 1998	Australia	1982 1992	0.8 2.3	0.16 0.3	2.6 3.0	0.5 0.6	3.4 5.3	0.56 0.9

*Annual age adjusted incidence per 100 000 population

incidence of these cancers often shrinks the substantial rise (up to 300-700%) in the incidence of esophageal adenocarcinoma, reducing it to nearly non-existent (Levi et al. 1990, Levi 1991, Armstrong and Borman 1996, Hansen et al. 1997), or to a more reasonable increase, 50 to 60% (Blot et al.1991, Lord et al. 1998).

5.4 Risk factors for adenocarcinoma of the esophagus and cardia

A strong correlation exists between GERD and esophageal adeno-carcinoma, and an association has also been found between GERD and cancer of the gastric cardia (Lagergren et al. 1999a). The most important risk factor for esophageal adenocarcinoma is, however, Barrett's esophagus. With long (>3 cm) segments of Barrett's epithelium, the risk of developing an adenocarcinoma has been estimated to be 30 to 125 times as high as in the normal population (Cameron et al. 1985, Hameeteman et al. 1989). Recently, this high cancer risk has been considered to be a publication bias; the newest, more reliable estimation of cancer risk in non-dysplastic Barrett's mucosa is 0.5% per year, which

TABLE 4. Complications by group.

Treatment modality No. of patients (%)	Laser (n=32)	Stent (n=20)
Early complication	2 (6.3)	6 (30)
Perforation	2 (6.3)	0
Bleeding	0	3 (15)
Infection	0	2 (10)
Malpositioning	-	2 (10)
Late complication	13 (40.6)	6 (30)
Obstruction*	12 (38)	5 (25)
Stent migration	1 (3.1)	1 (5)
Tumour overgrowth	0	3 (15)
Stent breakage	0	1 (5)
Bleeding	0	2 (10)
Aspiration	1 (3.1)	0
Pain, dysphagia	0	1 (5)
Regurgitation, oesophagitis	0	2 (10)

*Due to tumour growth after laser therapy, and tumour overgrowth (3), oesophageal stricture (1), and food bolus (1) after stent placement.

Discussion

The main aim of treatment for a patient with advanced adenocarcinoma of the oesophagus or GE junction is palliation of dysphagia, and our study shows that this aim could be achieved as effectively with placement of self-expandable metallic stents as with laser therapy, without differences in overall cost of treatment. No significant difference existed in this retrospective study in overall survival or in patient demographics between those with laser therapy and with SEMS (Table 1 and 3).

No prospective randomised studies compare laser therapy and SEMS in the treatment of malignant dysphagia purely due to carcinomas of the GE junction. Regarding more proximal location, one prospective randomised trial showed SEMS to offer better palliation of dysphagia than did laser therapy[14]. However, over 40% of the tumours involved were located in the middle or upper oesophagus[14]. One critical review of reports published on SEMS for palliation of stenosing tumours of the oesophagus observed a high rate of early and late complications such as stent migration, incomplete expansion, and tumour ingrowth[15]. SEMS have been proven superior to oesophageal intubation with plastic prostheses[7-9]. Similarly, laser therapy has provided better

palliation than have plastic prostheses[12, 16, 17]. Based on all these reports, no firm conclusion can be reached regarding the best palliation of tumours near the GE junction. On the other hand, one has to remember that a long, tortuous stricture, especially with extrinsic compression, is difficult to palliate with laser therapy[12].

Because of the short life-expectancy and high one-off costs, placement of SEMS did not reduce the overall cost of palliation despite the reduced need for reinterventions. The most important factor affecting the quality of life in these patients is severity of dysphagia[18]. It is debatable whether the increased number of interventions is even a burden to the patient, because regular contact with specialists may provide counselling and support of great importance to these dying patients. Overall, that the time spent in hospital did not differ between the study groups means that for none of these patients with their limited lifespan, was the opportunity to spend time with family and friends reduced.

That no survival difference existed between treatment groups agrees with previous findings[8, 16]. However, procedure-related complications and mortality cannot be disregarded. In this study, morbidity and early mortality were significantly more common with SEMS than with laser therapy. In the stent group higher morbidity and early mortality increased the overall costs and the cost per day of palliation. The early complication rate of 30% after placement of SEMS equals the figure recently reported in a critical review of SEMS[15]. Complication rates are high, especially in treatment of tumours near the GE junction[6]. The advantage of laser therapy is the low procedure-related morbidity and mortality rates, although perforation occurs in a few cases[19]. In addition, this study showed no difference in the rate of late complications between laser therapy and placement of SEMS.

No sign of significant difference between the study groups could be detected in total costs. This finding is likely to hold even with a more detailed and complex analysis, although this relatively small retrospective study has its potential flaws. Therefore, the choice between these endoscopic treatment modalities should be based on medical – not financial – arguments.

In conclusion, it seems that laser therapy palliates dysphagia of patients with adenocarcinoma at the distal oesophagus or at the GE junction effectively without increased costs or hospital stays and with lower morbidity and early mortality rates than for self-expanding

seems not even to affect life expectancy (Shaheen et al. 2000, Eckardt et al. 2001).

The substantial length of Barrett's (>8-10 cm) mucosa seems to be a risk factor in the development of cancer (Iftikhar et al. 1992, Dees et al. 1996, Weston et al. 1999, Rudolph et al. 2000), though the risk with short-segment Barrett's mucosa (<3 cm) has not been substantially lower than for longer segments (3-10 cm) (Rudolph et al. 2000). The presence of dysplasia – especially high-grade dysplasia (HGD) – hiatal hernia size, and the presence of Barrett's ulcer have been other features recognized as predictive of development of adenocarcinoma (Dees et al. 1996, Weston et al. 1999). The dysplasia risk, and therefore probably the overall malignant potential of intestinal metaplasia distal to the squamocolumnar junction is significantly less (Sharma et al. 2000).

In HGD, up to 61% of patients have developed esophageal adenocarcinoma during a median time of 8 months (Montgomery et al. 2001), and 39% of 262 patients with HGD in all the series found in the literature have already had cancer at the time of esophageal resection (Edwards et al. 1996, Heitmiller et al. 1996, Ferguson and Naunheim 1997, Cameron and Carpenter 1997, Catatrambone et al. 1999, Ngueyn et al. 2000, Zaninotto et al. 2000, Headrick et al. 2002).

Smoking and alcohol are well-known risk factors for esophageal squamous cell carcinoma. For esophageal and gastric cardia adenocarcinoma, although equivocal evidence has been reported, four recent studies revealed a modest risk from smoking (Kabat et al. 1993, Vaughan et al. 1995, Zhang et al. 1996, Gammon et al. 1997). This risk seems to be more than double that of the normal population, with a dose-response pattern (Vaughan et al. 1995, Zhang et al. 1996). Recent epidemiological studies demonstrate only a weak association or none between alcohol consumption and these adenocarcinomas (Vaughan et al. 1995, Zhang et al. 1996, Gammon et al. 1997).

Other reports have indicated a protective role for dietary fiber intake in risk for these adenocarcinomas (Brown et al. 1995, Zhang et al. 1997). Only two studies have evaluated the association of dietary fiber and adenocarcinoma of the esophagus or gastric cardia separately (Mayne et al. 2001, Terry et al. 2001). Both of these studies showed an inverse association between fiber intake and risk for adenocarcinoma of the gastric cardia, but only Mayne et al (2001) established an inverse association between fiber intake and esophageal adenocarcinoma, as well.

Obesity seems to be a risk factor for esophageal adenocarcinoma and for cancer of the gastric cardia (Brown et al. 1995, Vaughan et al. 1995, Chow et al. 1998a, Lagergren et al. 1999b). One possible explanation is that increased abdominal girth promotes gastroesophageal reflux, which, in turn, is a known risk factor for esophageal adenocarcinoma (Lagergren et al. 1999a). Higher prevalence of gastroesophageal reflux may also be the link between increased risk for esophageal adenocarcinoma and the use of drugs with the side-effect of relaxing the lower esophageal sphincter (LES) (Vaughan et al. 1998, Lagergren et al. 2000).

An inverse relation seems to exist between the incidence of esophageal and gastric cardial adenocarcinoma and the prevalence of *Helicobacter pylori* (Chow et al. 1998b, Hansen et al. 1999). The possible protective effect against esophageal adenocarcinoma of *H. pylori* infection with the cagA+ strain may be due to decreased intragastric acid production as a result of pangastritis and gastric atrophy (Richter et al. 1998).

5.5 Barrett's esophagus and adenocarcinoma

Long-lasting gastroesophageal reflux disease, oxidative stress, and angiogenesis in the esophageal mucosa each seems to play a role in the pathogenesis of Barrett's esophagus, and esophageal adenocarcinoma.

Gastroesophageal reflux

The definition of Barrett's esophagus has now evolved to these findings: biopsy-confirmed intestinal metaplasia with goblet cells in the tubular esophagus any distance proximal to the gastric folds (Sharma 2001). This specialized intestinal metaplasia is a complication of gastroesophageal reflux disease. Among 248 GERD patients in one Finnish series, prevalence of Barrett's esophagus was 4% (Voutilainen et al. 2000).

Long-lasting gastroesophageal reflux causes chronic esophageal mucosal damage with metaplastic epithelium replacing damaged squamous epithelium. The main contributors to this damage are acid and pepsin (Salo and Kivilaakso 1982, Zaninotto et al. 1992). Duodenal contents play a role in this process as well (Salo and Kivilaakso 1983, Vaezi and Richter 1996, Öberg et al. 2000, Martinez de Haro et al.

2001). An incompetent LES, the presence and size of any hiatal hernia, ineffective esophageal clearance, and delayed gastric emptying increase exposure of these reflux-contents in patients with Barrett's esophagus (Stein et al. 1993, Singh et al. 1994, Öberg et al. 1999, Cameron 1999). The presence of cytokeratins characteristic of normal esophageal squamous epithelium in Barrett's mucosa supports the current theory that the stem cells of the squamous mucosa undergo altered differentiation and give rise to intestinal metaplasia (Salo et al. 1996). It is assumed that this metaplastic epithelium is better able to resist the adverse effects of the duodenal and gastric contents.

Intestinal metaplasia in the distal esophagus, regardless of its length, has shown increased proliferative activity and has progressed to dysplasia and adenocarcinoma (Gulizia et al. 1999, Sharma et al. 2000). In this metaplasia-dysplasia-adenocarcinoma sequence, accumulation of changes occurs in genes controlling cell proliferation, apoptosis, cell cycle, cell adhesion, gene expression, and in DNA and in chromosomes (Wu et al. 1998, Wijnhoven et al. 2001, Jenkins et al. 2002). The balance between cell proliferation and cell loss is, therefore, disturbed (Wijnhoven et al. 2001).

The pathogenesis of adenocarcinoma at the gastric cardia is less clear. Whether the intestinal metaplasia at the gastric cardia is a consequence of gastroesophageal reflux or a manifestation of gastritis caused by *Helicobacter pylori* is disputed (Spechler 1999). In gastro-esophageal reflux disease, mucosal injury at the gastric cardia is highly localized to the region adjacent to the squamocolumnar junction (Lembo et al. 1999). It seems that incomplete intestinal metaplasia (specialized columnar epithelium) may result from reflux disease, and the complete type of intestinal metaplasia may be associated with atrophic gastritis (Voutilainen et al. 1999). In a recent study, of 16 patients, 11 (69%) had incomplete intestinal metaplasia in the mucosa adjacent to adenocarcinoma at the gastric cardia (Ruol et al. 2000). Adjacent to adenocarcinoma, low-grade and high-grade dysplasia have been discovered as well (Van Dekken et al. 2001).

Oxidative stress

Although the esophagitis-metaplasia-dysplasia-cancer sequence is clear, the molecular mechanisms leading to genetic changes, and also to adenocarcinoma are not well defined. In the development of adenocarcinoma, oxidative stress has been suggested as a driving force

(Cheng and Yang 2001). Oxidative stress plays a role in the pathomechanism by which tissue injury occurs in esophagitis and in Barrett's epithelium (Olyaee et al. 1995, Wetscher et al. 1995, Oh et al. 2001). In a recent epidemiological study, an inverse association appeared between antioxidants and the risk for adenocarcinoma of the esophagus (Terry et al. 2000). In addition to increased oxidative stress, low antioxidant capacity, seen as low content of glutathione and as reduction in glutathione S-transferase activity, may be a factor of relevance in this process (Peters et al. 1993, Van Lieshout et al. 1999). No direct link between reactive oxygen species and malignant transformation of the esophageal mucosa caused by GERD has, however, yet been established (Cheng and Yang 2001, Farhadi et al. 2002).

Free radicals such as the superoxide and hydroxyl radical are extremely reactive chemical species which can cause oxidative injury to cells by damaging proteins, cell membranes, or DNA. Deficiency in antioxidant defence further amplifies oxidative stress and tissue injury (Dreher and Junod 1996). The importance of oxidative stress has attracted notice in relation to formation of DNA adducts (Kasai and Nishimura 1984, Dreher and Junod 1996); high levels of DNA adducts have been discovered in Barrett's epithelium (Salminen, in press). By adding a small chemical group to a DNA-base, these DNA adducts can interfere with DNA replication and therefore initiate mutagenic and carcinogenic processes by producing mispaired DNA sequences (Denissenko et al. 1996, Ross and Nesnow 1999).

Angiogenesis and lymphangiogenesis

For the continuous growth of tumors beyond the diffusion limit of oxygen, they must recruit new blood vessels (Carmeliet and Jain 2000). This formation of new blood vessels from pre-existing ones – angiogenesis – occurs, therefore, in tumor progression. Recently, high vascularization in esophageal adenocarcinoma and the adjacent intestinal metaplasia was disclosed (Couvelard et al. 2000, Millikan et al. 2000). In brief, the process of angiogenesis consists of three steps: 1) Local degradation of capillary basement membrane, 2) migration and proliferation of endothelial cells, and 3) organization of endothelial cells into three-dimensional capillary tubes (Fidler et al. 2000). The angioarchitecture within Barrett's epithelium is uncharacterized. In tumor tissue, these new vessels are structurally and functionally abnormal (Carmeliet and Jain 2000).

The onset and process of angiogenesis requires a change in the local equilibrium between pro- and antiangiogenic factors (Liotta et al. 1991, Hanahan and Folkman 1996). This equilibrium can be unsettled by various signals including hypoxia, metabolic and mechanical stress, inflammatory response, and genetic mutations (Shweiki et al. 1992, Rak et al. 1995, Carmeliet and Jain 2000). In the metaplasia-dysplasia-adenocarcinoma sequence in the esophagus, several potential factors stimulating angiogenesis exist (Table 2). Vascular endothelial growth factor (VEGF), expressed both in Barrett's esophagus and in related adenocarcinoma, is considered the most critical driver of angiogenesis (Yancopoulos et al. 2000).

TABLE 2 Known angiogenesis activators found in the metaplasia-dysplasia-adenocarcinoma sequence in Barrett's esophagus

Angiogenesis activator	**Author**
Vascular endothelial growth factor (VEGF)	Couvelard et al. 2000
Transforming growth factor-beta (TGF-b)	Triadafilopoulo and Kumble 1996
Fibroblast growth factor (FGF)	Soslow et al. 1997
Matrix metalloproteinase (MMP)	Salmela et al. 2001
Cyclooxygenase (COX-2)	Morris et al. 2001
Nitric oxide synthase (NOS)	Soteras et al. 2000

Angiogenesis provides a vascular route for the hematogenous spread of cancer cells. In several cancers, angiogenesis has been revealed as a significant negative prognostic factor (Toi et al. 1993, Weidner 1995, Yuan et al. 2001), but in esophageal adenocarcinoma, results have been equivocal (Torres et al. 1999, Millikan et al. 2000, Couvelard et al. 2000). On the other hand, esophageal adenocarcinoma spreads early into the lymphatic system. This implicates lymphangiogenesis, the growth of new lymphatic vessels, in early lymphatic spreading of this disease. A strong promoter of lymphangiogenesis in tumor tissue is vascular endothelial growth factor C (VEGF-C) (Karpanen et al. 2001), which is expressed in several human cancers including esophageal squamous cell cancer (Akagi et al. 2000, Kitadai et al. 2001, Yonemura 2001). The expression of VEGF-C and tumor-related lymphangiogenesis has been correlated with increased dissemination of tumor cells into lymph nodes (Akagi et al. 2001, Skobe et al. 2001).

5.6 Staging

Pre-therapeutic staging of adenocarcinoma near the EG junction is a prerequisite for the proper selection of treatment. The main goal is to evaluate whether a complete tumor resection can be achieved.

Staging is usually conducted in accordance with International Union Against Cancer (UICC) TNM staging (UICC 1997) (Figure 3). TNM stage is determined by evaluation of tumor infiltration into the organ wall (T stage), of lymph node status (N stage), and of the presence or absence of distant metastases (M stage). The presence of distant metastases (M1 disease) is further divided into two subclasses: M1a (distant, nonregional lymph node metastases) and M1b (other distant metastases).

In the case of distant metastases, no curative treatment is possible. To assess for distant metastases (M1b disease), computed tomography (CT) is widely used. The problem even with modern CT technology is, however, its inability to detect small (< 1 cm in diameter) metastases. Overall, CT has a relatively low sensitivity, less than 50%, and specificity between 74% and 83% in detecting M1b disease (Luketich et al. 1999, Flamen et al. 2000). Recent studies indicate that positron emission tomography (PET) is superior to CT (accuracy 84% vs. 63%, $p<0.01$), or to combined use of CT and endoscopic ultrasound (EUS) (accuracy 82% vs. 64%, $p=0.004$) (Luketich et al. 1999, Flamen et al. 2000). PET frequently fails, however, to detect small and distant, especially liver and peritoneal, metastases (Luketich et al. 1999, Flamen et al. 2000). To avoid unnecessary laparotomy, a diagnostic laparoscopy can, therefore, be used in patients with locally advanced tumors (Stein et al. 1997).

Local tumor infiltration into surrounding structures and widespread lymph node involvement significantly reduces the likelihood of achieving a complete tumor resection. Endoscopic ultrasound predicts T stage in esophageal cancer most reliably with a diagnostic accuracy of 84% (Rösch 1995). In a recent study of adenocarcinoma of the esophagus and EG junction, T stage was correct in only 66% (Salminen et al. 1999). In these patients, EUS predicted resectability with 94% accuracy (Salminen et al. 1999).

Though in experienced hands using a combination of EUS and ultrasound, widespread lymphatic metastases can be predicted with high accuracy (96%), N staging is currently considered of little importance, because it cannot be assessed with sufficient accuracy (Stein 2001,

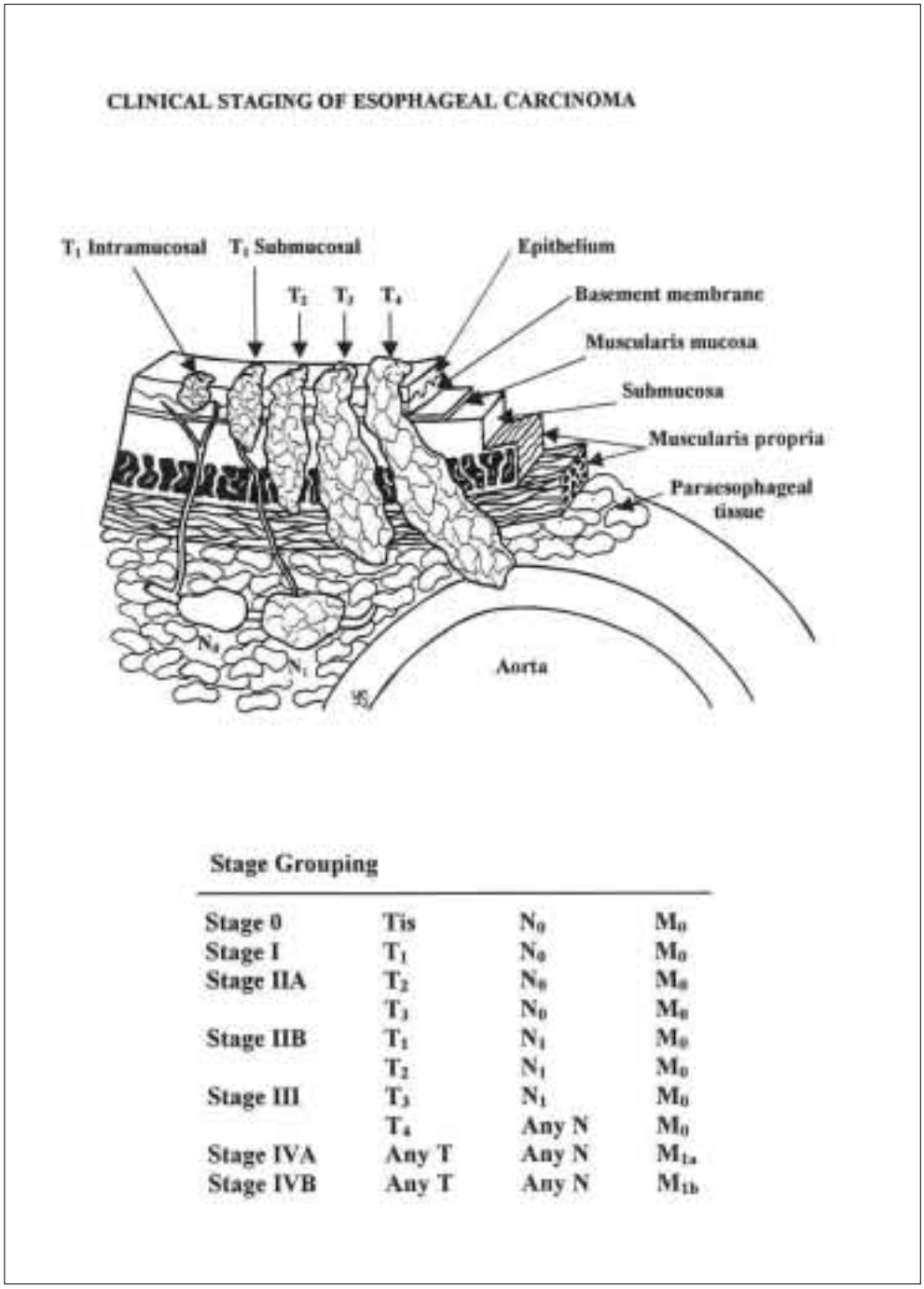

FIGURE 3 TNM staging of esophageal carcinoma

Natsugoe et al. 2001). In a recent meta-analysis, the accuracy of EUS in detection of N stage in esophageal cancer was 77% (Rösch 1995). In adenocarcinoma in the distal esophagus and EG junction, EUS predicted N stage correctly in 72% of patients (Salminen et al. 1999). The inability to pass the probe through obstructing tumors is a limitation which can have a major effect on reliability of EUS in determination of the status of celiac nodes (M1a disease) (Salminen et al. 1999). The ability of EUS to assess the status of celiac nodes, regardless of these limitations, is considered to be high (Catalano et al. 1999). Patients with EUS M1a disease have significantly worse 5-year survival than with non-detected M1a disease (30% vs. 13%) (Eloubeidi et al. 2001).

It is evident that lack of accuracy in these pre-therapeutic staging methods makes it difficult precisely to define completely resectable disease. The transmural nature of these tumors has, however, been predicted with high accuracy with EUS (Salminen et al. 1999). The prevalence of positive lymph nodes has been 83% in T3 and 96 to 100% in T4 tumors compared to 1 to 3% in mucosal, 19 to 21% in submucosal, and 46 to 77% in T2 tumors (Rice et al. 1998, Stein et al. 2000a). The chance for complete resection has depended on T-stage as well (69% in T3, 59% in T4) (Stein et al. 2001). Patients with T3/4 tumors detected by EUS may therefore be candidates for multimodality therapy (Stein et al. 2001). When the disease is limited to the esophageal wall (T1/2), primary resection is the treatment of choice.

5.7 Treatment

In the population-based study by Allum (1986) in the 1970's, 36% of patients with adenocarcinoma at the gastric cardia underwent radical resection, 19.9% received no treatment, and the others were treated palliatively, most either with resection or with esophageal intubation. Even in a recent analysis, only one-third of patients with adenocarcinoma at the esophagus could be offered surgery (Daly et al. 2000); in that large hospital-based series, up to 44% of patients received primarily only radiation, chemotherapy, or both, and 15.4% received no specific treatment. Though endoscopic treatment modalities such as stents or laser therapy play an important role in palliation of these patients, the overall role of these endoscopic interventions at the population level is not well characterized.

Surgical treatment

In adenocarcinoma of the distal esophagus or the EG junction, surgery is generally considered to offer the best chance for curing the patient and restoring satisfactory swallowing. Beyond this basic principle, controversies exist as to the proper choice of surgical approach and extent of resection, and as to the role of lymphadenectomy. To answer such questions, no good prospective randomized studies have been conducted. Choice of surgical approach depends on the location of the tumor, stage of the disease, patient characteristics, and, especially, the surgeon's attitude towards lymphadenectomy and resection margins. A combined right thoracotomy and laparotomy is the preferred approach (Siewert and Bumm 1997). This approach provides the best visibility to perform mediastinal lymphadenectomy and to resect the esophagus with a margin sufficiently wide.

In a recent study by Dexter (2001), the finding of a tumor within one millimeter of the proximal esophageal resection margin with potentially curable disease was a significant predictor both of local recurrence and of survival. Previously, the same local recurrence rate was detectable in patients with free proximal resection margins of less than 3 cm compared to those with positive margins (Molina et al. 1982). Though a safety margin of 2 to 3 cm is considered to be sufficient in intestinal-type tumor growth (Siewert et al. 2000), only with wide resections (10-12 cm margins) have there been no positive margins (Papachristou et al. 1980, Peracchia et al. 1991). The extent of the distal resection needed has been less well studied. Especially adenocarcinomas at the gastric cardia frequently (28%) have positive distal resection margins (Casson et al. 2000). These positive distal margins also have a negative effect on survival, leading Casson et al (2000) to recommend a minimum resection of macroscopically normal stomach to 5 cm below the tumor.

The role of radical lymphadenectomy in surgery for esophageal cancer is a debated topic. In patients with early adenocarcinoma near the EG junction, limited resection with locoregional lymphadenectomy and possibly with vagal preservation seems to be safe and preserves a good quality of life (Nigro et al. 1999b, Stein et al. 2000b). The long-term results of this limited approach are, however, lacking. In more advanced disease, radical surgery with lymphadenectomy seems to end in better control of local recurrence and improved pathologic staging, and the likelihood of obtaining complete resection (Altorki et al. 1997,

Lerut et al. 1999, Van de Ven et al. 1999, Hagen et al. 2001). The most important concern, of course, is whether more radical lymph node dissection really contributes to improvement in survival. Those patients who potentially would benefit from more extentive resections have only a few metastatic lymph nodes (Nigro et al. 1999a). In a recent analysis, 25% of patients with transmural esophageal adenocarcinoma and lymph node metastases were alive at 5 years (Hagen et al. 2001). In another study, patients with limited lymph node metastases (<5) had a 5-year survival rate of 37% (Collard 2001). In a large series by Orringer (1999), overall 5-year survival after transhiatal technique was 24%.

The systematic nature of the disease and the ineffective role of radical lymph node dissection in gastric cancer raise some questions as to the role of lymphadenectomy (Bonenkamp et al. 1999, O'Sullivan et al. 1999). More radical operations are therefore justified only if they can be performed without significantly increased mortality and morbidity. A prospective randomized study of 32 patients comparing a radical en-block technique with 2-field lymphadenectomy and standard resection showed prolonged duration of surgery and increased blood loss in the lymphadenectomy group but no difference in postoperative morbidity or mortality (Jacobi et al. 1997). Nor did two other randomized studies comparing transhiatal and transthoracic resections show any differences in postoperative complications (Goldminc et al. 1993, Chu et al. 1997). In a recent meta-analysis, transthoracic resections resulted in a higher risk for pulmonary complications, chylous leakages, and wound infections (Hulscher et al. 2001). In the same meta-analysis, on the other hand, the transhiatal technique more frequently resulted in anastomotic leakage and vocal cord paralysis; in addition, only transhiatal resections had severe bleedings or tracheal tears peroperatively. Though the perioperative mortality rate in that meta-analysis was significantly higher after transthoracic resection, the randomized trials had the opposite tendency, with lower mortality in the transthoracic group. The excellent results of Orringer in a large transhiatal series weigh heavily in this meta-analysis (Orringer et al. 1999, Hulscher et al. 2001). In experienced centers, low mortality rates can be achieved by the more radical en-block technique, as well (Altorki et al. 1997, Hagen et al. 2001, Collard 2001).

Previously, esophagectomy had the highest surgical mortality (29%) of any routinely performed surgical procedure (Earlam and Cunha-Melo 1980). Similarly, radical resection of adenocarcinoma at the gastric cardia carried a 30-day mortality of 19% (Allum et al. 1986). In

two recent meta-analyses, mortality rates after esophageal resection were 7.5% and 11.0% (Jamieson et al. 1998, Hulscher et al. 2001). The complication rate in surgery for adenocarcinoma near the EG junction, even in experienced units, has ranged from 28% to 71% (Ellis et al. 1997, Hagen et al. 2001). Increasing evidence indicates that surgical volume and experience both have major impact on surgical mortality and on early outcome after major cancer surgery, especially after esophagectomy (Begg et al. 1998, Sutton et al. 1998, Swisher 2000, Whooley et al. 2001).

In the 1960's and 70's, the 5-year survival rate after esophagectomy, according to Earlam's large review, was 12% (Earlam and Cunha-Melo 1980). Similarly, a population-based analysis of radical resection of adenocarcinoma at the gastric cardia revealed a 5-year survival rate of only 9.8% (Allum et al. 1986). In the late 1980's in Denmark, 5-year survival after surgery for esophageal adenocarcinomas was 17% (Bytzer et al. 1999), but in two recent Western meta-analyses, 5-year survival after esophagectomy was 20.6% and 21.4% (Jamieson et al. 1998, Hulscher et al. 2001). In recent selected surgical series, 5-year survival in adenocarcinoma of the distal esophagus and EG junction has been over 30% (Siewert et al. 2000, Collard 2001). Outcome of surgical treatment in the recent literature is shown in Table 3.

TABLE 3 Outcome of surgical treatment in patients with adenocarcinoma of the esophagus or esophagogastric junction in the recent literature

Author (year)	No. of patients (timing of treatment)	Morbidity (%)	30-day mortality (%)	5-year survival (%)
Harvey (1990)	58 (1954-88)	NA	9	8
Wilson (1990)	25 (1982-87)	40	0	0
Streitz (1991)	61 (1973-89)	21.3	3.3	23.7
Menke-Pluymers (1992)	85 (1978-88)	34	6	24
Moon (1992)	88 (1974-90)	43	10.3	13
Law (1992)	92 (1982-89)	NA	6.5	15
Gelfand (1992)	121 (1979-90)	NA	2.5†	21†
Lerut (1994)	63 (1975-91)	9.5	0	58.2
Stark (1996)	48 (1988-94)	NA	2.1	21
Ellis (1997)	303 (1979-94)	27.9†	2.5†	24.7†
Alexiou (1998)	339 (1987-97)	28.1†	5.4†	23.8†
Graham (1998)	153 (1985-97)	NA	4*	16
Hoff (1998)	70 (1988-96)	NA	0	43
Orringer (1999)	555 (1976-98)	NA	4.5*	24
Siewert (2000)	1002 (1982-99)	NA	3.8	32.3
Collard (2001)	183 (1984-2000)	NA	4.3	35.3
Mattioli (2001)	116 (1972-98)	NA	6.9	26.2
Altorki (2001)	81 (1988-98)	49	3.6†	40†
Hagen (2001)	100 (1982-2000)	71	6	52

NA, not available; *Hospital mortality
†Morbidity, mortality, and 5-year survival refer to overall number of patients in studies by Ellis (n=454), Alexiou (n=523), Gelfand (n=160), and Altorki (n=111).

Endoscopic treatment

Even at presentation, over 60% of patients with adenocarcinoma near the EG junction have incurable disease, either because of their advanced stage or poor general physical condition (Allum et al. 1986, Daly et al. 2000). For the majority, the main aims of treatment are palliation of dysphagia, prevention of aspiration, and improvement in quality of life. The role of palliative surgery is very limited, because of the related morbidity, mortality, and short life-expectancy (Sugimachi et al. 1982, Mannell et al. 1988).

Continuous debate in the literature confirms the fact that none of the palliative methods to treat esophageal cancer is entirely optimal. Obstructive carcinomas of the EG junction are especially difficult to palliate (Warren 2000, Kubba and Krasner 2000). Most clinicians elect primarily one of the endoscopic treatment modalities, which can be classified as esophageal stents – either rigid plastic or self-expanding metallic stents (SEMS) – and such local tumor ablation techniques as laser therapy.

Laser therapy has provided better palliation than have plastic prostheses (Alderson and Wright 1990, Carter et al. 1992). Similarly, self-expanding metallic stents have been proven superior to esophageal intubation with plastic prostheses (Knyrim et al. 1993, DePalma et al. 1996, Siersema et al. 1998). Due to a lower complication rate, shorter hospital stay, and simplicity of placement, expandable stents have gained wider acceptance than have the traditional plastic stents (Knyrim et al. 1993, DePalma et al. 1996, Siersema et al. 1998). Regardless of these improvements, a critical review of reports on SEMS observed a high rate of early and late complications such as stent migration, incomplete expansion, and tumor ingrowth (Ell and May 1997). Covered stents are prone to migration at the EG junction; the particular problem of uncovered stents is tumor ingrowth (Adam et al. 1997, Kozarek et al. 1997, Vakil et al. 2001).

Because stenting of tumors near the EG junction predisposes to reflux, migration, and ingrowth, the preferred palliative method in this area is often laser therapy (Wengrower et al. 1998, Gevers et al. 1998). No prospective randomized studies compare laser therapy and SEMS in the treatment of malignant dysphagia purely due to carcinomas of the EG junction. Regarding a more proximal location, one prospective randomized trial showed SEMS to offer better palliation of dysphagia than did laser therapy, but over 40% of the tumors involved were

located in the middle or upper esophagus (Adam et al. 1997).

Based on all these reports, no firm conclusion can be reached regarding the best palliation of tumors near the EG junction. No survival difference has appeared between different endoscopic treatment groups (Carter et al. 1992, DePalma et al. 1996). One has to remember, however, that a long, tortuous stricture, especially with extrinsic compression, is difficult to palliate with laser therapy (Alderson and Wright 1990).

Multimodality therapy

In an attempt to improve the results of surgical therapy for esophageal cancer, preoperative chemotherapy, radiation, or both have been added to enhance local control, increase resection rate, provide better systemic control of the disease, and improve survival. A meta-analysis including both main histological subtypes of esophageal cancer (squamous cell and adenocarcinoma), and the only existing prospective randomized trial including mainly patients with adenocarcinoma (73%) demonstrated no improvement in resectability or survival after preoperative radiotherapy (Arnott et al. 1992, 1998).

The results of randomized studies of preoperative chemotherapy including a large number of esophageal adenocarcinoma patients are conflicting. In the multicenter North American trial, median (15 vs. 16 months) and 2-year (35 vs. 37%) survivals were similar in patients receiving chemotherapy and surgery versus surgery alone (Kelsen et al. 1998). Conversely, the results of a recently completed randomized trial showed, after neoadjuvant chemotherapy, a higher microscopically complete resection rate (60 vs. 54%, $p<0.0001$), an improved median (16.8 vs. 13.3 months; difference 107 days, 95% CI 30-196), and 2-year survival (43 vs. 34%; difference 9%, 95% CI 3-14) (Medical Research Council 2002).

In a recent meta-analysis, those studies in which the majority of patients had esophageal adenocarcinoma showed preoperative chemoradiotherapy to have a 24% pathologically complete response rate which varied between 17% and 41% (Naunheim et al. 1995, Forastiere et al. 1999, Geh et al. 2001). Median survival was between 16 and 31 months and 5-year survival up to 36% (Geh et al. 2001). A prospective randomized study by Walsh (1996) showed a survival benefit in favor of chemoradiotherapy compared to surgery alone (median survival 16 vs. 11 months, $p=0.01$; 3-year 32 vs. 6%, $p=0.01$)

with 22% complete pathological response. The other randomized trial, as well, showed some trend toward benefit from chemoradiotherapy (median 17.6 vs 16.9 months; 3-year 30 vs. 16%, p=0.15), but the study had power to detect only relatively large differences (Urba et al. 2001). It seems evident that those patients with a histologic complete response do benefit from preoperative chemoradiation (3-year survival 64 vs. 19%, p=0.01) (Urba et al. 2001). On the other hand, this kind of neoadjuvant treatment has potentially deleterious effects on patients' working capacity and increases risk for complications (Liedman et al. 2001).

5.8 Prognosis in adenocarcinoma of the esophagus and esophagogastric junction

Before the 1980's, the 5-year survival of esophageal adenocarcinoma was 2.7% and 3.7% at the EG junction (Allum et al. 1986, Matthews and Walker 1990). In the 1980's, survival at one year was less than 30% and remains less than 10% at 5 years (Farrow and Vaughan 1996, Bytzer et al. 1999, Dolan et al. 1999).

Patients ineligible for treatment generally survive for about 2 months (Allum et al. 1986, Harvey et al. 1990). In advanced disease, possibly with organ metastases or peritoneal carcinosis, chemotherapy or radiation as a single treatment modality is ineffective (Whittington et al. 1990), and median survival after palliative radiation has been less than 6 months (Cederqvist et al. 1980, Harvey et al. 1990). In patients with a good response rate to chemotherapy, median survival can be up to 9 months (Waters et al. 1999). Combined radiation and chemotherapy in palliative treatment have had similar results (Coia et al. 1988). Only selected patients with adenocarcinoma near the EG junction have lived past 5 years when treated with chemoradiotherapy with curative intent (Coia et al. 1988, Cooper et al. 1999). Patients with malignant dysphagia treated with endoscopic treatment modalities have generally had a median survival of between 3 and 6 months (Loizou et al. 1991, Carter et al. 1992, Knyrim et al. 1993).

In patients with locoregional disease, the most important prognostic factor is complete macroscopic and microscopic tumor resection (R0 resection) (Hölscher et al. 1995, Siewert et al. 2000, Collard 2001). In recent studies, 5-year survival after R0 resection has

been 39% to 48%, compared to only 0 to 14% after incomplete resection (Hölscher et al. 1995, Siewert et al. 2000, Collard 2001).

After a complete resection, the major independent prognostic factors are depth to which the tumor has invaded the esophageal wall, lymph node status, number of positive lymph nodes, and ratio of involved to uninvolved nodes (lymph node ratio) (Lerut et al. 1994, Hölscher et al. 1995, Collard 2001, Hagen et al. 2001). Tumor depth predicts both prevalence and the number of involved nodes (Rice et al. 1998, Hagen et al. 2001). In a series by Collard (2001), node-negative patients with tumors limited to the esophageal wall had an 84% 5-year survival rate compared to 44% in patients with transmural node-negative tumors. When the number of involved nodes increases to more than 4 to 6, or the lymph node ratio is above 0.3, probability of long-time survival falls to less than 10% (Hölscher et al. 1995, Bonavina et al. 1999, Collard 2001). The extent of lymph node involvement is underestimated in routine histological examination, and it seems that lymph node micrometastases also have a negative effect on long-term survival (Bonavina et al. 1999).

DNA content analysis can be a valuable adjunct to the current prognostic evaluation (Wu et al. 1998, Böttger et al. 1999). Böttger et al (1999) suggested that patients with aneuploid DNA do not benefit from surgery alone. Other factors that may have an adverse effect on prognosis are low experience of the center and the surgeon (Sutton et al. 1998), increased number of blood transfusions required perioperatively (Karl et al. 2000, Langley et al. 2002), surgical morbidity (Ando et al. 2000), preoperative weight loss (Fein et al. 1985), absence of a peritumoral lymphoid infiltrate (Torres et al. 1999), and expression of certain immunohistochemical tumor markers such as high-level expression of p53, low level of transforming growth factor-α, low level of P-glycoprotein, and expression of epidermal growth factor receptor and of the c-erB-2 oncogene (Flejou et al. 1994, Yacoub et al. 1997, Schneider et al. 2000, Aloia et al. 2001). A marker profile (a combination of negative markers) could, ideally, guide the selection of patients for neoadjuvant or adjuvant therapies (Aloia et al. 2001).

6 AIMS OF THE PRESENT STUDY

I To evaluate changes in the incidence of adenocarcinoma of the esophagus and gastric cardia in Finland during the 20-year period 1976 to 1995.

II To evaluate the role of oxidative stress and radical scavenger capacity in the pathogenesis and malignant transformation of Barrett's esophagus by measuring the parameters of oxidative metabolism and DNA adducts in GERD without and with endoscopic esophagitis, in Barrett's metaplasia without and with dysplasia, in esophageal/esophagogastric junction adenocarcinoma, and in a control group.

III To evaluate the extent and role of angiogenesis and lymphangiogenesis in Barrett's mucosa and adenocarcinoma, and the morphology of this new vascular bed.

IV To evaluate the outcome of patients with adenocarcinoma at the distal esophagus and esophagogastric junction undergoing current treatment and to compare the results of different types of therapeutic procedures.

V To compare relative lifetime costs and clinical results of the Nd:YAG laser to those of SEMS as alternative forms of primary palliation of dysphagia for adenocarcinoma of the distal esophagus and esophagogastric junction.

7 PATIENTS AND METHODS

7.1 Patients

The primary data for Studies I and IV came from the Finnish Cancer Registry (FCR). FCR, population-based and covering all parts of Finland, receives notifications of tumors independently from hospitals, physicians, pathological and hematological laboratories, and forensic autopsies. In addition, all death certificates in which cancer is mentioned are transferred each year from the files of Statistics Finland to the Cancer Registry. Multiple sources of notification at different phases of the disease improve registration coverage. On average, there are five notifications per cancer case. The quality of the Finnish Cancer Registry has been evaluated through linkage of the files of FCR with hospital discharge registry records. For solid tumors, coverage has been shown to be more than 99% (Teppo et al. 1994).

Study I

All primary malignant neoplasms of the esophagus (n=4302) (International Classification of Diseases for Oncology [ICDO] site code 150) and adenocarcinoma of the gastric cardia (n=1956) (ICDO site code 151.0) diagnosed between 1976 and 1995 in Finland, excluding rare types of esophageal cancer, were included in this analysis (World Health Organization 1976). The total number of esophageal cancers so excluded was 112 (2.6%). Esophageal cancers were divided according to ICDO morphology criteria into squamous-cell carcinoma, adenocarcinoma, neoplasms not otherwise specified, and those without histology (World Health Organization 1976).

Study II

This study included 52 patients. Mean age was 54.6 years (range 25-77): Thirteen had symptomatic GERD with pathological 24-h pH measurement, of whom eight had normal esophageal mucosa, and five mild grade-1 or -2 endoscopic esophagitis according to the Savary-Miller classification system (Savary and Miller 1978). In GERD, the histologic findings were classified according to the modified morphologic criteria of Richardson et al (1983). Endoscopic normal

esophageal mucosa revealed no change or indefinite changes in seven patients and mild changes in one; in grade-1 or –2 esophagitis, four patients had no change or indefinite changes, and one had mild changes. Thirteen had Barrett's esophagus with histologically proven intestinal metaplasia in the distal esophagus, of whom eight had intestinal metaplasia without dysplasia, and five low-grade dysplasia. Dysplasia was classified according to previously established criteria (Riddell et al. 1983). All patients with Barrett's esophagus had reflux symptoms and pathological 24-h pH measurements. Of the 19 patients with adenocarcinoma of the distal esophagus/esophagogastric junction, six had adenocarcinoma in a histologically confirmed Barrett's esophagus. Controls were seven patients without symptoms or endoscopic evidence of esophageal pathology.

Study III

Barrett's mucosa samples were collected from 15 patients who underwent surgical resection of Barrett's dysplasia (4 patients) or adenocarcinoma (11 patients) between March 1998 and November 2000. Previously, the presence of specialized intestinal metaplasia in the esophagus had been confirmed.

Study IV

A search in the Finnish Cancer Registry identified 482 primary adenocarcinomas of the esophagus (ICDO site code 150) and adenocarcinomas of the gastric cardia (ICDO site code 151.0) (World Health Organization 1976), or registrations mentioning one of these from 1990 to 1998 in Uusimaa and Pirkanmaa, two Finnish health-care districts with a total population of 1 750 000. Each diagnosis had been made endoscopially or at autopsy and confirmed by histologic examination of the biopsy specimen. The histology and location of each tumor were verified; 73 gastric-cancer patients were excluded, plus one each with esophageal squamous cancer, esophageal adenosquamous cancer, adenocarcinoma in the cervical esophagus, pancreatic cancer, lung cancer, and cancer in some unknown location. One patient had no cancer. The total number of cases so excluded was 80 (16.6%). The final analysis was limited to 402 type I and II adenocarcinomas at the EG junction according to Siewert's topographic classification (Siewert et al. 1987). Of the 402 patients (mean age 68.3, range 35-93), males numbered 282 (mean age 66.1, range 35-93), and females 120 (73.5 years, 36-93).

Study V

Patients were identified in the hospital discharge registry records. Between January 1990 and December 1998, 52 patients with esophageal or esophagogastric adenocarcinomas underwent palliative treatment due to advanced stage of the disease or high surgical risk; 40 patients had histologically confirmed adenocarcinoma at the distal esophagus and 12 at the gastric cardia. The primary palliative therapy was laser in 32 patients (mean age 73.3 years, range 48-91) and stent in 20 (mean age 70.1, range 52-87). All patients were new referrals with no previous intervention or therapy. In addition to endoscopic treatment, 16, 6 after stent placement (30%) and 10 after laser therapy (31%), received chemotherapy (1), radiotherapy (13), or both (2), based on decisions made at the interdisciplinary meetings.

7.2 Methods

Epidemiological analysis

Incidence rates were standardized for age to the world standard population and expressed per 100 000 person-years. Trends in incidence rates were evaluated annually and for 5-year calendar periods during 1976 to 1995.

Tissue-sample collection

All samples were taken either at endoscopy, with biopsy forceps, or during surgery, from the resected specimen. In Study II, patients were told to avoid any acid-suppressive treatment (proton pump inhibitors, H_2-blockers, or all others) for 2 weeks before the sampling. In the control group, samples were taken 5 cm above the esophagogastric junction. These were immediately frozen and stored at -70 °C (II). In Study III, the surgical specimens were processed on the day of collection.

Analysis of superoxide dismutase and myeloperoxidase activities and of glutathione content

Myeloperoxidase (MP) activity was determined by modification of a previous method of Suzuki in which the enzyme catalyzes the oxidation of 3,3',5,5'-tetramethylbenzidine by H_2O_2 to yield a blue chromogen with a maximum wavelength of 655 nm (Suzuki 1983). MP activity is expressed as units/milligram protein (U/mg protein).

Superoxide dismutase (SOD) activity was determined by the method reported by Laihia in which the xanthine/xanthine oxidase-dependent chemiluminescence was enhanced by both lucinogenin and linoleate (Laihia 1993). SOD activity is also expressed as U/mg protein.

Glutathione (GSH) content was estimated by Saville's method (Saville 1985). GSH concentrations are expressed as nmol/mg protein.

DNA adduct analysis

The ^{32}P-postlabeling technique was used to analyze total aromatic DNA adducts. Tissue samples frozen in liquid nitrogen were homogenized in a Mikro-Dismembrator (Braun, Melsugen, Germany). DNA isolation was performed essentially as described by Gupta (1984). DNA was digested enzymatically to 3'-mononucleotides as described (Hemminki et al. 1995). First, DNA was incubated for 2 h at 37 °C with micrococcal nuclease, then for 2 h at 37 °C with spleen phosphodiesterase in added 20 mM ammonium acetate, pH 5.0. Pi nuclease was used to dephosphorylate the normal nucleotides. The modified nucleotides were converted to 32-P-postlabeled diphosphates in a mixture containing T4 polynucleotide kinase and ATP. TLC analysis was carried out on PEI-cellulose TLC plates (Macherey-Nagel, Duren, Germany) (Hemminki et al. 1995). The adducts were detected in a Bio-Rad Image Analysis System (Bio-Rad Laboratories, Hercules, CA, USA). The average levels of DNA adducts are expressed as adducts/10^9 nucleotides. The limit of sensitivity of the assay is $1/10^{10}$.

Immunohistochemistry and quantification of blood vessels

Five- to ten-µm thick, paraformaldehyde-fixed paraffin-embedded tissue sections of resection specimens were stained with hematoxylin-eosin (Sigma, St Louis, MO, USA) and alcian blue 8GX, pH 2.5 (BDH Laboratory supplies pool, UK) -neutral red (Sigma) to assess tissue histology, and to localize Barrett's epithelium-specific goblet cells, and blood vessels. To quantify blood vessels densities, paraffin-embedded sections were deparaffined and treated with 0.3% H_2O_2 in phosphate-buffered saline-1% Tween (PBS-T; ICN Biomedicall Inc, Aurora, OH, USA) for 30 min, trypsinized with 0.1% trypsin in 0.1% $CaCl_2$ for 10 min, washed three times with PBS-T, blocked with 1.5% goat normal serum (Vector Laboratories, Burlingame, CA, USA)-1% bovine serum albumin (Sigma) in PBS-T for 20 min, incubated with monoclonal antibody EN4 (anti-CD31, Monosan, Uden, the Netherlands) for 60

min, washed three times with PBS-T, incubated with secondary biotinylated goat anti-mouse Ab (Vector) for 30 min, washed three times with PBS-T, and detected with the ABC-kit (Vector). Thereafter, cell nuclei were counterstained with hematoxylin. Blood vessels stained positive for human endothelium were quantified in 200X magnification microscopic fields (Olympus BX, Tokyo, Japan) and average counts of nine fields rich in vasculature from the mucosa as well as from the periphery of the submucosal tissue were determined. The mean score value and standard deviation were calculated for each specimen.

Whole mounts

For three-dimensional studies, a whole-mount method was adapted from Ryan et al (1998). One- to two-mm thick whole-mount sections were fixed with Carnoy's fixative (absolute ethanol:chloroform:acetic acid; 6:3:1) at room temperature for 1h. Endogenous peroxidase activity was blocked by incubation in 5% H_2O_2 in methanol. After being blocked for 1h with 3% instant skim milk and 0.1% Triton X-100 (Sigma-Aldrich, Munich, Germany) in PBS (PBS-MT), the sections were stained for endothelium-specific markers (PAL-E and EN4), angiogenic growth factors (VEGF)-A and VEGF-C, angiogenic VEGF receptors (VEGFR)-1, VEGFR-2 and VEGFR-3, matrix metalloproteinases (MMP)-2 and MMP-9, and smooth muscle cell actin (SMA). The primary antibodies diluted in PBS-MT (15 µg/ml) were incubated overnight at 4 °C. PAL-E (which recognizes an undefined endothelial antigen present in microvessels, but not in arteries) and EN4 (recognizes the endothelium-specific transmembrane protein CD31 that is expressed both in vascular and lymphatic endothelium) were purchased from Monosan (Immunodiagnostics, Hämeenlinna, Finland). The polyclonal antibodies against VEGF-A, VEGF-C, VEGFR1-3, MMP-2, and MMP-9 were all from Santa Cruz Biotechnology Inc, CA, USA. The following day, the sections were washed five times in PBS-MT for 1h, and thereafter they were incubated overnight at 4 °C with horseradish peroxidase (HRP)-conjugated secondary antibodies (DAKO, Copenhagen, Denmark, or Vector) diluted in PBS-MT (1:200). The sections were washed five times in PBS-MT for 1h, and color was developed with 0.3 mg/ml diaminobentzidine (DAB substrate kit; Vector) and 0.03% H_2O_2. HRP-conjugated smooth muscle actin monoclonal antibodies were from DAKO. Whole mount sections were viewed and photographed at 10x magnification (Leica MZFLIII microscope, Solms, Germany).

Clinical data acquisition

In Study IV, the medical records of all patients were retrieved from 23 health-care units, including two private hospitals. The following items were recorded: patient age and sex, date of diagnosis and treatment, type and place of primary treatment, type of operation and possible neoadjuvant or adjuvant therapies, fatal postoperative complications, disease status at last follow-up contact, and date and cause of death. Death certificates of those patients undergoing surgery and dying outside the treatment unit came from the Finnish Central Statistical Office. Median length of follow-up for surgical patients was 8.0 years (3.7-12.6). The outcome of patients in the various treatment groups was analyzed.

Data for Study V were collected from the patient records of Helsinki and Tampere University Hospitals. Patient demographics and data on endoscopic procedures and on pre- and post-treatreatment dysphagia plus follow-up data were registered. All patients were followed from presentation to death.

Esophageal resections

Survival of patients who underwent 2-field lymphadenectomy (n=42) was compared to survival after other less extensive dissections done through a transthoracic, transabdominal, or transhiatal approach (n=129). Standard transthoracic esophagectomy generally included only the removal of the esophagus without lymph nodes. In the transhiatal technique, the patient underwent esophagectomy by blunt dissection through the esophageal hiatus and thoracic inlet. In transabdominal surgery, extended gastrectomy was performed with esophageal resection as proximal as possible.

Our conventional 2-field lymphadenectomy included en-bloc esophagectomy with removal of adjacent lymphatic and areolar tissue between the tracheal bifurcation and the superior border of the pancreas. The block of tissue removed included, along with the bronchial, subcarinal, paraesophageal, parahiatal, celiac, left gastric, and splenic artery lymph nodes, a rim of the diaphragmatic muscle around the hiatus, the thoracic duct, both the right and left mediastinal pleura, and the lesser curve of the stomach with a 10 cm distal resection margin. The dissection was bounded anteriorly by the main bronchi and pericardium, and posteriorly by the vertebral column and aorta.

Endoscopic treatment modalities

All endoscopic treatments were performed under deep sedation conducted by an anesthesiologist. A standard fluoroscopically guided insertion technique with guidewire and radio-opaque markers was used to insert self-expanding metallic stents. Laser power was supplied by an Nd:YAG laser (Surgical Laser Technologies, Malvern, USA) via an Olympus (Tokyo, Japan) endoscope with power settings of 13 watts normally used. Tumor tissue was treated under direct vision by a contact technique. Most patients were scheduled routinely for a repeat laser treatment one to two months after initial therapy. Esophagography with water-soluble contrast material was done routinely after stent application and after laser therapy. In the absence of any signs of perforation, patients were first allowed only fluids orally. Subsequently, every patient received dietary advice. Swallowing ability was graded clinically before and after treatment: 0, swallows normally; 1, able to swallow some solid food; 2, able to eat semisolids only; 3, able to swallow fluids only; and 4, complete dysphagia (Nicholson et al. 1999).

Cost analysis

To compare total costs of the different palliative therapies, the following resource information was collected in detail: days spent in hospital, time in the endoscopic theatre, total number of various interventions, and retail costs of stents. Cost analysis was performed by summing up the cumulative costs for each individual over his or her remaining life-span. Costs are expressed as physical units (time, number) and in financial terms. Two assumptions were made: First, initial diagnostic procedures between the groups were similar. Secondly, these patients used the same community health care resources, whatever the palliative treatment. These costs were therefore not included in the analysis. In addition, because differences in survival between those undergoing the two palliative therapies would influence total costs for these treatment modalities, costs were expressed as total cost as well as cost per day of remaining life. Costs in financial terms were expressed as the current purchase cost of a specific stent (760-1420 EUR) and unit costs according to estimations of the hospital finance department. One day as an inpatient was estimated to cost 235 EUR. Cost for placement of SEMS was estimated as 264 EUR, versus 505 EUR for laser therapy. The unit costs for these endoscopic procedures included the cost of staff, materials, medication, and equipment.

7.3 Statistical analysis

Statistical calculations were carried out with SAS software (Studies II, V) and with Basic and Advanced model modules of SPSS software (Studies I, IV). The conventional level of 5% was considered statistically significant. The following tests were used:

Study I Poisson and linear regression techniques

Study II Non-parametric Kruskal-Wallis test, Wilcoxon rank sum test, Spearman's correlation coefficient

Study IV Chi-square test, Kaplan-Meier method, Log-rank test

Study V Mann-Whitney test, Fisher's exact test, Pearson's χ^2

8 RESULTS

8.1 Incidence of adenocarcinoma of the esophagus and cardia in Finland between 1976 and 1995

The incidence of esophageal adenocarcinoma in Finland increased significantly only in men (Figure 4) with the average annual rate of increase being 8.8% (95% CI: 5.9 to 14.7%). The total increase in the age-adjusted incidence rate was almost 300% during the 20-year-long period, from 0.28 to 0.77 per 10^5. By 1995, adenocarcinoma accounted for 27% of all esophageal malignancies among men. In neither sex was any change evident in the age-adjusted incidence of cancer of the gastric cardia, remaining around 2.1 per 10^5 in men, and around 0.5 per 10^5 in women.

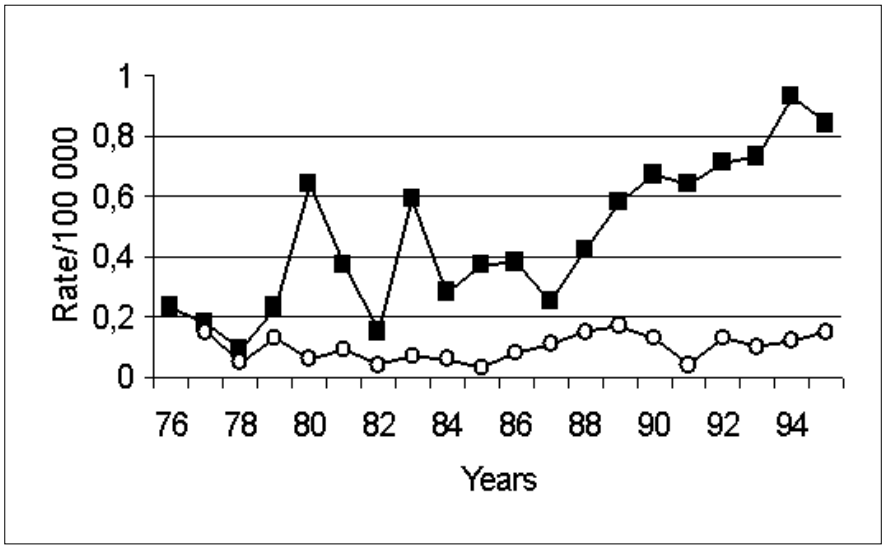

FIGURE 4 Age-adjusted incidence rates of esophageal adenocarcinoma in Finland, 1976-1995, by gender (■ male, O female)

During 1990 to 1995, the combined incidence rate for esophageal adenocarcinoma and cancer of the gastric cardia was 2.9 per 10^5 in men and 0.6 per 10^5 in women (Figure 5). The increase in this combined incidence rate in men was only slight, and no change occurred in women (Figure 5).

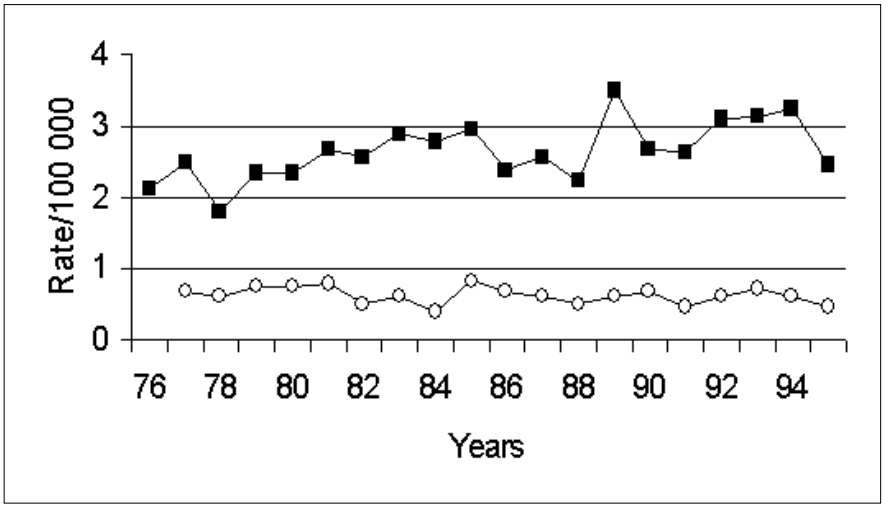

FIGURE 5 Age-adjusted incidence rates of combined esophageal adenocarcinoma and cancer of gastric cardia in Finland, 1976-1995, by gender (■ male, O female)

8.2 Oxidative stress in malignant transformation of Barrett's epithelium

Figures for the determination of myeloperoxidase and superoxide dismutase activity, glutathione content, and DNA adduct levels are shown in Table 4. In the GERD-esophagitis-metaplasia-dysplasia-adenocarcinoma sequence, glutathione content was progressively lower, and myeloperoxidase activity higher than in controls, but plateauing at Barrett's epithelium without dysplasia. Only in Barrett's mucosa with dysplasia did SOD activity differ significantly from that of the controls. In addition, SOD activity was significantly higher in Barrett's epithelium without and with dysplasia than in GERD without esophagitis. At the same time, mean DNA adduct levels were significantly higher than those of the control group in all five patient groups. Though the levels between these groups did not differ significantly, the level was highest in Barrett's epithelium without dysplasia, and progressively lower in Barrett's with dysplasia and with adenocarcinoma.

In the pooled data, Spearman's correlation analyses between GSH contents and DNA adducts showed a negative correlation (-0.28, $p<0.05$). No correlation existed between SOD or MP activity and DNA adduct levels.

TABLE 4 Descriptive statistics with p-values by parameter and group

Parameter	Control	GERD, no esophagitis	GERD+ esophagitis	Barrett	Barrett + dysplasia	Carcinoma
No. of patients	7	8	5	8	5	19
GSH (nmol/mg protein)						
Mean ± SEM	2.93 ± 0.31	2.09 ± 0.17	1.56 ± 0.17	1.34 ± 0.11	1.21 ± 0.12	1.33 ± 0.32
Median (Range)	2.96 (1.35-3.88)	2.14 (1.44-2.66)	1.51 (1.10-2.14)	1.30 (0.80-1.86)	1.31 (0.91-1.48)	1.02 (0.34-6.29)
p-value*	-	0.043	0.035	0.005	0.015	0.002
p-value†	0.043	-	0.067	0.006	0.007	0.004
SOD (U/mg protein)						
Mean ± SEM	0.111 ± 0.004	0.091 ± 0.015	0.110 ± 0.023	0.166 ± 0.027	0.200 ± 0.036	0.244 ± 0.074
Median (Range)	0.110 (0.100-0.130)	0.083 (0.046-0.158)	0.111 (0.035-0.161)	0.130 (0.093-0.290)	0.167 (0.130-0.317)	0.205 (0.020-1.51)
p-value*	-	0.181	0.870	0.413	0.007	0.174
p-value†	0.181	-	0.509	0.031	0.023	0.084
MP (U/mg protein)						
Mean ± SEM	0.24 ± 0.10	0.57 ± 0.45	1.99 ± 0.98	4.18 ± 0.93	4.14 ± 1.34	2.16 ± 0.66
Median (Range)	0.13 (0.02-0.78)	0.12 (0.03-3.74)	0.80 (0.14-4.64)	4.15 (0.03-8.15)	4.73 (0.85-7.70)	1.45 (0.21-12.67)
p-value*	-	0.602	0.042	0.013	0.006	<0.001
p-value†	0.602	-	0.048	0.031	0.010	0.002
DNA adducts/10^9 nucleotides						
Mean ± SEM	0.1 ± 0.08	11.6 ± 1.75	11.0 ± 1.85	17.3 ± 6.13	11.9 ± 1.75	8.9 ± 1.05
Median (Range)	0.0 (0.0-0.5)	10.8 (5.1-22.5)	10.8 (4.6-14.9)	11.9 (5.3-58.7)	12.3 (5.8-15.9)	7.9 (2.9-21.5)
p-value*	-	0.001	0.005	0.001	0.005	<0.001
p-value†	0.001	-	0.942	0.637	0.464	0.117

* P-values based on Wilcoxon rank sum test (pairwise comparisons between group and control).

† P-values based on Wilcoxon rank sum test (pairwise comparisons between group and GERD).

8.3 Angiogenesis and lymphangiogenesis in Barrett's epithelium and in esophageal adenocarcinoma

Barrett's salmon-pink mucosa was characterized by intense infiltration of endothelium-specific protein CD31-positive angiogenic blood vessels (Figure 6D). Microvessel density was doubled (±SD) in Barrett's epithelium (83.0±61.3) and was two- to three-fold in advanced adenocarcinoma (112.5±46.3) above that of normal esophageal mucosa (39.4±22.9), the number of capillaries remaining unchanged.

The whole-mount technique showed that only a few blood vessels penetrated into normal esophageal mucosa (Figures 6A and 7A). In Barrett's epithelium, and in related dysplasia and adenocarcinoma, new angiogenic microvessels infiltrated the entire mucosa (Figures 6B, and 7B-D). The angioarchitecture within Barrett's epithelium consisted of new microvessels that were very small and deformed, containing tortuosities, corkscrew structures, blind ends, and abnormal branching (Figure 6B).

Barrett's epithelium overexpressed vascular endothelial growth factor A and its receptor, VEGFR-2. The new blood vessels expressed the matrix metalloproteinases MMP-2 and MMP-9 on their exterior surfaces. In paraffin sections, an increasing percentage of vessels were devoid of smooth muscle actin in Barrett's epithelium (5%), dysplasia (25%), and adenocarcinoma (40%).

Lymphangiogenic growth factor VEGF-C was not expressed in normal esophageal mucosa, but its increased expression during the progression of Barrett's epithelium to dysplasia and to adenocarcinoma was evident. In parallel, expression of lymphangiogenic receptor VEGFR-3 was upregulated, particularly in dysplasia and adenocarcinoma (Figures 7E and F). The lymphatics of normal and metaplastic tissue were compact; in dysplasia and adenocacinoma they were more loose in structure (Figures 7E and F). The metastatic lymph nodes were positive for both VEGF-C and VEGFR-3 expression.

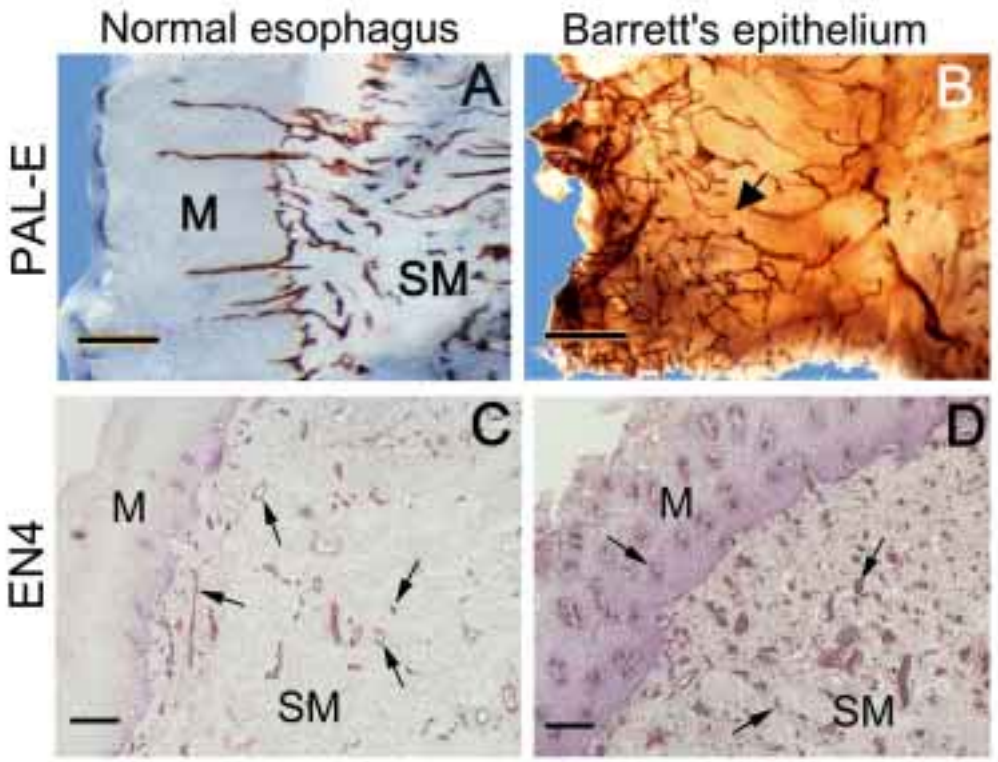

FIGURE 6 Barrett's epithelium is neovascularized. Whole mount (A and B) and paraffin sections (C and D) from normal esophagus and Barrett's epithelium were stained with antibodies against the undefined vascular endothelial marker PAL-E (A and B) or hematoxylin and EN4 (C and D). Endothelium-specific markers, monoclonal antibodies EN4 and PAL-E, stain capillaries and microvessels in both mucosa (M) and submucosa (SM). The blood-vessel architecture of normal esophagus (A) is distorted by new netlike blood vessel ingrowth in Barrett's epithelium (B). Note the strong increase in density of new blood vessels penetrating mucosa adjacent to Barrett's epithelium (arrow in panel D) in comparison to that of normal esophageal mucosa (C); also note equal thickness of mucosa layers. Scale bars: 20 μm, A and B; 50 μm, C and D.

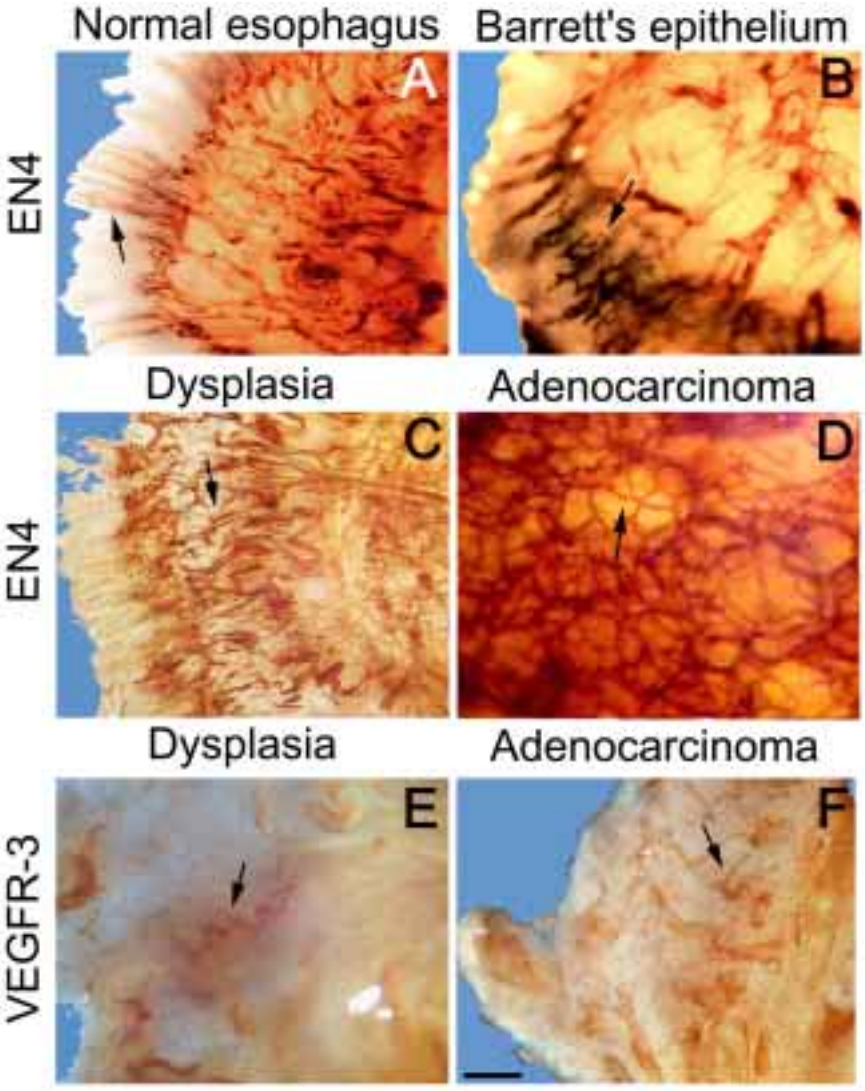

FIGURE 7 Whole-mount sections showing metaplasia-dysplasia-adenocarcinoma sequence in Barrett's esophagus stained with EN4 antibody staining both blood vessels and lymphatic vessels (A-D), or stained with anti-VEGFR-3 (E-F). The pre-existing vascular bed in submucosa and some blood vessels nourishing the mucosa are clearly visible in normal esophageal mucosa (A; arrow), whereas in Barrett's epithelium (B; arrow), dysplasia (C; arrow), and adenocarcinoma (D; arrow), the vascular bed infiltrates the whole mucosa. Anti-VEGFR-3 stains fewer vessels (E and F) than does EN4 (A-D), and VEGFR-3-positive lymphatic vessels (E and F) are morphologically distinct from blood vessels (D; see also Figs. 6A and 6B). E and F show the appearance of lymphatic vessels in dysplasia (E) and adenocarcinoma (F); panel F shows invasion of lymphatic vessel into adenocarcinoma tumor stroma, as well.
Scale bars: 20 μm, A-F.

8.4 Treatment and outcome of patients with adenocarcinoma of the esophagus and esophagogastric junction

Of the 402 patients, 171 patients underwent resection, and 19, explorative surgery (Table 5), making the resectability rate of these patients 171 of 190 (90.0%). Of the remaining 212, 136 were treated palliatively, mainly with endoscopic treatment modalities, and 76 received no treatment because of advanced stage, poor general physical condition, or both (Table 5).

TABLE 5 Primary treatment for adenocarcinoma of esophagus and cardia

Treatment modality	
Surgical approach	**171 (42.5%)**
Transthoracic	104
Transhiatal	21
Transabdominal	46
Explorative operation	**19 (4.7%)**
Only exploration	7
+ stent +radio- and/or chemotherapy	6
+ stent	3
+ laser	1
+ gastrostomy	1
+ chemotherapy	1
Palliation	**136 (33.8%)**
Laser	54
Laser + chemo- and/or radiotherapy	13
Laser + brachytherapy	1
Stent	34
Stent + chemo- and/or radiotherapy	6
Dilation	5
Brachytherapy	1
Chemo- and/or radiotherapy	14
Jejunostomy/gastrostomy	6
Percutaneus endoscopic gastrostomy	1
Endoscopic excision	1
No treatment	**76 (18.9%)**
Total	**402**

Overall, 5-year survival for patients with adenocarcinoma near the esophagogastric junction was 12.5%. Patients without treatment (median survival 36.5 days, range 0 days-68.1 months), with palliation (median survival 116.5 days, range 0 days-59.5 months), or with

exploratory surgery (median survival 211 days, range 113 days-26.6 months) had a dismal prognosis (Figure 8). Altogether, only one of 231 survived 5 years, making the rate less than one percent. After resection, median survival was 17.6 months (0-101.1), and the Kaplan-Meier estimate of survival at 5 years was 29.0%. However, the 5-year survival rate was significantly better in patients with 2-field lymphadenectomy (n=42) than in patients with less extensive surgery (n=129), when all deaths (50.0% vs. 23.2%, p=0.005) or only cancer deaths (55.0% vs. 28.2%, p=0.0036) were included.

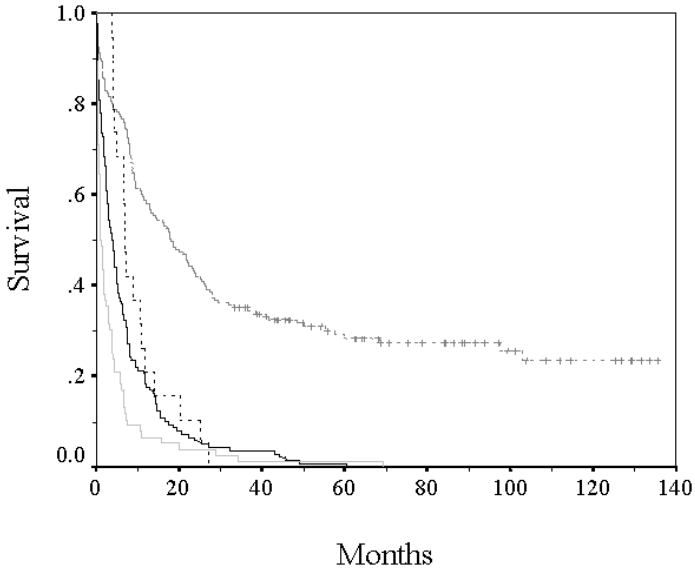

FIGURE 8 Five-year survival of 402 patients with adenocarcinoma of the distal esophagus and at the GE junction according to treatment method (resection —, explorative surgery - - -, palliation —, no treatment —)

Among the 171 patients who underwent resection, 15 (8.8%) died within 30 days and 31 (18.1%) within 90 days, with the main causes of death not differing between these two groups (Table 6). One of these patients died because of disease-related general weakness within 30 days and four of these from disease progress within 90 days. No statistically significant difference appeared between conventional 2-field lymphadenectomy and less invasive procedures in 30-day (7.1% vs. 9.3%) and in 90-day (11.9% vs. 20.2%) surgical mortality.

In follow-up, 13 of 123 (10.6%) patients operated on died without evidence of disease recurrence (Table 7), but overall, 341 of 354 (96.3%) of those not surviving died of their disease.

TABLE 6 Cause of death in patients dying within 30 and 90 days postoperatively

Complication	30 days	31-90 days	Total
Myocardial infarction	4	2	6
Cardiomyopathia and heart insufficiency	-	1	1
Cerebrovascular accident	1	1	2
Colon conduit necrosis / perforation	1	1	2
Anastomotic leak + sepsis	-	1	1
Liver failure	1	-	1
Pancreatitis	1	1	2
Colon perforation	1	-	1
Pneumonia	4	2	6
Aspiration/Pneumonia +ARDS	1	2	3
Lung embolism	-	1	1
Disease (General weakness)	1	4	5
Total (%)	**15 (8.8)**	**16 (9.4)**	**31 (18.1)**

TABLE 7 Cause of late death (>90 days) in surgical patients (n=123) without evidence of disease recurrence

Cause	N=13 (10.6%)
Pneumonia	3
Lung cancer	2
Chronic obstructive lung disease	1
Myocardial infarction	1
Cerebral infarction	1
Thoracic aortic aneurysm	1
Rectal cancer	1
Breast cancer	1
Alcohol liver damage	1
Intoxication	1

8.5 Outcome and costs of laser coagulation and self-expanding metallic stents

The technical success rate for the stent group was 18 of 20 (90%) and for laser therapy was 30 of 32 (94%). In two patients, SEMS were incorrectly inserted. Two unsuccessful laser therapies caused one fatal perforation and one total esophageal obstruction. The magnitude of improvement in dysphagia between the study groups did not differ (Table 8).

Patients in the stent group experienced significantly more (p=0.043) complications than did those in the laser group (Table 8). Hospital

mortality was also higher in the stent group (4 vs. 1; 20% vs. 3.1%, p=0.066). The only death caused by laser therapy was due to perforation. Causes of death after stent placement were due to pneumonia, sepsis, intestinal ischemia, and aspiration. The rate of long-term complications did not differ between groups, nor was there any significant difference in inter-group survival (p=0.225) (Table 8).

TABLE 8 Outcome of endoscopic treatment for 52 patients

Treatment modality	**Laser (n=32)**	**Stent (n=20)**
Technical success (%)	94	90
Median post-treatment dysphagia score (range)	2 (0-4)	2 (2-4)
Median improvement in dysphagia score (range)	1 (-1-3)	1 (-2-2)
Early complications (%)	6.3	30*
Late complications (%)	41	30
Hospital mortality (%)	3.1	20
30-day mortality (%)	3.1	40†
Survival (days) (means ± SD)	144 ± 138	139 ± 158

*P=0.043 and †p=0.0011 in comparison with laser therapy

Costs by group can be expressed as physical units and in financial terms (Table 9). The number of interventions was significantly higher (p=0.0048) for laser therapy than for the stent group. The total amount of time required by endoscopies was 118 min (10 min-12.6 hours) for the laser group and 38 min (10-100 min) for the stent group (p=0.0048). No difference existed between the groups in time spent in hospital (p=0.370). Overall costs and cost per day of palliation did not differ significantly between the expansible stent group (respectively, 5360 EUR, range 1820-14590; 175 EUR, range 5-620) and the laser therapy group (5450 EUR, range 1110-31775; 85 EUR, range 6-1175 EUR).

TABLE 9 Costs (means ± SD) by group, expressed as physical units and in financial terms (in EUROS).

Treatment modality	**Laser (n=32)**	**Stent (n=20)**
No. of interventions	3.4 ± 4.0	1.9 ± 1.6*
No. of stents	0.5 ± 0.6	1.4 ± 0.5†
No. of laser treatments	2.6 ± 3.6	0.05 ± 0.2†
No. of endoscopies	0.2 ± 0.37	0.3 ± 0.73
Other interventions/admissions	0.2 ± 0.49	0.3 ± 0.47
Days spent in hospital	15.1 ± 14.8	12.9 ± 11.5
Time spent in endoscopic theatre (min)	118 ± 152	38 ± 25*
Stent costs	470 ± 715	1705 ± 695†
Procedure costs	1530 ± 1800	620 ±610‡
In-patient costs	3460 ± 3505	3040 ± 2720
Total costs	5450 ± 5500	5360 ± 3650
Cost per day of survival	85 ± 205	175 ± 205

*P=0.0048, †p<0.0001, and ‡p=0.0002 in comparison with laser therapy

9 DISCUSSION

9.1 Reliability of data

Studies based on registry data can be no better than data provided by the original sources. Several epidemiological studies of esophageal adenocarcinoma have omitted cancer of the gastric cardia (Yang and Davis 1988, Hesketh et al. 1989, Hansson et al. 1993, McKinney et al. 1995). In addition, data have been based on relatively small populations (Levi 1991, Pera et al. 1993), or completeness of records has been less than 90% (Armstrong and Borman 1996). Both the quality of the data and the level of quality control of the Finnish Cancer Registry have been well evaluated (Teppo et al. 1994). Coverage of the Registry for solid tumors is excellent (>99%). Completeness of the data should thus cause no bias in Studies I and IV. Moreover, we must assume no subtype bias among histologically verified cases (I). At the Finnish Cancer Registry, one and the same pathologist evaluated all the histologically problematic cases throughout the entire study period.

9.2 Epidemiology of adenocarcinoma near the esophagogastric junction

This study shows a significant increase with time in the incidence of esophageal adenocarcinoma in Finnish men. At the same time, incidence of esophageal adenocarcinoma in women and cancer of the gastric cardia in both sexes have remained relatively stable. This is also the trend in several other countries such as Australia, New Zealand, Norway, Scotland, Sweden, and Switzerland (Levi et al. 1990, Levi 1991, Hansson et al. 1993, McKinney et al. 1995, Armstrong and Borman 1996, Hansen et al. 1997, Lord et al. 1998). In some countries (USA and England), esophageal adenocarcinoma in women and cancer of the gastric cardia in both genders are both on the increase, as well (Blot et al. 1991, Dolan et al. 1999).

At one time, adenocarcinomas close to the EG junction were classified as being of gastric origin. With heightened awareness of esophageal adenocarcinoma, change in incidence may reflect a change

in these tumors' classification. For example, the study by Webb and Busuttil (1978) included 52 adenocarcinomas of the esophagus and esophagogastric junction. Of these, 22 had hiatal hernias with a mean upper tumor level at 31 cm in the esophagus. Only two of these were classified as primary esophageal adenocarcinomas. Thus, a substantial degree of misclassification has taken place. Evaluation of the incidence rates of esophageal adenocarcinoma becomes even more vulnerable to error when the clinical difficulties in establishing the exact origin of a tumor at the EG junction and the ambiguous definition of the gastric cardia in the literature are included.

The problem of distinguishing distal esophageal adenocarcinoma from cancer of the gastric cardia could be further magnified by the difficulty in separating cardia tumors from non-cardia gastric cancer. The increasing incidence of cardia cancer can be explained by the misclassification of gastric tumors (Ekström et al. 1999). Based on the present Study (I), the incidence of cardia cancer in Finland has remained unchanged. In Study IV, of 482 adenocarcinomas near the EG junction, 73 (15.1%) had, however, to be excluded from the study due to their subcardial location (Siewert type III). In addition, gastric cardia and non-cardia cancers have been far more common than esophageal adenocarcinoma. Thus, a proportionally small degree of misclassification of these tumors to a more oral location would cause a substantial rise in the incidence of esophageal adenocarcinoma.

If the combined rates of esophageal and gastric cardia adenocarcinomas were calculated, incidence rates would not change, or at least the increase in several countries would seem more reasonable (Hansen et al. 1997, Lord et al. 1998, Blot et al. 1991, Armstrong and Borman 1996, Levi 1991, Levi et al. 1990). In Finland, these combined incidence rates have also risen steadily, but not dramatically. Therefore, to get a truthful picture of changes in the occurrence of these cancers, when incidences of distal esophageal adenocarcinoma are reported, the focus should be on all the adenocarcinomas near the EG junction.

9.3 Why is the incidence of adenocarcinoma increasing?

The reason for the continuous rise in the incidence of adenocarcinoma near the EG junction is unknown. Little evidence exists to show that the prevalence of Barrett's metaplasia, the most important risk factor for

esophageal adenocarcinoma, has increased over time (Watson et al. 1999). Nor do consistent data exist on the changing prevalence of GERD.

Four recent studies have revealed a modestly increased risk for esophageal and gastric cardia adenocarcinoma in smokers (Kabat et al. 1993, Vaughan et al. 1995, Zhang et al. 1996, Gammon et al. 1997). It seems that smoking cannot explain the recent rise in incidence of adenocarcinoma near the EG junction, because prevalence of cigarette smoking is decreasing simultaneously with the increase in cancer rate (Pierce et al. 1989). The risk for adenocarcinoma of the esophagus and gastric cardia persists, however, for nearly 30 years after cessation of smoking (Gammon et al. 1997). In addition, that group suggests that in these cancers cigarette carcinogens act in an early stage of carcinogenesis. The pattern of smoking prevalence during the 20th century (increasing up to the 1970's) may thus contribute to recent changes in incidence of adenocarcinoma in the esophagus and gastric cardia (Pierce et al. 1989).

The contribution of alcohol to the increasing incidence of adenocarcinoma of the esophagus and gastric cardia is most likely to be minimal. Recent epidemiological studies demonstrate only a weak or no association between alcohol consumption and these adenocarcinomas (Vaughan et al. 1995, Zhang et al. 1996, Gammon et al. 1997).

Obesity seems to be a risk factor for esophageal adenocarcinoma and also for cancer of the gastric cardia (Brown et al. 1995, Vaughan et al. 1995, Chow et al. 1998a, Lagergren et al. 1999b). The growing prevalence of obesity in Western countries and the rising rates of esophageal adenocarcinoma are parallel phenomena. Possibly by causing increased gastroesophageal reflux, obesity may be of more and more importance as an indirect risk factor for this disease.

It is also estimated that 10% of the esophageal adenocarcinomas may be attributable to the use of LES-relaxing drugs (Lagergren et al. 2000). Our study did not, however, seek any association between these drugs or other potential risk factors and the rising incidence of adenocarcinoma near the EG junction.

9.4 Pathogenesis of esophageal adenocarcinoma

Simultaneous formation of DNA adducts, increased oxidative stress (increased MP activity), and decreased antioxidant capacity (reduced GSH content) in the esophagitis-metaplasia-dysplasia-adenocarcinoma sequence of Barrett's esophagus indicates the important role in the pathogenesis and malignant transformation of Barrett's epithelium played by oxidative stress. At the same time, this sequence was characterized by an increased frequency of highly abnormal microvessels, an increasing percentage of immature vessels, and an increased expression of VEGF-A and VEGF-C.

Gastroesophageal reflux disease has been shown to increase the production of oxygen free radicals in the esophageal mucosa in studies measuring free radicals by means of chemiluminescence assay and either lipid peroxidation or myeloperoxidase activity in patients with reflux esophagitis or Barrett's epithelium (Wetscher et al. 1995, Olyaee et al. 1995). In rats, reflux-related esophageal mucosal damage and lipid peroxidation may be reduced by antioxidants (Oh et al. 2001). Our study supports these findings, and in addition, in the present study, the increase in DNA adducts simultaneously with oxidative stress in complicated GERD strengthens the role of gastroesophageal reflux in the pathogenesis of esophageal adenocarcinoma. Though the size of the present study is limited, it appears to establish direct evidence to link oxidative stress with esophageal adenocarcinoma. An epidemiological association between higher intake of antioxidants and decreased risk for esophageal adenocarcinoma exists, as well (Terry et al. 2000). Oxidative stress can therefore be considered one of the important driving forces for carcinogenesis in gastroesophageal reflux disease and in Barrett's epithelium.

Some carcinogens may enhance endogenous DNA adduct formation by an indirect mechanism such as induction of oxidative stress (Nestmann et al. 1996). The efficiency of the local metabolism will also affect exogenous DNA adduct formation, because a large proportion of genotoxic agents require activation to electrophilic compounds (De Flora et al. 1996). The step-by-step increase seen in MP activity indicates increased oxidative stress related to the severity of reflux disease. In addition to amplified oxidative stress, activation of carcinogens by MP is a possible mechanism resulting in DNA adduct formation, tissue injury, and carcinogenesis (Petruska et al. 1992, Williams 2001). In mice, MP

has transformed a respiratory carcinogen to an ultimate carcinogenic metabolite, and furthermore, has enhanced DNA adduct formation (Petruska et al. 1992).

In our study, MP activity and DNA adducts were highest in Barrett's esophagus rather than in adenocarcinoma. The cause of this depleted MP activity in adenocarcinoma is unclear. In tumor stenosis it may reflect decreased gastroesophageal reflux-related oxidative stress and inflammation, and therefore a dose-response relationship between the level of adducts and oxidative stress. Previously, etheno-DNA adduct levels were found to be lower in carcinoma than in pre-neoplastic colonic polyps (Schmid et al. 2000). Similarly, in tumor tissues, DNA adduct levels were lower than in tumor-adjacent tissue (Wang et al. 1998). These findings were in close agreement with our data. As a result, the level of DNA adducts seems to be higher during carcinogenesis and not in the final stage of cancer. Though DNA adducts play a role in risk for cancer induction and progression, the long latency period of cancer development may lead to the loss of DNA adducts as a consequence of accumulation of multiple genetic abnormalities in genes and on chromosomes (Nestmann et al. 1996, Winjnhoven et al. 2001).

In the present study, DNA adducts were already higher and GSH levels lower in GERD without esophagitis than in controls, indicating the early role of oxidative stress in reflux-related esophageal mucosal damage. With further suppression of antioxidant capacity (GSH), and with increased MP activity in esophagitis and in Barrett's epithelium, mucosa is exposed to amplified oxidative stress; a low content of GSH in Barrett's epithelium has indeed been observed (Peters et al. 1993). In an experimental reflux model involving ligation of the proximal jejunum in rats, mucosal decrement of glutathione was discovered in esophagitis (Oh et al. 2001). In that rat model, antioxidants attenuated the depletion in GSH levels. The present study shows a negative correlation between GSH content and DNA adduct formation, indicating that the low antioxidant capacity of the esophageal mucosa in Barrett's esophagus elevates DNA adduct formation and the risk for carcinogenesis. Hence, reflux-related oxidative stress seems to deplete GSH and enhance cellular sensitivity to various agents. In GERD, the lower GSH content may, however, be due as well to the impairment of the glutathione redox capacity, which occurs in cultured endothelial cells at an acidic pH (Ikebuchi et al. 1996).

Endothelial cell proliferation and microvascular remodeling occur at an early stage in chronic inflammation (Ezaki et al. 2001), enabling metabolic support for the tissues and allowing inflammatory cells to reach the diseased area. These cells release angiogenesis activators such as VEGF, angiopoietin 1, FGF, and TGF, among many others, in abundance (Carmeliet and Jain 2000). Several of these potential proangiogenic factors, such as MMP, VEGF, TGF, and FGF, have been discovered in the metaplasia-dysplasia-adenocarcinoma sequence of Barrett's esophagus (Triadafilopoulo and Kumble 1996, Soslow et al. 1997, Salmela et al. 2001). In our study, high expression of vascular endothelial growth factor and its receptor, and of matrix metalloproteinases suggests their importance in angiogenesis in Barrett's epithelium and related adenocarcinoma. These results, taken together, suggest an interesting functional interplay between angiogenic cells and new invading blood vessels in neovascularization of Barrett's mucosa.

Accelerated angiogenesis, assessed by higher microvessel density in microscopic fields, has been discovered in Barrett's epithelium and esophageal adenocarcinoma (Torres et al. 1999, Millikan et al. 2000, Couvelard et al. 2000). In this study, the microvessel density was doubled in Barrett's epithelium and was two- to three-fold in advanced adenocarcinoma above that in normal esophageal mucosa. Furthermore, the whole-mount technique provided three-dimensional evidence that during the early stage of tumor development in Barrett's epithelium the rich new vascular bed is already highly abnormal.

In several cancers such as breast and lung cancer, the greater the degree of angiogenesis detected in a primary tumor, the worse its prognosis (Toi et al. 1993, Weidner 1995, Yuan et al. 2001). In Barrett's carcinoma, a direct relationship between angiogenesis and metastasis remains to be established (Torres et al. 1999, Millikan et al. 2000). On the other hand, esophageal adenocarcinoma spreads early into the lymphatic system (Rice et al. 1998, Stein et al. 2000). Because expression of VEGF-C and its receptor VEGFR-3 in adenocarcinoma overlapped, it seems that VEGF-C may induce, as suggested in gastric cancer, proliferation of lymphatic vessels in the stroma of a tumor via activation of VEGFR-3 (Yonemura et al. 2001). The structure of lymphatics in dysplasia and cancer was loose, and they were also seen to penetrate the adenocarcinoma tumor stroma (Study III). It is reasonable to assume that in these circumstances, lymphatic vessels offer less resistance and more contact area for penetration of cancer

cells into the lymphatic system than into blood vessels. Tumor lymphangiogenesis may therefore be an important phenomenon for the lymph node metastasis formation which is frequent in esophageal adenocarcinoma.

9.5 Treatment

To our knowledge, this may be the first study to establish, in one clearly defined geographical area, and for 9 years, the fate of every patient undergoing modern treatment for adenocarcinoma at the distal esophagus and at the EG junction (Study IV). Overall, prognosis was still poor. Only 12.5% survived longer than 5 years. Operative resection offered the best chance for a cure with a 5-year survival rate of 29.0%. Less than one percent of patients treated with other methods were alive at 5 years. On the other hand, half the adenocarcinoma patients eligible for major surgery with 2-field lymphadenectomy had a chance to survive long-term. In advanced disease, these patients were palliated as effectively with placement of self-expandable metallic stents as with laser therapy, without differences in overall cost of therapy (Study V).

The 5-year survival rate after esophagectomy according to Earlam's large review was 12% in the 1960's and 1970's (Earlam and Cunha-Melo 1980). Similarly, a population-based analysis revealed an only 9.8% 5-year survival for radical resection of adenocarcinoma at the gastric cardia (Allum et al. 1980). The 5-year survival rate of 29.0% in our unselected material was similar to that recently reported by Siewert et al (32.3%) and Collard (35.3%) (2000; 2001). Overall survival of these patients has improved during recent decades, reflecting earlier diagnosis and improvement in the results of surgical therapy. Because the potentialities of radical surgery for adenocarcinoma near the EG junction are much greater than 20 or 30 years ago, surgery should be considered the primary mode of therapy for patients without contraindications.

Previously, esophagectomy had the highest surgical mortality (29%) of any routinely performed surgical procedure (Earlam and Cunha-Melo 1980). Similarly, radical resection of adenocarcinoma at the gastric cardia carried a 19% 30-day mortality (Allum et al. 1980). In a recent meta-analysis including 50 articles published between 1990 and 1999,

in-hospital mortality among 7584 patients after esophagectomy was 7.5% (Hulscher et al. 2001). Our study revealed an 8.8% 30-day and an 18.1% 90-day death rate for surgical treatment of adenocarcinoma near the EG junction.

Centers with large experience have achieved lower mortality rates (Orringer et al. 1999, Siewert et al. 2000, Collard 2001), and increasing evidence does show that surgical volume and experience has a major impact on surgical mortality after major cancer surgery, especially after esophagectomy (Miller et al. 1997, Begg et al. 1998, Patti et al. 1998, Swisher et al. 2000). In addition to better patient selection and overall experience, progressive refinement in surgical techniques and in perioperative care of patients is able to reduce both the morbidity and mortality after esophagectomy and to improve survival (Sutton et al. 1998, Whooley et al. 2001).

In surgery for esophageal cancer, the role of radical lymphadenectomy is a debated topic. No prospective randomized study has evaluated its role in surgical treatment of adenocarcinoma of the esophagus and EG junction. The most important concern is whether a more radical lymph node dissection really contributes to an increase in survival. Those patients who would potentially benefit from more extensive resections are those with only a few metastatic lymph nodes (Nigro et al. 1999). Two recent analyses revealed 5-year survival rates of 40% and 52% for patients with adenocarcinoma after en-bloc esophagectomy (Altorki and Skinner 2001, Hagen et al. 2001). In our population-based series, comparable results (5-year survival 50% vs. 23% after less extensive surgery) were also achieved in patients who underwent en-bloc esophagectomy in Helsinki and Tampere University hospitals. Therefore, in centers with considerable experience, such radical surgery should be favored for patients eligible for major surgery.

Before the 1980's, the role of oncological therapy was considered very limited in the treatment of this adenocarcinoma (Earlam and Cunha-Melo 1980). In the present population-based analysis, only 9.7% of 402 patients received radiation, chemotherapy, or both, alone or in combination with endoscopic treatment modalities. This is contrary to a recent hospital-based evaluation revealing that 44% of patients with adenocarcinoma of the esophagus received primarily only oncological therapy (Daly et al. 2000). Many of these patients are in an advanced stage or are in poor physical condition, or both, and are unable to tolerate treatments with high frequencies of severe side-

effects (Hejna et al. 1996, Cooper et al. 1999). In advanced disease, the response rate to chemotherapy or radiochemotherapy has been between 14% and up to 57% and has lasted only a few months (Khansur et al. 1994, Highley et al. 1994, Hejna et al. 1996, Enzinger et al. 1999). Therefore, oncological therapy by itself still plays only a limited role in the overall treatment of patients with adenocarcinoma near the EG junction. The role of multimodality therapy is evolving, with some evidence of neoadjuvant radiochemotherapy improving survival (Walsh et al. 1996). At this point, however, the role of preoperative chemoradiotherapy in the treatment of adenocarcinoma near the EG junction remains unresolved. Before those patients who benefit from chemoradiotherapy can be clearly identified, others may still suffer the associated complications. Multimodality treatment should, therefore, be offered only to patients with locally advanced tumors with strong suspicion of lymph node metastases.

The role of endoscopic treatment modalities for palliation of dysphagia and improvement of quality of life are of great importance. No prospective randomized studies compare laser therapy and self-expanding metallic stents in the treatment of malignant dysphagia entirely due to adenocarcinomas near the EG junction. SEMS have proven superior to esophageal intubation with plastic prostheses (Knyrim et al. 1993, DePalma et al. 1996, Siersema et al. 1998). Similarly, laser therapy has provided better palliation than have plastic prostheses (Alderson and Wright 1990, Carter et al. 1992). Based on Study V, it seems that laser therapy palliates dysphagia of patients with adenocarcinoma at the distal esophagus or at the EG junction effectively without increased costs or hospital stays and with lower morbidity and mortality rates than for self-expanding metallic stents. Laser therapy is therefore warranted for patients with advanced adenocarcinoma near the EG junction with neither a long, tortuous stricture nor extensive extrinsic compression. Because the treatment, regardless of the primary method, in many cases has to be changed during the course of the therapy, these endoscopic treatment modalities should be considered complementary rather than mutually exclusive.

Regardless of increased awareness of this disease, of improvement in staging, and of a more radical surgical approach, even today little can likely be done to improve overall prognosis for the whole population of patients with adenocarcinoma near the EG junction. Probably the only means to achieve a better prognosis for the majority is earlier

diagnosis. On the other hand, management of these tumors is evolving continuously, with some evidence, for example, that neoadjuvant radiochemotherapy improves survival (Walsh et al. 1996); only those patients with a response do, however, benefit from it, and others may still suffer from its associated complications (Heath et al. 2000, Liedman et al. 2001, Urba et al. 2001). Study IV clarifies the outcome to be expected after current treatment modalities in unselected patients and provides a benchmark against which new therapies can be assessed.

10 SUMMARY

Adenocarcinoma near the esophagogastric junction has been one of the most lethal malignancies, with less than 5% of patients surviving in the long term. In this thesis we studied the epidemiology, pathogenesis, and treatment of this disease.

The incidence of esophageal adenocarcinoma has increased significantly in Finland only in men. In men the combined incidence of adenocarcinomas in the esophagus and gastric cardia has increased steadily as well, but this increase is not as dramatic as in esophageal adenocarcinoma.

Simultaneous formation of DNA adducts, increased oxidative stress, and decreased antioxidant capacity have revealed the important role played in the pathogenesis and malignant transformation of Barrett's epithelium by oxidative stress. This metaplasia-dysplasia-carcinoma sequence in Barrett's esophagus was also characterized by increased density of microvessels, overexpression of VEGF-A and its receptor, and of MMP-9, and by an increasing percentage of immature blood vessels. In addition, the whole-mount technique offered three-dimensional evidence that the morphology of the rich new vascular bed is already highly abnormal in non-malignant Barrett's epithelium, and the structure of the lymphatics in dysplasia and cancer is loose. In these stages, expression of VEGF-C and VEGFR-3 was upregulated, as well. Lymphangiogenesis was suggested to be an important phenomenon for the frequent lymph node metastasis formation.

It seems that for patients having adenocarcinoma at the distal esophagus or at the esophagogastric junction, laser therapy palliates dysphagia more effectively without increased costs or hospital stays, and with lower morbidity and mortality rates than do self-expanding metallic stents. Overall prognosis in this dreadful disease is still poor, and only surgical treatment is able to offer a cure. A substantial percentage of patients eligible for major surgery now achieve long-term survival.

11 CONCLUSIONS

I The combined incidence of esophageal and gastric cardial adenocarcinomas shrinks the substantial rise in the incidence of esophageal adenocarcinoma in Finnish men to a more reasonable increase. To obtain an accurate picture of changes in the occurrence of these adenocarcinomas, the focus should be on all these adenocarcinomas near the esophagogastric junction, when incidences of distal esophageal adenocarcinoma are reported.

II Simultaneous formation of DNA adducts, an increased myeloperoxidase-related oxidative stress, a decreased antioxidant capacity (glutathione content) and a negative correlation between glutathione content and DNA adducts in the GERD-esophagitis-metaplasia-dysplasia-adenocarcinoma sequence of Barrett's esophagus appear to be direct evidence linking oxidative stress to the malignant transformation of Barrett's epithelium.

III Barrett's esophagus is strongly neovascularized. High expression of vascular endothelial growth factor and its receptor, and matrix metalloproteinases suggests their important role in angiogenesis in Barrett's epithelium and related adenocarcinoma. Furthermore, in esophageal adenocarcinoma, the tumor lymphangiogenesis may be an important phenomenon in the frequent lymph node metastasis formation.

IV The overall prognosis for adenocarcinoma near the EG junction is poor, but because a substantial percentage of patients eligible for major surgery achieve long-term survival, a chance for radical surgery with 2-field lymphadenectomy should be offered to them.

V Based on our results, laser therapy is warranted for patients who have advanced adenocarcinoma near the EG junction with neither a long, tortuous stricture nor extensive extrinsic compression. Because the treatment, regardless of the primary method, in many cases has to be changed during the course of therapy, these endoscopic treatment modalities should be considered complementary rather than mutually exclusive.

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