Benefits of palliative systemic second line therapy in locally advanced unresectable and metastatic esophageal squamous cell carcinoma

eingereicht von

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zur Erlangung des akademischen Grades

Doktor(in) der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt am

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Graz, 07.06.2021

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Graz, am 07.06.2021 *Moritz Müller eh*

Danksagungen

Ich möchte mich sehr herzlich bei all jenen bedanken, die mich während meines Studiums und beim Verfassen dieser Arbeit so tatkräftig unterstützt haben. Mein besonderer Dank gilt zu allererst Herrn Dr. med. univ. Jakob Riedl und Herrn Assoz. Prof. Priv.-Doz. Dr.med.univ.et scient.med. Armin Gerger die mir ermöglicht haben an der klinischen Abteilung für Onkologie wissenschaftlich tätig zu sein. Danken möchte ich ihnen auch ganz besonders für ihr außerordentlich großes Engagement und ihre gute Betreuung hinsichtlich des Verfassens dieser Arbeit. Eine bessere Betreuung hätte ich mir wirklich nicht vorstellen können. Mein ganz besonderer Dank gilt Jakob Riedl, den ich während dieser Zeit als guten Freund, mit einem stets offenen Ohr, gewinnen konnte. Ganz besonders möchte ich mich bei meinen Eltern Claudia und Michael, sowie meinem Bruder Laurin bedanken, ohne die das Alles niemals möglich gewesen wäre. Ihre unglaubliche Unterstützung hat mir meinen Weg ermöglicht. Zuletzt möchte ich ganz besonders meinen langjährigen Freunden David und Rahul danken, die mich mit ihrer beispiellosen Freundschaft, Warmherzigkeit und Hilfsbereitschaft durch mein Studium begleitet haben.

Index

Abbreviation

1

1LTX .....*first-line chemotherapy*

2

2LCTX.....*Second-line palliative chemotherapy*
2LTX .....*second-line chemotherapy*

5

5-FU.....*5-Fluoruracil*

A

AC.....*Adenocarcinoma*
ADCC .....*Antibody-dependent cellular cytotoxicity*
aESCC .....*advanced esophageal squamous cell carcinoma*
AJCC ..... *American Joint committee on Cancer*
ASC .....*Active symptom control*, *Active symptom control*
ATE .....*Average treatment effect*
AUC.....*Area under curve*

B

BE .....*Barrett's esophagus*
BMI..... *Body mass index*

C

CA 19-9 ..... *Carbohydrate antigen 19-9*
CCI ..... *Charleson Comorbidity Index*
CEA .....*Carcinoembryonal antigen*
CF .....*Cisplatin+ 5-Fluoruracil*
COX..... *cyclooxygenase inhibitors*
CPS .....*Combined positive score*
CPT-11 ..... Camptothecin-11
CR..... *Complete remission*
CRP.....*C-reactive protein levels*
CT ..... *Computed tomography*
cTNM .....*Clinical TNM*

D

DCF ..... *Docetaxel+cisplatin+fluoruracil*
DNA .....*Deoxyribonucleic acid*
DTX.....*Docetaxel*

E

eAC..... *Esophageal adeno carcinoma*
ECF..... *Epirubicin+Cisplatin+Fluoruracil*
ECOG .....*Eastern Cooperative Oncology Group*
ECX ..... *Epirubicin+cisplatin+capecitabine*
EGF..... *Epithelial growth factor*
EMA .....*European medicine agency*
EMR ..... *Endoscopic mucosal resection*

EOF ..... *Epirubicin+oxaliplatin+fluoruracil*
EOX ..... *Epirubicin+oxaliplatin+fluoruracil*
ERBB2 ..... *erb-b2 receptor tyrosine kinase 2*
ESCC ..... *esophageal squamous cell carcinoma*
ESD ..... *Endoscopic submucosal dissection*
ESMO ..... *European Society for Medical Oncology*
EUS ..... *Endoscopic ultrasound*

F

FDA ..... *Food and drug administration*
FISH ..... *Fluorescence in situ hybridization*
FLO ..... *fluoruracil+leucovorin+oxaliplatin*
FLOT ..... *Folinic acid+fluoruracil+oxaliplatin+docetaxel*
FOLFIRI ..... *Folinic acid+fluoruracil+irinotecan*
FOLFOX ..... *Folinic acid+ fluoruracil+oxaliplatin*

G

GEJ ..... *Gastroesophageal junction*
GERD ..... *Gastroesophageal reflux disease*
GFR ..... *Glomerular filtration rate*

H

HER2 ..... *Human epidermal growth factor receptor 2*
HR ..... *Hazard ratio*

I

IHC ..... *Immunohistochemistry*
IPTW *inverse-probability-of-treatment-weighting*, *inverse-probability-of-treatment-weights*

M

MCT ..... *Monochemotherapy*

N

NCCN ..... *National comprehensive cancer network*
NSAID ..... *non-steroidal anti-inflammatory drug*

O

OR ..... *Odd´s Ratio*
ORR ..... *Objective response rate*
OS ..... *Overall survival*

P

PCT ..... *Polychemotherapy*
PD ..... *Progressive disease*
PD-1 ..... *Programmed cell death protein 1*
PDL-1/2 ..... *Programmed cell death ligand 1 and 2*
PDR ..... *programmed cell death receptor*
PDT ..... *Photodynamic therapy*
PET ..... *Positron emission tomography*
PFS ..... *Progression free survival*
PH ..... *Proportionality of hazards*
PJS ..... *Peutz-Jeghers syndrome*

PR ..... *Partial remission*
PS ..... *Propensity score*
PTEN ..... *phosphatase and tensin homolog*
pTNM ..... *Pathological TNM*
PTX ..... *Paclitaxel*

R

RNA ..... *Ribonucleic acid*
RPB ..... *Retinoblastoma protein*
RR ..... *Risk ratio*

S

SCC ..... *Squamous cell carcinoma*
SD ..... *Stable disease*
SMDs ..... *Standardized mean differences*

T

TCF ..... *Taxane+cisplatin+fluoruracil*
TNM ..... *Tumor-nodus-metastasis*
ToGA ..... *Trastuzumab for Gastric Cancer*
TTF ..... *Time to treatment failure*

V

VEGF ..... *Vascular endothelial growth factor*

W

WHO ..... *World health organization*

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Zusammenfassung

Hintergrund:

Die Datenlage bezüglich etablierter Therapiestrategien des fortgeschrittenen Plattenepithelkarzinom des Ösophagus ist sehr beschränkt. Dies ist die erste Arbeit, die die Wirksamkeit der systemischen palliativen Zweitlinientherapie (2LCTX) mit der des reinen „active symptom conrol“ (ASC) in fortgeschrittenen Plattenepithelkarzinomen des Ösophagus vergleicht.

Methoden:

Wir führten eine trizentrische retrospektive Kohortenstudie (n=166) mit allen behandelten Patient*innen mit Plattenepithelkarzinom des Ösophagus durch, die eine Progression der Krankheit nach der palliativen Erstlinie zeigten.

Wir implementierten ein Propensity Score Model (PS), um die Wirksamkeitsdaten, vor allem das Gesamtüberleben, in Patient*innen mit 2LTX+ASC versus ASC vergleichen zu können. Hierfür nahmen wir uns einen „inverse-probability-of-treatment-weighting“ (IPTW) Schätzer zur Hilfe.

Ergebnisse:

Nach Progression der Krankheit in der 1LTX wurden 74 Patient*innen (45%) mit ASC weiterbetreut und 92 Patient*innen (55%) erhielten 2LTX+ASC. Am häufigsten wurden Docetaxel (36%) und Paclitaxel (18%) als Chemotherapeutika verwendet. In der unbereinigten Analyse war der OS signifikant länger in Patient*innen die 2LTX+ASC erhielten. Diese Patient*innen hatten jedoch eine höhere Prävalenz von vorteilhaften prognostischen Faktoren wie besseren ECOG Performance Status, längere Dauer der palliativen Erstlinie und niedrigere CRP-Ausgangslevel. Dieses Ungleichgewicht konnte mithilfe der IPTW vollständig entfernen. In der IPTW-bereinigten Analyse zeigte sich der Zusammenhang der Zweitlinientherapie und einem längeren Gesamtüberleben zwar abgeschwächt, konnte jedoch weiterhin erkannt werden. Das mediane Gesamtüberleben war 6,1 Monate in der Gruppe der palliativen Zweitlinie und 3,2 Monate in der ASC-Gruppe. (IPTW-adjustiere Hazard ratio=0.40, 95%CI: 0.24-0.69, p=0.001).

In der durchgeführten Subgruppenanalyse zeigte sich fast durchwegs ein Vorteil auch bei Patient*innen mit ECOG Performance Status ≥1 und Alter ≥ 65.

Schlussforgerung:

Diese Studie unterstützt die Annahme, das ein Vorteil im Gesamtüberleben von Patient*innen mit fortgeschrittenem Plattenepithelkarzinom des Ösophagus durch die palliative Zweitlinie entsteht.

Abstract

Background:

The level of evidence for established treatment regimens in the 2nd line therapy (2LTX) of advanced esophageal squamous cell carcinoma (aESCC) is limited. This is the first study that reports efficacy data comparing 2LTX versus active symptom control (ASC) in aESCC.

Methods:

We conducted a tri-centre retrospective cohort study (n=166), including all consecutively treated patients with aESCC who had experienced disease progression on palliative 1st line therapy (1LTX). A propensity score model using inverse-probability-of-treatment-weighting (IPTW) was implemented for comparative efficacy analysis of overall survival (OS) in patients with 2LTX+ASC versus ASC.

Results:

After progression on 1LTX, 74 (45%) patients were treated with ASC while 92 (55%) received 2LTX+ASC. The most frequent 2LTX regimens were docetaxel (36%) and paclitaxel (18%). In unadjusted analysis, 2LTX+ASC was associated with significantly longer OS compared to ASC only. However, patients in the 2LTX+ASC had a significantly higher prevalence of favourable prognostic factors such as better ECOG performance status, longer duration of 1LTX and lower baseline CRP levels. These imbalances could be fully removed by re-weighting the data with the IPTW. In the IPTW-adjusted analysis the favourable association between 2nd-line therapy and longer overall survival weakened but prevailed. The median OS was 6.1 months in the 2LTX group and 3.2 months in the ASC group, respectively (IPTW-adjusted Hazard ratio=0.40, 95%CI: 0.24-0.69, p=0.001). Importantly, the benefit of 2LTX was consistent across several clinical subgroups, including patients with ECOG performance status ≥1 and age ≥ 65.

Conclusion:

This real-world study supports the concept that 2LTX prolongs survival in patients with aESCC.

1 Introduction

With over 570,000 newly diagnosed cases per year, esophageal cancer is the ninth most common cancer in the world. Regarding the total cancer mortality, 5,3 percent is conceited by this cancer. (1) The five-year relative survival rate of 45% for localized, 24% for regional and 5% for distant cancer stage is low, especially in advanced cancer stages. (2) The two main histological subtypes, squamous cell carcinoma (SCC) and adenocarcinoma (AC), show regional differences. Because data for esophageal squamous cell carcinoma (ESCC) are mainly collected within Asian populations, there is a lack of clear evidence for western countries. (3) Complete surgical resection, either endoscopic mucosal resection or esophagectomy, is the only curative treatment. The incidence of advanced stages is high, with around 35 percent of patients presenting with distant metastasis at diagnosis. (3, 4) Treatment options for advanced esophageal SCC are very limited and data is insufficient. A combination therapy is the preferred option in clinical practice for fit patients. First line palliative chemotherapy (1LTX) with cisplatin and 5-fluoruracil as doublet combination is to this day state of the art. (5, 6) The treatment with FOLFOX is also considered as an alternative. (7) For further lines of chemotherapy after treatment failure in the 1LTX evidence is less proven. In second-line chemotherapy (2LTX) mostly monotherapy is the standard of care. A few phase II studies show benefits of irinotecan, paclitaxel and docetaxel in fit pretreated patients. Burkart et al. evaluated the efficacy of monotherapy with irinotecan in thirteen platinum pretreated patients. The median progression-free survival (PFS) was two months, the median overall survival (OS) was eight months and the one-year survival rate was sixteen percent. In a second phase II study Muro et al. used a single agent regime with docetaxel achieving a median survival of 8.1 months and a one-year-survival rate of thirty-five percent. No differences in efficacy can be seen between docetaxel and paclitaxel. (8) Vinorelbine is also connected to a response rate of fifteen percent in pretreated patients and considered as a treatment alternative. (9)

Recently, first results of the KEYNOTE-590 were presented. In patients with locally advanced unresectable or metastatic esophageal cancer systemic therapy with the programmed cell death protein-1 (PD-1) inhibitor Pembrolizumab in combination with frontline chemotherapy is superior to chemotherapy alone. This is promising and might become the new standard of care in this setting. (10)

The ATTRACTION-3 trial (2019) has proved the PD-1 inhibitor nivolumab being superior over chemotherapy, with paclitaxel or docetaxel, as second line treatment in patients with advanced esophageal squamous cell carcinoma (aESCC) (11).

However, due to the fact that no randomized clinical trial has shown the superiority of 2LTX compared to active symptom control (ASC) in esophageal SCC, there is no evidence of 2LTX being superior.

To address this issue, we conducted a tri-center retrospective study including all consecutive patients undergoing either 2LTX or ASC after treatment failure in 1LTX. These patients were selected from three different academic centers in Austria. We implemented a propensity score analysis using inverse-probability-of-treatment-weights (IPTW) to rigorously account for non-random treatment assignment. To the best of our knowledge this is the largest study reporting propensity score adjusted efficacy data comparing 2LTX plus ASC to ASC alone in treatment of esophageal SCC.

1.1 Epidemiology

1.1.1 Incidence

With an estimated 572,034 newly diagnosed cases of esophageal cancer and 508,858 cancer-caused deaths worldwide, esophageal cancer is a serious healthcare problem. With 335,080 new cases and a cumulative risk of 1,53 in eastern Asia the incidences of esophageal cancer are much higher compared to a cumulative risk of 0,37 and 15,616 new cases in central and eastern Europe.

Furthermore, the incidence rates vary up to 12-fold between countries. The rates are highest in Eastern Asia, Southern Africa and Eastern Africa ranging from 12,2 to 7,5 per 100,000 and lowest in Central America, Western Africa and Northern Africa ranging from 0,96 to 1,5 per 100,000. The countries with the highest incidence rates are known as the "esophageal cancer belt" or high risk areas stretching from northern Iran through the central Asian republics to north central China. (1)

In these regions SCC is responsible for over 90 percent of the diagnosed cases, whereas AC predominates in Europe or in western countries. (12, 13)

This indicates that lifestyle factors as well as nutritional factors may play a critical role in the development of this disease. A poor nutritional status, smoking and alcohol are risk factors for SCC whilst obesity and gastroesophageal reflux disease (GERD) are the major risk factors for AC. (3, 14)

However, the incidence of SCC is in decline. In certain high-risk areas this is suspected to be because of better economic situations and dietary improvements, whereas in low-risk areas, such as Austria, it is suspected to be caused by a decline of nicotine consumption.

On the other hand, these countries are experiencing a consistent rise in AC(-diagnosis) incidence rates which could correlate to the increasing obesity and GERD. (1)

1.1.2 Mortality

With over 500,000 deaths per year, esophageal cancer is ranked sixth place worldwide. (1)

With 4,5 per 100,000 in 1983 and 4,4 per 100,000 in 2016 the mortality rate is surprisingly constant in Austria over the last 30 years. (15)

1.2 Etiology, pathogenesis and risk factors

1.2.1 Etiology and pathogenesis

In comparison to other gastrointestinal cancers such as the colorectal carcinoma, the pathogenesis of esophageal cancer is still not well understood.
The pathogenesis of AC and SCC differs significantly.

Adenocarcinoma

It is generally presumed that most of the esophageal adenocarcinomas are caused by chronic gastroesophageal reflux, increasing the risk six-fold. In 5 to 8 percent patients develop a Barrett's esophagus (BE) because of chronic irritation of the distal esophagus through gastric acid. This explains why most of the AC are located either in the distal esophagus or the gastroesophageal junction. Barrett's esophagus is microscopically characterized by an intestinal metaplasia. This is the process of squamous epithelium, which is usually found in the esophagus, being replaced by villiform and specialized columnar epithelium. Within this new epithelium some mutations could lead to a dysplasia providing the next step to a carcinoma. Transformation of the mucosa consists of change in the glandular architecture, crowding of cell nuclei and hyperchromatism.

Patients with Barrett's esophagus have a 0,5 percent risk of developing a neoplasia.
Genes like those encoding for p53, bcl-2, p16, p27, cyclin D1, RPB, EGF and other genes promoting tumor development are identified in playing a role in the pathogenesis of adenocarcinoma. (16)

Squamous cell carcinoma

Chronic inflammation and irritation are main triggers for the development of esophageal squamous cell carcinoma. Several risk factors, such as alcohol and smoking, which account for this will be discussed in the following. (16)

1.2.2 Risk factors

Hereditary factors

Familial aggregations in SCC and Barret-esophagus, which is linked to AC, are described in some high-risk regions. However, it remains unclear if this is due to genetic factors or just to an increased predisposition as far as risk factors and socio-economic factors are concerned. (17, 18) To what extent hereditary factors are involved remains unclear since there are some studies that didn't recognize any correlation. (19)
Furthermore, a higher risk of esophageal cancer can be seen in some hereditary diseases with a generally increased risk of both gastrointestinal and non-gastrointestinal cancers:

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder which is associated with an increased lifetime risk of predominately gastrointestinal cancer especially of the types colorectal, stomach, small bowel and pancreas. Giadiello et al. also found a significant increase in esophageal cancer. (20, 21) Clinical presentation consists of multiple hamartomatouse gastrointestinal polyps, mucocutaneous pigmentation as well as the increased risk of gastrointestinal and non-gastrointestinal cancers (predominantly breast). The median age at diagnosis is around 45 years. (21-24)

Germline mutations of the PTEN gene also increase the risk of developing esophageal cancer. The mutation can cause Crowden syndrome which is characterized by multiple hamartomas in various tissues, dermatologic manifestations and an increased risk of colorectal, breast, skin and thyroid as well as esophageal cancer. (25, 26) PTEN is considered a tumor suppressor gene. Loss of function mutation on chromosome 10q23 is part of the oncogenesis of these cancers. (27, 28)

Non-hereditary risk factors

Gender

Throughout the world the risk of developing esophageal cancer is almost 3-fold higher in men than in women. In central Europe men carry a 6-times higher risk with increased incidence rates between 0.81 per 10.000 for women compared to 5,8 per 10.000 for men. (1)

1.2.2.1 Squamous cell carcinoma

Socio-economic factors:

There is evidence that socioeconomic factors play a role in the development of esophageal cancer. Especially socioeconomic markers like income and education seem to impact the global distribution. (29) In fact it is uncertain if those markers do not go hand in hand with other risk factors such as smoking or alcohol consumption. In high risk areas such as Eastern Africa or Eastern Asia a higher incidence is linked to poor nutrition such as low fruit intake which is more likely effected by a low social status, a low income and a low level of education. (18)

Smoking and alcohol

Throughout all regions, alcohol consumption and smoking proved to be major risk factors for SCC. (30, 31)
Although smoking seemed to be a problem throughout high and low risk regions, high evidence suggests that smoking represents a major risk factor especially in low risk countries like the United states or Germany/Austria. Whereas in high risk regions smoking plays a slightly minor role. (32)
Cigarette smoking, as well as smoking cigars and pipes seems to increase the risk of developing SCC. (33, 34)
Excessive alcohol consumption is also related to the pathogenesis of SCC. High doses of alcohol significantly increase the risk. Hard liquor is mentioned to be more harmful. However, especially the cumulative dose of alcohol determines the risk. According to a study by Pandeya et al., low intake of 170 grams per week is not associated with an increased risk while higher intakes of alcohol have a significant linear effect. (31) In addition, alcohol and smoking seem to have a positive synergistic effect. (35-37)

Furthermore, drinking is linked to many other problems subsequently. In addition to a higher cancer-related mortality there are more treatment-related complications, higher healthcare costs and longer recovery. (38)

Dietary factors

There are several dietary factors that seem to play a role in the pathogenesis of SCC.
Firstly, there are several foods containing n-nitroso compounds associated with a genotoxic potential inducing alkyl adducts in the DNA. There is a correlation between developing lesions and the extent of present substances. (39, 40) Pickled vegetables or other preserved foods are high sources of n-nitroso compounds. (41) In addition, mycotoxins like aflatoxin seem to be capable of producing n-nitroso compounds. (42)
Secondly, dietary copper sources like areca nuts or betel quid (consumed mostly in high incidence areas) are linked to the development of esophageal SCC. (43)
Thermic injuries induced by hot temperature beverages may also cause this development. Apparently, there is a crucial difference between drinking warm tea (<60°C), hot tea (60-64°C) and very hot tea (>64°C), which shows increasing risk through rising temperatures. (44, 45)
Several other factors like red meat consumption (46) as well as low levels of selenium, zinc and folate may also affect the risk. (47-50) Whereas high intake of fresh fruits and vegetables are considered a protective factor. (51)

1.2.2.2 Adenocarcinoma

Gastroesophageal reflux disease

Intestinal metaplasia of the lower esophagus caused by chronic reflux is likely to progress to Barrett´s-esophagus. These changes in the epithelium are the major risk factor for development of esophageal adenocarcinoma and have the greatest effects on carcinogenesis in the distal esophagus. According to a study from Bytzer et al, 113 of 524 patients with AC have a history of symptomatic chronic reflux or gastro esophageal reflux disease . (52)
The risk of developing an adenocarcinoma in BE patients is at least 30-fold above the general population, whereas the absolute annual risk is only 0,12%. (53)

Smoking

Based on a pooled analysis from the international BEACON consortium, patients with BE who smoked were at a two-times higher risk of developing an esophageal AC (OR 1,96) and an AC of the gastroesophageal junction (OR 2,18). This study also concludes a high dose-response association between pack-years and disease outcome.

Longer smoking cessation (>10 years) leads to a risk reduction of developing an AC in comparison to current smokers (<10 years OR 0,82; > or = 10 years 0,71). (54)

Alcohol

In contrast to alcohol being a major risk factor for esophageal SCC, a meta-analysis from Tramacere et al. concluded an absence of association between drinking and esophageal AC, with a relative risk of drinkers versus non-drinkers of 0,96 overall. (55)

Obesity and metabolic syndrome

Nutritional habits as well as obesity evidentially play an important role in the development of adenocarcinoma of the esophagus. A meta-analysis showed a significant link between body-mass-index (BMI) and AC of the distal esophagus, gastroesophageal junction and gastric cardia. With an overall risk ratio (RR) of 1,71 for BMI 25-30 Kg/m² and 2,34 for BMI >30 Kg/m², the risk of obese people of developing AC is around twice as high as in the general population. They also concluded a rising RR of 1,11 with every 5Kg/m². (56)
Obesity leads to a higher intraabdominal/intragastric pressure, dysfunction of the low esophageal sphincter and a higher risk for a hiatal hernia. These changes cause GERD, Barrett's esophagus and finally an esophageal adenocarcinoma. (57, 58)
However, Drahos et al. described a connection between metabolic syndrome and esophageal adenocarcinoma (eAC) regardless of the GERD status.
Several obsogenic effects are recognized as co-factors, including secretion of various proinflammatory cytokines, hypertension, dysregulated fasting glucose and dyslipidemia. (59, 60)
Studies showed that high dietary intake of fiber, beta-carotine, folate, vitamin C and B6 are protective factors, whereas diets high in cholesterol, vitamin B12, and animal protein increase the risk. (61-63)

Medication

Some studies demonstrated an association between the intake of drugs such as nitroglycerin, beta adrenergic agonists, anticholinergics, aminophylline and benzodiazepine which decrease the pressure of the lower esophageal sphincter and an elevated risk of GERD,

Barrett's esophagus and esophageal adenocarcinoma. They assumed that around 10 percent of these medical conditions may be attributed to those drugs. In contrast, an epidemiological study from the BEACON committee assumed non-steroidal anti-inflammatory drug (NSAID) intake to be a protective factor. Using cyclooxygenase inhibitors (COX) is positively correlated to a decreased risk of developing esophageal cancer (OR 0,68). A high frequent intake over more than ten years sowed an even greater effect (OR 0,56) regardless the patients reflux status. (64)

1.3 Pathology

1.3.1 Localization

Three out of four adenocarcinomas arise in the distal esophagus or the gastroesophageal junction. Whereas squamous cell carcinomas are usually located more proximal but in general in the middle and the distal third of the esophagus. Esophageal carcinoma of the proximal third of the esophagus is rarely found. (16, 65)

1.3.2 Macroscopic appearance

Early forms of esophageal carcinoma present as superficial plaques, ulcerated lesions or nodules. Later more advanced forms appear such as strictures as well as ulcerated or circumferential masses occluding the esophageal lumen in varying severity. A study from Yendamuri et al. considered the length of the lesion as an independent predictor for long-term survival. (66)

1.3.3 Histology

Squamous cell carcinoma is microscopically characterized as cells with a keratinocyte-like appearance. Highly differentiated tumor cells are characterized by eosinophilic cytoplasm, a low mitotic activity and more or less keratinization. In comparison, low differentiated tumors have scant cytoplasm, a high mitotic rate and nuclear polymorphism.
Additionally, some tumors also have a glandular differentiation showing either tubular glands or mucin producing cells in some regions. A desmoplastic stoma reaction is

commonly seen in the surrounding of invasive tumors. Existing histological subtypes are spindle cell, verrucose cell and basaloid cell carcinoma. (67, 68)

Adenocarcinomas of the distal esophagus, gastroesophageal junction and the stomach are commonly classified by the Lauren´s classification, as long as there are no major histological differences between these different cancer sites. Intestinal and diffuse adenocarcinomas are distinguished by a different cell cohesity and differences in glandular differentiation. The intestinal adenocarcinoma shows a higher cell cohesity as well as glandular differentiation. There is also a third group which consists of mixed adenocarcinomas showing a combination of patterns. (67, 69)
The world health organization (WHO) distinguishes between tubular, papillary and mucinous adenocarcinoma as well as signet cell carcinoma. These classifications are mainly applied to cases of gastric cancer, but according to published cases, tumor of the esophagus and the gastroesophageal junction show the same spectrum of differences. (67)
The adenosqamous carcinoma, which can be found in around 0,5 percent of cases, is a rare combination of the histological subtypes. (67)

1.3.4 Grading

Based on its stage of differentiation, the esophageal carcinoma can be divided into four stages, with G1 being a well differentiated and G4 an undifferentiated neoplasia. (70)

Histologic grade	
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Table 1: Grading criteria (71)

1.3.5 Staging

Esophageal cancer is most commonly staged by the tumor-nodus-metastasis system (TNM) of the American Joint committee on Cancer (AJCC) combining tumor-node-metastasis subclassification.

There are two different forms of evaluation. Staging is based on radiologic imaging (cTNM) or on pathological examination (pTNM).

T (Tumor) stands for the depth of invasion, N (Nodule) for the nodular involvement and M (Metastasis) for the distant metastasis. Using these criteria, esophageal cancer can be classified into four different stages.

The detailed 7th edition of TNM staging manual (71, 72):

T status	
T1	Invasion into the lamina propria, muscularis mucosae, or submucosa
T2	Invasion into muscularis propria
T3	Invasion into adventitia
T4a	Invades resectable adjacent structures (pleura, pericardium, diaphragm)
T4b	Invades unresectable adjacent structures (aorta, vertebral body, trachea)
N status	
N0	No regional lymph node metastases
N1	1 to 2 positive regional lymph nodes
N2	3 to 6 positive regional lymph nodes
N3	7 or more positive regional lymph nodes
M status	
M0	No distant metastases
M1	Distant metastases

Table 2: TNM-Classification

I	T1	N0,N1	M0

II	T2	N0,N1	M0
	T3	N0	M0
III	T1,T2	N2	M0
	T3	N1,N2	M0
IVa	T4a,T4b	any N	M0
	any T	N3	M0
IVb	any T	any N	M1

Table 3: Tumor stage squamous cell carcinoma

I	T1	N0	M0
IIa	T1	N1	M0
IIb	T2	N0	M0
III	T1	N2	M0
	T2	N1,N2	M0
	T3, T4a	N0, N1, N2	M0
IVa	T4b	N0, N1, N2	M0
	anyT	N3	M0
IVb	anyT	any N	M1

Table 4: Tumor stage adenocarcinoma

1.3.6 Infiltration and Metastasis

Around 50 percent of patients with esophageal carcinoma present with locally advanced or metastatic disease at the time of diagnosis. (16) Hematogenous spread, metastasis in regional or distant lymph nodes as well as invasion into surrounding tissue is possible.

Adenocarcinoma causes 40 percent and squamous cell carcinoma 60 percent of metastasis. Most common sites of distant metastases are the liver, lungs, bone and adrenal glands.

Besides these locations, esophageal cancers can also rarely metastasize to the skin, eye and muscle. (73, 74)

In the case of a carcinoma of the proximal third of the esophagus, lymphatic metastasis mainly occur in regional cervical and mediastinal nodes. Tumors of the middle third predominately involve mediastinal and gastric nodes, whereas such from the lower third and the gastroesophageal junction usually metastasize into the mediastinal and abdominal lymph nodes. (67)

By infiltrating contiguous organs, esophageal carcinoma preferentially affects the mediastinum, tracheobronchial tree, lung, aorta, pericardium and heart. (67)

1.4 Clinical management

1.4.1 Clinical presentation

Early stage esophageal carcinomas are mostly asymptomatic. Around 74 percent of patients present with progressive dysphagia over the course of a couple of months. This can be accompanied by a reduction of oral intake and a reduced nutritional status. 57,3 percent of cases show the side effect of synchronous weight loss. (75, 76) Other symptoms include therapy resistant heartburn and retrosternal tightness as well as blood loss causing an iron deficiency, which is related to chronic fatigue. Other less common clinical symptoms are paralysis of the laryngeal nerve or infiltration into the tracheobronchial tree leading to pneumonia, cough and hoarseness. (76, 77)

1.4.2 Diagnostic tools

Esophagogastroscopy

Esophagogastroscopy, which is mainly used for primary examination at the stage of clinical symptoms, is the best method to evaluate masses in the esophagus, the gastroesophageal junction and the gastric cardia. Biopsies of suspect lesions should be taken for histologic examination. The first endoscopic biopsy confirms the diagnosis in 93 percent of cases.

According to Graham et al., extracting at least seven biopsies could significantly improve the correctness of diagnosis because of an increased sensitivity of over > 98 percent. (78)
In the case of potential airway infiltration by a carcinoma of the upper esophagus, a tracheobronchoscopy should be performed preoperatively. (79)

Endoscopic ultrasound

The endoscopic ultrasound (EUS) is an additional method for both initial and pretreatment locoregional staging. It provides a high resolution and accuracy of imaging. (80) The histological wall structure correlates very well with the sonographic layers provided by the device.
Five layers can be defined

1. Superficial mucosa
2. Deep mucosa
3. Submucosa as well as the acoustic transition between submucosa and muscularis
4. Muscularis propria as well as the acoustic transition between submucosa and muscularis
5. Serosa and subserosal fat

EUS can be used for radiologic tumor staging of the tumor size, infiltration depth and regional lymph node status. A meta-analysis containing 49 studies showed a sensitivity of 81,6% in T1, which was raised to a pooled sensitivity of 92,4% in T4. Thereby proving that the EUS performs better in advanced tumor stages. (81)
Tumors that are limited to the mucosa and submucosa are staged as T1. Infiltration of the muscularis propria without transmural appearance describes a T2 tumor. T3 is defined as infiltrating the adventitia whereas T4 tumors reach beyond the adventitia effecting surrounding structures. (72)

Staging includes locoregional lymph nodes. According to Catalano et al., endoscopic ultrasound has a sensitivity of 89,1% and a specificity of 91,7% for malignant lymph nodes. Malignancy criteria are echo-poor lymph nodes with a round shape and sharply demarcated borders, which are greater than 10 mm. (82) A complete assessment of the N-stage including a fine needle aspiration of suspect nodes is associated with a high accuracy in diagnosing lymphogenic spread. (83)

Evaluation of distant metastasis

Since the treatment algorithm of metastatic and non-metastatic esophageal cancer differs significantly, staging for distant metastasis is essential. Metastases most commonly appear in the liver, lungs, bone and adrenal glands. (74)
Mostly computed tomography (CT) of the chest, abdomen and pelvis with or without integrated positron emission tomography scan are used when evaluating organ metastasis. 18F-fluoro-2-deoxy-D-glucose positron emission tomography scan (PET) is likely to be more sensitive than CT. According to the ESMO-Guidelines PET-CT is helpful to identify undetected distant metastases and should be performed especially in case of potential esophagectomy. Additionally, endoscopic ultrasound, diagnostic laparoscopy/ thoracoscopy and brain imaging can be performed. (84-86)

Tumor markers

A study from Mealy et al. showed a significantly higher serum level of carcinoembryonal antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) in patients with esophageal cancer compared to patients with a benign esophageal disease. However, with a sensitivity of 64% and a specificity of 80%, combining the mentioned markers was insufficient for screening and to achieve a positive predictive value for treatment. (87) Therefore, the routine use of tumor markers as diagnostic tools or to monitor treatment effect is not recommended.

1.4.3 Treatment

Treatment of esophageal cancer is based on a multimodal approach consisting of surgical procedures, radiotherapy, antineoplastic medication including cytotoxic chemotherapy, targeted treatment as well as immunotherapy.
The primary goal of treatment in early stages is a curative one. If this approach is not achievable, the aim of therapy consists of slowing down disease progression and extending the patient's lifespan.
In addition, symptomatic therapy, also known as best supportive care, is an essential part of treatment. This includes therapy of pain, other tumor associated symptoms, handling of

therapy associated problems such as emesis and providing psychiatric support for the patients and their families.
Potential treatment decisions are either curative or palliative. The determined algorithm is primarily based on the disease stage, general constitution and individual comorbidities.
Furthermore, in recent years the molecular tumor profile has become more important for treatment decisions.
In the following the different treatment modalities will be presented separately. Finally, detailed treatment algorithms for localized and advanced esophageal cancer will be explained.

1.4.3.1 Endoscopic therapy

a. Endoscopic resection

Endoscopic resection includes both endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) and is an alternative to radical esophagectomy in patients with early disease stage, especially stage T1a. In superficial esophageal squamous cell carcinoma ESD was associated with an increased five-year recurrence free survival of 95,2% compared to 73,4% in the EMR group. (88-90) Although an endoscopic resection is less invasive, the procedure is very operator-dependent and should be performed in specialized centers.
In a meta-analysis from Sun et al. efficacy and complications of ESD were investigated. With an en bloc resection rate of 99 percent and an overall R0 resection rate of 90 percent ESD is highly effective. The complication rate was low, with stenosis and perforation being the most common in 5 percent and 1 percent of cases, respectively. (91) EMR is combined with a photodynamic therapy and in some cases with argon-plasma-coagulation. The outcome may be improved in cases of Barrett's esophagus and early esophageal adenocarcinoma. (92, 93) The use of radio frequency ablation in Barrett's esophagus remains controversial. (94) In low-grade intraepithelial neoplasia radio frequency ablation could eliminate over 90 percent of lesions. (95)

b. Endoscopic cryotherapy

Another therapeutic option in early stage localized esophageal carcinoma is an endoscopic cryotherapy. A multicenter, retrospective cohort study showed that liquid nitrogen spray cryotherapy was effective and safe in patients in whom conventional therapy (endoscopic resection, photodynamic therapy, esophagectomy, chemotherapy and radiotherapy) failed. (96)

1.4.3.2 Surgery

Surgery is the main column of treating regional limited lesions curatively. Resection is essential even in the case of a metastatic spread affecting the locoregional lymph knots.
Potentially resectable are localized tumors, being limited to the esophagus, as well as regional tumors, showing metastasis in the regional lymph nodes (perhaps with preoperative treatment). (77) In approximately 18 percent of cases the situation is local and in 32 percent it is regional at the time of staging. These two stages combined show that up to 50 percent of newly diagnosed cases of esophageal carcinoma are potentially resectable. (97)
Localization, TNM-stage and histology are the criteria for determining the resection-type.

a. Cervical esophagus

In fact, most of the cervical esophageal carcinomas are treated with chemotherapy and radiotherapy. Surgery is only performed if it's the patient's preference. (98)
Cervical esophagectomy with gastric interposition is the preferred procedure. However, when parts of the pharynx are affected, surgery should be escalated to the pharynx and hypopharynx. (99)

b. Thoracic esophagus

The most commonly performed procedures are transhiatal esophagectomy, Ivor-Lewis transthoracic esophagectomy and McKeown tri-incisional esophagectomy. (100) Usually gastric interposition is used for anastomosis. However, parts of the jejunum and the colon can also be considered. (101, 102)

Trans-hiatal esophagectomy is performed in cervical and thoracal cancer as well as cancer of the gastroesophageal junction. Access is accomplished by mid-line laparotomy and left neck incision. (103)

Major postoperative complications are anastomotic leaks, atelectasis, pneumonia, intrathoracic hemorrhage, recurrent laryngeal nerve paralysis, chylothorax and tracheal laceration with a postoperative mortality of four percent. (104)

The advantages of avoiding a thoracotomy include lowering the risk of intrathoracal anastomosis leak as well as general respiratory complications caused by injuring intrathoracal structures.

Ivor-Lewis transthoracic esophagectomy, like all transthoracic approaches**,** has the advantage of visualizing the oncologic situation. Better surgical access is achieved in most cases. Main complications, due to the transthoracic access, are pneumothorax, pleural effusion, pneumonia, aspiration bronchiolitis, empyema, and respiratory failure as well as mediastinitis and sepsis. (89, 105)

McKeown tri-incisional esophagectomy is also a transthoracic approach, which is commonly performed in patients with cancer located at the gastroesophageal junction as well as the middle and lower esophagus. Right thoracotomy and laparotomy followed by a left neck incision is the operative access. The main complications are the same as with the Ivor-Lewis approach. (105)

c. Gastroesophageal junction

Tumors located at the gastroesophageal junction should be treated with a transhiatal or transthoracal esophagectomy combined with a complete or proximal gastrectomy.
(106)

Many minimal-invasive variations of these basic surgeries were developed, such as the minimal invasive or hybrid Ivor-Lewis esophagectomy (thoracoscopy + laparotomy or thoracotomy + laparoscopy) and the laparoscopic trans-hiatal esophagectomy. A meta-analysis showed that patients undergoing minimal invasive surgery may benefit from a shorter hospital stay, reduced risk of respiratory complications and a reduced overall morbidity. (107)

Lymphadenectomy

There is some conflicting evidence regarding the extent of lymph nodes removal. Based on their study, Peyre et al. suggest the removal of at least 23 lymph nodes to reach the best possible outcome. (108) However, other studies did not consider the total number as a prognostic factor for recurrence. (109)

Two different types of lymphadenectomy are performed. While a two-field resection includes nodes of the mediastinum and the upper abdomen, an extended three-field resection removes mediastinal, abdominal and cervical lymph nodes. The extent of the lymphadenectomy is mainly determined by factors such as location, invasion depth, lymphovascular invasion and the status of the paratracheal lymph. (110, 111)

1.4.3.3 Radiotherapy

Radiotherapy in a curative setting

Radiotherapy represents the second column of cancer therapies.

Different tissues react differently to radiation due to the tissue related regeneration capacity, which is lower in neoplastic lesions.

Radiotherapy plays a key role in the curative treatment approach, especially in cancers of the esophagus with limited local spread. Although radiotherapy by itself is also effective, combined therapy algorithms are associated with a better overall survival. Neoadjuvant, perioperative, adjuvant and definitive chemoradiotherapies are frequently used options. (112-116)

The CROSS study from van Hagen et al. showed that patients who were treated with chemoradiotherapy plus surgery had significantly longer overall survival than patients who only underwent surgery. Chemoradiotherapy concurrently combined a weekly fractionated dose of 41,5 Gy with the chemotherapeutic substances 5-fluoruracil and paclitaxel. The survival benefit was shown both for adenocarcinoma as well as squamous cell carcinoma. (117)

Preoperative chemoradiotherapy commonly consists of a dose of 41.4 Gy in 25 fractions (1,8-2 Gy) per day for five days a week over a span of six to eight weeks. (117)

In advanced situations a higher radiation dose of 50.4 Gy may be favorable. Higher doses do not seem effective. (118)

Radiotherapy in a palliative setting

The main goals of palliative radiotherapy are improving the quality of life and the reduction of pain.

1.4.3.4 Chemotherapy

Besides radiotherapy and surgery, chemotherapy is the third main column of cancer treatment. Many different cytotoxic drugs are commonly used in the treatment of EC. As mentioned in the previous section, these toxic substances can be combined with radiotherapy for adjuvant purposes or in order to achieve suitability for surgery. Not only monochemotherapy (MCT) but also polychemotherapy (PCT) is a highly valuated instrument. Over the last years new targeted substances have been discovered and established which are mainly used in the palliative setting.

a. Fluoruracil

5-Fluoruracil (5-FU), a pyrimidine-analogue, is one of the main chemotherapeutic substances used in the treatment of esophageal carcinoma. Two main mechanisms of action have been discovered. First, by an inhibition of the enzyme thymidylate-synthase, the synthesis of thymidine by methylation of uridine is prevented. In the presence of folinic acid (e.g. leucovorin) the antimetabolite is locked in the catalytic center of the synthase and prevents the synthesis of nucleotides enhancing the cytotoxic effect. This is why many PCT schemes, such as FOLFOX and FOLFIRI, combine these substances. Secondly, 5-FU incorporates itself as a false nucleotide in the ribonucleic acid (RNA) and DNA.
The 5-FU prodrug capecitabine (Xeloda®) is given orally.
Trepper et al. established the standard CF scheme in 2008. This describes a 35-day cycle including 1,000 mg/m2/day continuous infusion days 1 to 4 and days 29 to 32. Fluoruracil is combined with Cisplatin. (119, 120p. 909ff)

Most common adverse effects: (120p. 909ff)

- Myelosuppression
- Stomatitis/ Mucositis/ Esophagitis
- Diarrhea
- Dermatitis

- Alopecia

Capecitabine mainly induces Hand foot syndrome and gastrointestinal ailments.

b. Platinum

Since Rosenberg discovered the effect of platinum in the 1960s, it is one of the most frequently used chemotherapeutic drugs. Three different complexes are in use: cisplatin, carboplatin and oxaliplatin. The molecular effect consists of linking up DNA-strands preferentially between N-7 of guanine and adenine. Links in the same molecule are called intrastrand-crosslinks and those between two molecules of DNA are called interstrand-crosslinks. Oxaliplatin is expected to have the highest cytotoxicity.
In the standard CF scheme, 100mg/m(2) are given over 30 minutes on days 1 and 29 together with 5-fluoruracil. (119)
Because cisplatin is highly nephrotoxic, it could be replaced by carboplatin. In this case, the dose is calculated on the basis of the plasma concentration per time (area under curve, AUC) and the renal function (glomerular filtration rate, GFR). (120p. 900ff)

Most common adverse effects:(120p. 900ff)

- Nephrotoxicity (particularly cisplatin)
- Ototoxicity (particularly cisplatin)
- Emesis (particularly cisplatin)
- Peripheral neuropathy (particularly cisplatin)
- Myelosuppression (particularly carboplatin)
- Neurotoxicity (particularly oxaliplatin)

c. Taxane

Paclitaxel (PTX) and docetaxel (DTX) belong to the mitosis inhibitors because they promote the polymerization and inhibit the depolymerization of tubulin during mitosis. Van Hagen et al. incorporated Paclitaxel plus carboplatin in a neoadjuvant polychemotherapy followed

by radiation. This scheme was associated with a better outcome than surgery alone. (117, 120p. 914f)

Most common adverse events:(120p. 914f)
Paclitaxel:

- Myelosuppression
- Hypersensitivity reaction
- Peripheral neuropathy

Docetaxel :

- Myelosuppression
- Peripheral neuropathy
- Edemas
- Skin toxicity

d. Irinotecan

The original active substance Camptothecin was already discovered in the 1950s. With an improved water solubility irinotecan and topotecan were included as chemotherapeutic substances in cancer therapy. These drugs inhibit the topoisomerase I, which is responsible for reducing the torsional stress on the DNA. This stress is induced during replication and transcription.
In order to prevent stress, this enzyme cuts one strand of DNA and causes relaxation by rotation. Irinotecan leads to an irreversible damage in the replicating cell by stabilizing the cleavable complex of topoisomerase I and DNA as well as further inducing strand breaks. (120p. 918ff)
In a randomized phase III trail from Bouché et al. a benefit in the median progression free survival and the median overall survival of patients with metastatic gastric cancer receiving fluorouracil leucovorin in combination with irinotecan was observed in comparison to those receiving fluorouracil and leucovorin alone or in combination with cisplatin. (121)

Most common adverse events: (120p. 918ff)

- Myelodepression
- Late diarrhea

- Cholinergic syndrome

e. Epirubicin

Epirubicin is a partially synthetic member of the anthracyclines. There are a few molecular mechanisms that explain the cytotoxic effect of these drugs. The first mechanism is the intercalation in the DNA double helix. As a result, the synthesis of DNA and RNA is disturbed.
Secondly, this agent causes DNA strand breaks by forming and stabilizing a complex of enzyme and DNA. Thirdly, these substances induce reactive oxygen species (ROS) along with all their cytotoxic effects and effects on the genome. (120p. 921ff)
The regimes ECF, ECX, EOF and EOX contain epirubicin. (122)

Most common adverse events: (120p. 921ff)

- Myelosuppression
- Cardiotoxicity
- Ulcerations in case of paravasal application

Therapy regimes

- CF
    - Cisplatin
    - Fluoruracil
- ECF
    - Epicrubicin
    - Cisplatin
    - Fluoruracil
- EOF
    - Epirubicin
    - Oxaliplatin
    - Fluoruracil
- TCF/DCF

    - Docetaxel
    - Cisplatin
    - Fluoruracil
- FOLFOX
    - Folinic acid
    - Fluoruracil
    - Oxaliplatin
- FOLFIRI
    - Folinic acid
    - Fluoruracil
    - Irinotecan
- FLOT
    - Folinic acid
    - Fluoruracil
    - Oxaliplatin
    - Docetaxel

f. Targeted therapy

During the last decade new therapeutic approaches have shown an improved prognosis of many tumors. These targeted therapies consisting of so-called biologicals intervene in the cell cycle and signaling of tumor cells and thus inhibit proliferation and carcinogenesis. On the one hand, these drugs are molecules which target intracellular signaling pathways controlling proliferation, DNA repair or apoptosis. On the other hand, they are recombinant human or humanized antibodies ending with “-zumab” or “mumab”, acting antiproliferative or as immune modulators.

For example, trastuzumab, a monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2/ ERBB2), is used in HER2 positive breast cancer as well as HER2 positive adenocarcinoma of the gastroesophageal junction and the stomach. In a phase three

study an improved overall survival in patients with advanced gastric cancer or cancer of the gastroesophageal junction (GEJ) was shown. The median overall survival was raised from 11.1 months to 13.8 months. (120p. 948-957, 123) The addition of trastuzumab to chemotherapy costs around 56.000 USD. In gastric and gastroesophageal cancer cost-effectiveness is ambivalently discussed. (124)
In the following some of the most commonly used biologicals will be presented.

Trastuzumab

As described above, Trastuzumab (Herceptin®) is a monoclonal antibody against HER2. The growth factor receptor is part of the family of tyrosine kinase receptors. The monoclonal antibody prevents the dimerization and the separation of the extracellular part of the receptor. Additionally, by binding the receptor, it is internalized and broken down. A third discussed mechanism is the activation of the antibody-dependent cellular cytotoxicity (ADCC).
The receptor status is commonly evaluated through fluorescence in situ hybridization (FISH) (+/-) and immunohistochemistry (IHC) depending on the percentage of expression (IHC +/++/+++). (125)
The benefits of trastuzumab in cancers of the upper gastrointestinal tract were evaluated in the ToGA trail, a phase III study for HER2 positive carcinomas. The standard palliative first-line chemotherapy consisting of cisplatin and either 5-FU or capecitabin was combined with Herceptin or given alone. A significantly improved overall survival was observed in the group (IHC++ and FISH+ or IHC+++) with the combination of chemotherapy and Herceptin. (123)

Most common adverse events:

- Fever
- Anaphylactic reaction
- Bronchospasm
- Higher cardiotoxicity in combination with anthracycline (120p. 948f)

Pembrolizumab

Programmed cell death ligand 1 and 2 (PDL-1/2) are small molecules which bind to the programmed cell death receptor (PDR) and further induce apoptosis of lymphocytes. Pembrolizumab is an immune checkpoint inhibitor. By antagonizing PDL-1 the immune response against tumor cells is enhanced.
The use of Pembrolizumab requires a high percentage of PDL-1 expression as well as a high combined positive score (CPS) over 10. CPS is evaluated by measuring all cells with a PDL-1 overexpression divided by the total number of cancer cells. (126) The KEYNOTE-180 trail suggests that the therapy should be considered as third-line after two or more unsuccessful chemotherapies in the palliative setting. (127)
An ongoing phase 3 study is investigating the use of pembrolizumab in addition to the first-line treatment of advanced esophageal carcinoma with CPS >10. (128)
Pembrolizumab is even considered in the neoadjuvant setting of localized gastric and gastroesophageal cancer. (129)

Most common adverse events:

- Hyper-/hypothyroidism
- Diarrhea
- Pruritus
- Vitiligo
- Pneumonitis (130)

Ramucirumab

Vascular endothelial growth factor (VEGF) mediates the neo-vascularization in cancer cells. (131) As an anti-angiogenetic antibody, ramucirumab targets exactly this mechanism by preventing the binding of VEGF to the VEGF-receptor.
A survival benefit of patients with disease progression after first-line chemotherapy treated with ramucirumab was shown in two phase III studies, the REGARD trail (Ramucirumab monotherapy) and in the RAINBOW trail (Ramucirumab plus paclitaxel weekly). Those patients had a significantly better median progression free survival and median overall survival in comparison to placebo. (132, 133)

Most common adverse events:

- Neutropenia/leukopenia
- Fatigue
- Hypertension
- Anemia
- Abdominal pain (133)

1.4.3.5 Stage dependent treatment

1.4.3.5.1 Limited disease (cT1-T2 cN0 M0)

Resection is the primary therapy in limited disease. This approach is achieved by either endoscopic techniques including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) or esophagectomy.
For very early stages of both adenocarcinoma and squamous cell carcinoma (cTis/cT1a, N0) ESD is the preferred therapy showing better rates concerning endoscopic en bloc resection, curative resection and local recurrence than EMR. (134) In more advanced early stages curative resection is more likely when esophagectomy is performed. Therefore, the Ivor-Lewis transthoracic esophagectomy is the recommended technique, being superior to trans-hiatal approaches. (135)
Neoadjuvant chemoradiotherapy seems to have no effects on R0 resection rate and survival. This is suggested by an analysis of a phase III study comparing preoperative chemotherapy with following surgery to surgery alone. (136)
For comorbid patients or patients unwilling to undergo surgery, definitive chemoradiotherapy is more preferable than radiotherapy alone. Therefore four courses of cisplatin and 5-FU combined with a radiation dose of 50.4 Gy in 1.8 Gy fractions is recommended. (77)

1.4.3.5.2 Locally advanced disease (cT3-T4 or cN1-N3 M0)

Since complete resection (R0) cannot be achieved in the majority of locally advanced diseases, these tumors cannot be targeted with resection alone.
Many studies, such as a meta-analysis from Sjoquist et al. provide strong evidence that preoperative chemotherapy or chemoradiotherapy is beneficial in terms of survival. (137)

For squamous cell carcinoma the CROSS trail provides evidence for a standard of therapy in patients with T1N1 or T2-3N0 disease. According to Shapiro et al., weekly given carboplatin combined with paclitaxel followed by surgery have the best overall survival in patients with locally advanced esophageal cancer. Therefor it is considered standard of care. (138)

In fact, some studies did not show any improvement of survival in patients receiving neoadjuvant chemoradiotherapy compared to definitive chemoradiotherapy. (139, 140) Definitive chemoradiotherapy should be considered in cervically localized tumors.(141)

For adenocarcinoma large studies confirmed that preoperative chemotherapy with cisplatin and fluorouracil combined with radiotherapy showed an improved survival of patients. Therefor it is commonly considered as the standard of therapy. (77, 137) Additionally, perioperative chemotherapy seems to improve the 5-year survival, over-all survival and progression free survival compared to surgery alone. (142)
Adjuvant chemoradiotherapy should be considered in patients with good performance status. Especially in a R1 situation a postoperative therapy seems to have an impact on the recurrence rate. Therefore, fluorouracil plus leucovorin, capecitabine, or capecitabine plus cisplatin should be taken into consideration. (143)

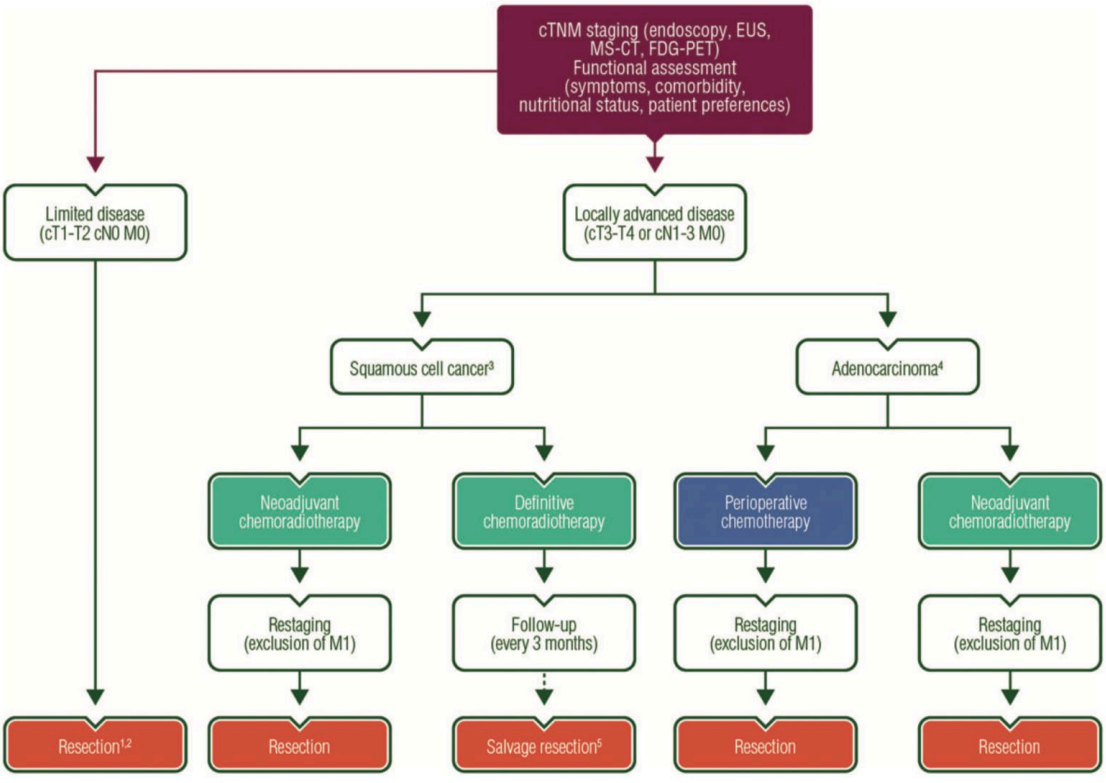

Figure 1: Algorithm for the treatment of local/locoregional resectable thoracic esophageal cancer. (144)

1.4.3.5.3 Advanced unresectable/ metastatic disease (M1)

The prognosis of locally advanced unresectable or metastatic esophageal carcinoma is poor. Therefore, the main goal of therapy in these cases should be improving quality of life, reducing symptoms as well as prolonging life. (77, 97)

In order to evaluate different chemotherapeutic drugs it is important to mention that many clinical trials combined gastric adenocarcinomas with those of the distal esophagus and the gastroesophageal junction.

Adenocarcinoma:

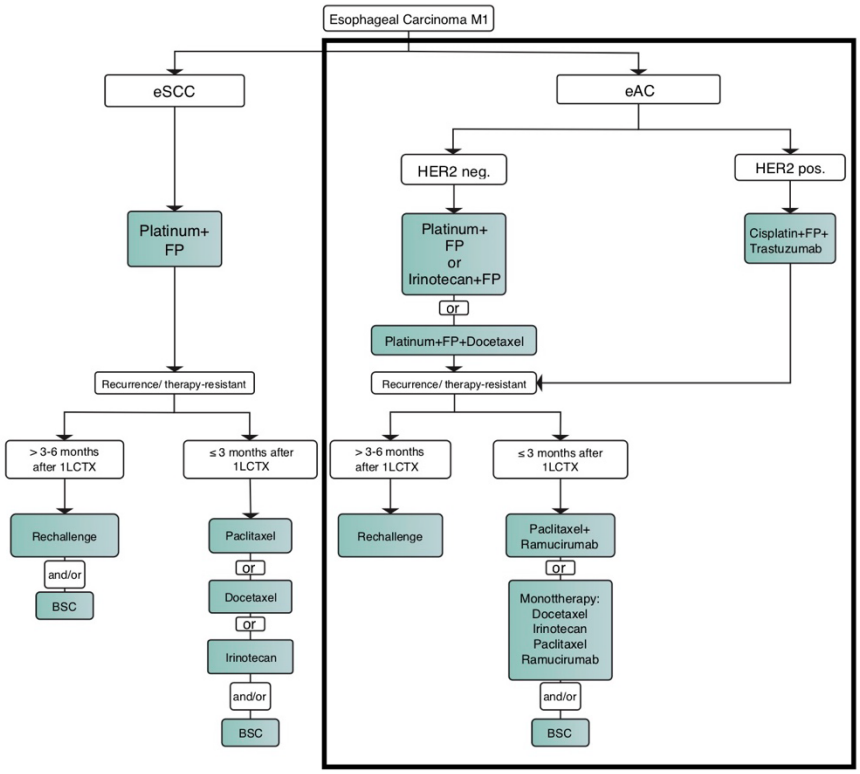

Figure 2: Palliative chemotherapy Adenocarcinoma (71)

First-line treatment:

The status of expression of human epidermal growth factor receptor 2 (HER2) is essential for therapy decision.

HER2-neg. AC:

- Doublet Platin plus fluoruracil:

According to ESMO clinical practice guidelines 2016, doublet therapy with cisplatin and 5-FU is the standard of care in HER2 negative adenocarcinomas. (77)
Cunningham et al. showed that the combination with oxaliplatin plus capecitabine is as effective as cisplatin plus 5-FU and thus represents a feasible alternative. (122)
According to a phase III study of Al-Batran et al., the combination of fluoruracil, leucovorin and oxaliplatin (FLO) shows significantly reduced toxicity as well as improved efficacy compared to fluoruracil, leucovorin and cisplatin, especially in older patients. (9)

- Doublet Irinotecan plus fluoruracil:

Treatment with FOLFIRI provides a platinum-free alternative to doublet combinations with platinum. Results of Dank et al. show IF being as effective as CF with a significantly improved time to treatment failure (TTF) for the irinotecan combination. (9)

- Triplet Platin plus fluoruracil plus docetaxel:

In patients in good condition an extension of the double therapy cisplatin plus 5-FU with docetaxel could be evaluated. A study by Van Custem et al. showed a significant improvement in “time to progression”, survival and response-rate. However, this was also associated with an increased toxicity of therapy. (145)

HER2-pos. AC:

For human epidermal growth factor receptor positive AC (HER2+) the ToGA-study (Trastuzumab for Gastric Cancer) achieved an improved median overall survival (13.8 months compared to 11.1 months; p=0,0046) by combining standard chemotherapy with Trastuzumab. Especially in patients with high expression of the HER2 protein (IHC double positive plus positive immunefluorescence or IHC triple positive) the benefits were noticeably linked to the extended therapy. (123)

Second-line treatment:

Fuchs et al. showed a survival benefit of those patients with esophagogastric adenocarcinoma treated with the VEGFR 2 monoclonal antibody ramucirumab compared to placebo (median overall survival 5.2 compared to 2.8 months). (132) According to the RAINBOW study, the combination of ramucirumab and paclitaxel also showed increased overall survival compared to paclitaxel plus placebo. (133)
Thus current guidelines of the national comprehensive cancer network (NCCN) recommend combination of ramucirumab in combination with paclitaxel or monotherapy with docetaxel, paclitaxel or irinotecan.

Squamous cell carcinoma:

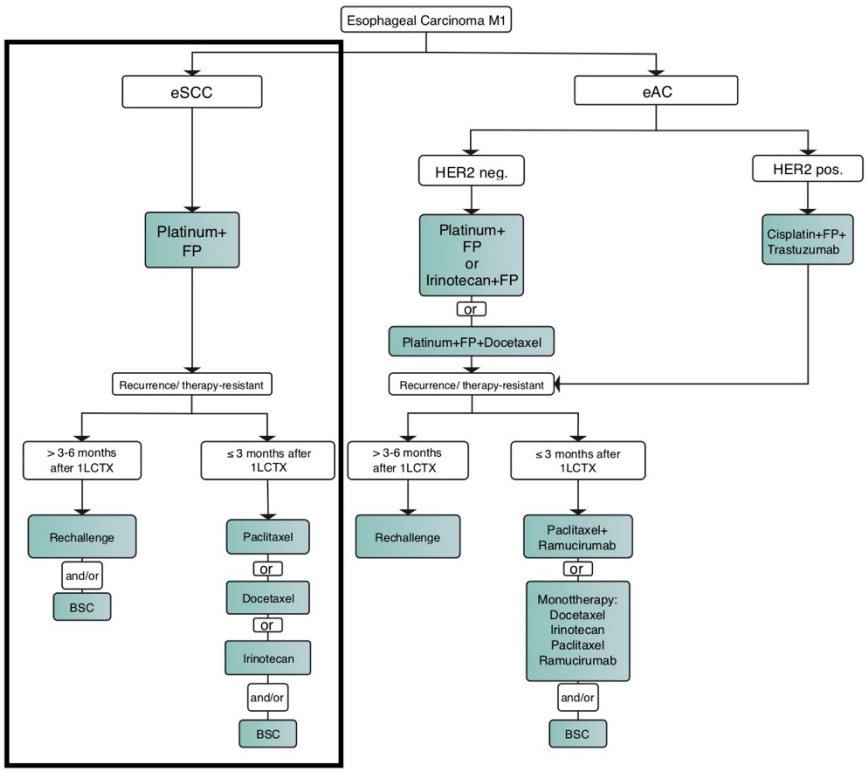

Figure 3: Palliative chemotherapy squamous cell carcinoma (71)

First-line treatment:

According to the ESMO guidelines from 2016, the combination of cisplatin and 5-fluoruracil is the standard of treatment in esophageal squamous cell carcinomas. (77, 146) A retrospective study from Hiramito et al. showed an overall response rate of 37,2 percent as well as a median PFS and OS of 4.8 and 10.4 months 187 patients with metastatic or recurrent esophageal ESCC treated with cisplatin plus 5- fluoruracil, respectively. (5) In a phase II study from Wang et al. also a good antitumor activity for the combination regimen FOLFOX was observed. (7)

Second-line treatment:

Since palliative second-line chemotherapy in esophageal SCC is the main subject of this thesis, this will be discussed in more detail in the following.

However, to date there are only few small phase II studies, as well as retrospective data analysis which have evaluated chemotherapeutic drugs for second-line treatment in esophageal SCC. This makes it difficult to interpret the data.

There are few regimes commonly used as second-line treatment in the palliative setting. For fit patients a second-line chemotherapy can be considered. For patients with poorer performance status a purely symptomatic treatment is recommended.

The highest evidence was shown by small phase II studies evaluating benefits of docetaxel in different doses. Muro et al. used a 70mg/m2 regime of docetaxel every 21 days. 49 patients were evaluable mostly with SCC (94%). The median survival was 8,1 months and the one-year-survival rate 35%. Ten patients (20%) achieved a partial response, six were previously treated with platinum. Although RR was good, 88% developed neutropenia and 18% febrile neutropenia. (147)

In a retrospective investigation using taxanes (Docetaxel 70mg/m2 three-weekly and Paclitaxel 100mg weekly for six weeks, with one week rest), Shirakawa et al. showed a PFS of 2,3 months and an OS of 6,1 months in the PTX cohort. In the DTX group the PFS was 2,3 months and the OS 5,3 months.

Response Rates differed from 20,7% in the PTX to 5,9% in the DTX group. All patients included were pretreated with platinum.

(148)

In a small prospective phase II study Burkart et al. evaluated the efficacy of monotherapy with irinotecan in thirteen platinum pretreated patients. The regime was CPT-11 100mg/m2 on days 1, 8, 15 and 28. As toxicity was low the treatment was escalated to a maximum dosage of 240mg/m2. The response assessment showed two partial remission (PR), three stable disease (SD) and eight progressive disease (PD). The median PFS was two months, the median OS was eight months and the one-year survival rate was 16 percent. (149)

Vinorelbin may be an effective agent in 2LTX of advanced ESCC as well. Conroy et al. conducted a phase II study using vinorelbine 25mg/m2 weekly. Of 46 Patients 16 had a previous line of palliative chemotherapy. One of these 16 Patients (6%) had a complete remission. Overall response rate was 15%. (9)

Taxane-based combinations were evaluated in several studies. Combination therapies were mostly accompanied by severe side-effects and low benefits concerning the overall RR and PFS. For example, combination of capecitabine (1,000mg/m2 twice daily on day 1-14) and docetaxel (75mg/m2 on day 1 every 3 weeks) showed an overall response rate of 46%, a median PFS of 6,1 months and a median survival of 15,8 months. Severe neutropenia was seen in nearly half of the patients (46%), questioning the benefits. (150)
The combination of irinotecan plus docetaxel seems not to be beneficial, considering the severe side effects. (151)

A combination containing docetaxel, cisplatin and 5-FU (DCF) showed some potential benefits. In one study by Tanaka et al. pretreated patients received docetaxel 60mg/m2 on day one and cisplatin 10mg/m2 as well as 5-FU 500mg on day 1-5 repeated every 3 weeks. Overall RR was 35%, PFS 4 months and OS 8 months. However, severe neutropenia occurred in 65% of treated patients. (8)

Immunotherapy has recently been more in the focus and seems promising for future treatment options.
In the ATTRACTION III study 419 patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma were randomly assigned to either 2LTX (PTX 100mg/m2 or DTX 75mg/m2) or nivolumab (240mg every two weeks). The nivolumab group had a significantly higher overall survival of 10.5 months compared to the 8.0 months in the chemotherapy group, which was independent of of tumor programmed cell

death ligand 1 expression level. (152) Based on these findings nivolumab received an approval of the food and drug administration (FDA) for second line treatment in patients with metastatic esophageal squamous cell carcinoma. An approval of the European medicine agency (EMA) has not been granted yet.

In the phase III KEYNOTE 181 study 628 patients with advanced or metastatic EC were randomized. 401 of these had esophageal SCC and 222 a combined positive score (CPS) ≥10. Subject of this study was to compare OS in 2LTX (taxanes, irinotecan, vinorelbine) to pembrolizumab. Pembrolizumab was superior to chemotherapy in patients with a CPS ≥10,which led to an FDA approval in this setting. However, in the overall cohort of patients with ESCC no statistical survival benefit for Pembrolizumab could be shown. (153)

Later lines of palliative chemotherapy:

Immunotherapy with the immune checkpoint inhibitors pembrolizumab or nivolumab might be a new treatment option in later lines of palliative treatment. An Asian phase III study aimed to prove efficacy of nivolumab in patients with pretreated advanced gastric or gastro-esophageal cancer. These patients were pretreated, refractory or intolerant with/to at least two lines of palliative treatment. Primary endpoint was overall survival. 493 patients were underwent randomization. Median OS was 5.26 months in nivolumab treated patients versus 4.14 months in the placebo group and 12-months overall survival rate was 26.2% compared to 10.9%. (154) These beneficial effects could be seen in a Caucasian cohort, too. (155)

Palliative supportive Treatment

In a palliative situation some supportive modalities could be contemplated. Their purpose is mostly supporting palliative chemotherapy (see palliative radiation) as well as improving the patient's ailments such as dysphagia, malnutrition and cachexia.

1. Photodynamic therapy (PDT)
2. Brachytherapy
3. Balloon dilatation
4. Stenting

1.4.4 Prognosis

According to the American cancer society the prognosis is poor.
Combined five-year survival rate of all stages is 20 percent. (156)

Stage	5-year relative survival rate
Localized	47 %
Regional	25 %
Distant	5%

Table 5: Prognosis (97)

2 Material and Methodes

2.1 Database Esophageal and gastric cancer

As a part of this thesis, a retrospective database was set up. All patients with cancer of upper, middle and lower esophagus as well as gastric cardia treated at the Division of Oncology, Department of Internal Medicine; Medical University of Graz in the period from 2005 to 2019, were included. Data collection was divided into seven forms. (Baseline characteristics, curative treatment, surgery, palliative treatment, palliative supportive treatment, complications and best supportive care/ death) Potentially 654 variables could be recorded for each patient. These variables include demographic data (sex, age, anthropometrics), tumor characteristics (TNM, localization, molecular characteristic), and comorbidities. Furthermore all important variables concerning curative and palliative treatment. Over all 446 patients with esophageal squamous cell carcinoma or adenocarcinoma were captured as part of this thesis. In further course this database will be extended covering all cancers of the upper gastrointestinal tract treated at the Division of Oncology, Medical University of Graz from 2005 to 2020.

An overview of the most important variables is given in Table 6.

Variable	**Overall**	**in %**
Sex		
Female	54	12%
Male	392	88%
Histology		
Adenocarcinoma	267	61%
Squamous Cell Carcinoma	171	39%
Localization		
Esophagus	297	67%
GEJ	46	10%
Cardia	100	23%
Localization Esophagus		
Upper	50	16%
Middle	55	17%
Lower	188	59%
Missing	24	8%

Metastasis	286	64%
synchronous	134	30%
metachronous	152	34%
curative Therapy	261	59%
Induction	49	11%
Neoadjuvant	94	21%
Definitive	31	7%
Perioperative	0	0%
Adjuvant	44	10%
Palliative Therapy		
1st Line	248	55%
2nd Line	113	25%
3rd Line	43	10%
4th Line	13	3%
5th Line	2	<1%
BSC	170	38%

Table 6: Overview Database Esophageal Cancer

Figure 4-7 is giving an overview over the distribution as far as localization, sex, histology and received palliative chemotherapy is concerned.
This cohort provided the raw data used for the study, which is described in the following.

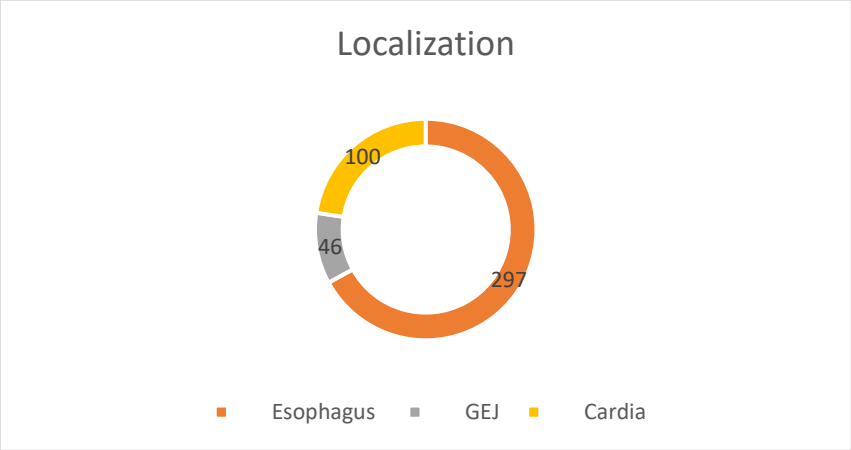

Figure 4: Overall cohort distribution by tumor location

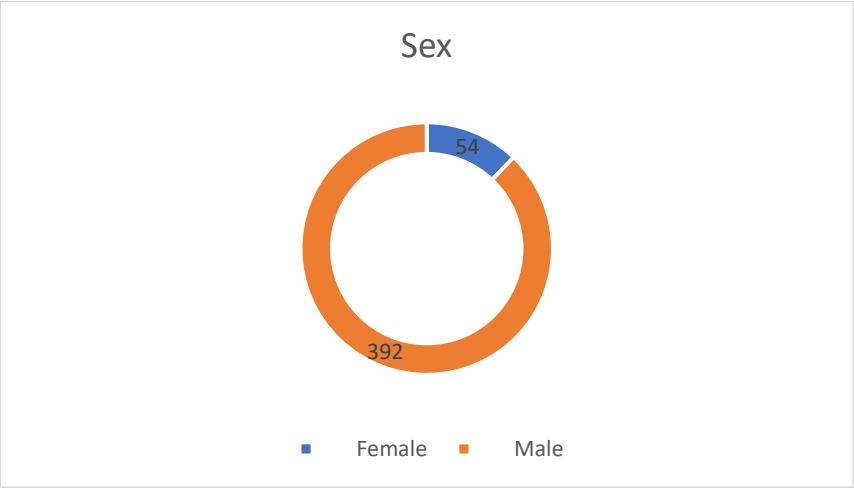

Figure 5: Overall cohort distribution by sex

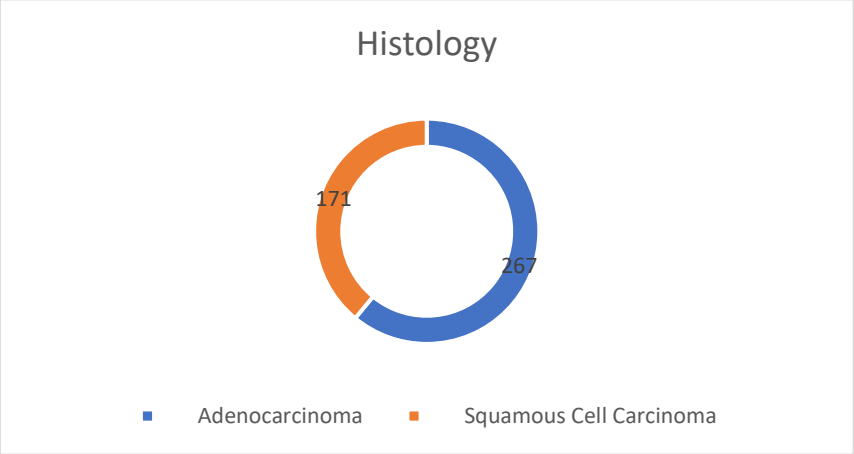

Figure 6: Overall cohort distribution by histology

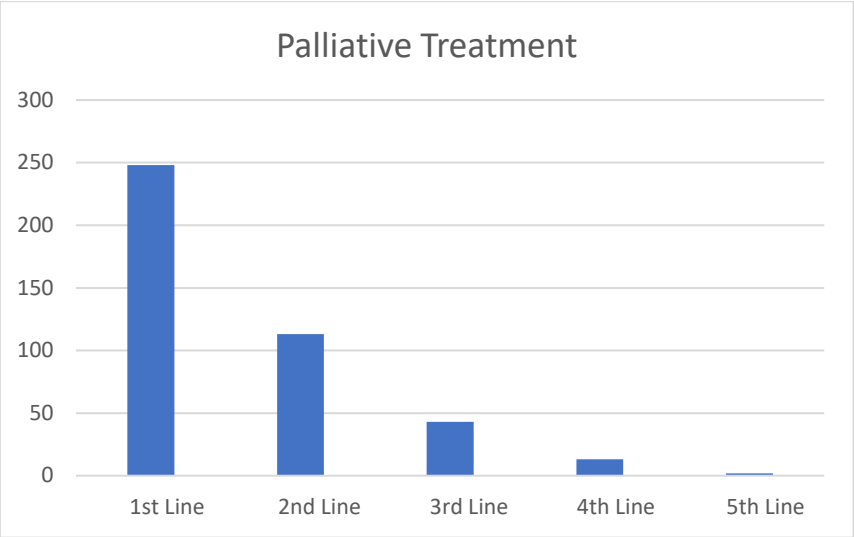

Figure 7: Overall cohort distribution by palliative treatment

2.2 Study design and patient cohort

This retrospective cohort study was performed at three academic centres in Austria (Medical University of Graz, Paracelsus Medical University Salzburg and Medical University of Innsbruck).

All patients with histologically and radiologically confirmed metastatic or locally advanced inoperable esophageal squamous cell carcinoma who were 18 years or older and who had progression on or after receiving palliative 1st-line therapy at one of the respective centres between Jan, 1st, 2006 and Apr, 30th, 2020 were considered for this study (n=191). Of this cohort patients who had ongoing palliative first line at the date of data acquisition (n=4) and patients who died during 1st-line therapy (n=21) were excluded, resulting in an analysis population of n=187 patients.

2.3 Data acquisition and outcome

Baseline and outcome data were retrospectively collected from the respective in-house electronic healthcare databases as well as from the central registry of the Austrian Social Security Providers Association for all-cause death as reported previously (157, 158). To uniformly assess the survival time for both study groups, the baseline date was defined as the termination date of palliative first line treatment, in detail the date when the last cycle of first line treatment was administered.

The primary endpoint of the study was the overall survival defined as the time from baseline until death-from-any-cause or censoring alive. The co-secondary endpoints in the subgroup of patients who received second line treatment, were the investigator-assessed objective response rate (ORR), i.e. the composite of complete or partial remission, the OS measured from the date of start of second line therapy until death from any cause or censoring alive as well as the progression free survival measured from date of start of second line treatment until radiographically assessed disease progression, death from any cause or censoring alive.

This study was approved by the institutional review board of the leading center (Ethics Committee of the Medical University of Graz, Austria; document number 32-660 ex 19/20). All methods and analyses were performed in accordance with the relevant local and national guidelines and regulations.

2.4 Statistical methods

All statistical analyses were performed with Stata 15.0 (Stata Corp., Houston, TX, USA). Continuous variables were summarized as medians [25^{th}-75^{th} percentile], whereas count data were reported as absolute frequencies (column %). The distribution of baseline variables between the two treatment groups was analyzed with rank-sum tests, χ^2-tests, and Fisher's exact tests, as appropriate. Standardized mean differences (SMDs) were implemented to gauge the magnitude of difference in the distribution of baseline variables between the two treatment groups (159). The propensity score was predicted from a multivariable logistic regression model with treatment assignment as the dependent variable and by including all baseline variables as explanatory variables that had a p-value for difference between the two treatment groups of ≤ 0.10 or an SMD≥ 0.15.
This multivariable propensity score model was fitted on multiply-imputed data to account for missingness in selected variables. Multiple imputation was performed with a chained equations algorithm with 10 imputation datasets, predictive mean matching for missing categorical variables, and linear regression for missing continuous variables without including the outcome in the imputation model (160).

Based on the propensity score, we then obtained the inverse probability of treatment weight (IPTW) according to the average treatment effect (ATE) principle (161). Following best

practice recommendations, we then re-calculated SMDs with IPTW-weighted data in order to gauge whether the propensity score modelling process achieved adequate balance (159). Median follow-up was estimated with the reverse Kaplan-Meier method (162), and follow-up was truncated at 24 months.

The primary outcome of the study, Overall survival (OS), was computed with Kaplan-Meier estimators. The proportionality of hazards (PH) assumption according to treatment group was tested with a PH test on the Schoenfeld residuals of a univariable Cox model, and because this test revealed very strong evidence for a departure from the PH assumption, all subsequent analyses were performed with Royston-Parmar models that specifically accounted for non-proportionality (Stata routine stpm2 with 3 degrees of freedom for the time-dependent "effect" of treatment and 2 degrees of freedom for the time-invariant "effect" of treatment, directly modelling on the log(cumulative hazard) scale) (163).

In sensitivity analyses, we (1) estimated the progression-free survival (PFS) in patients who had received 2nd-line therapy, (2) compared crude OS estimates for taxane vs. non-taxane based 2nd-line therapy, (3) quantified non-proportionality of the association between 2nd-line therapy and OS outcomes, and (4) performed IPTW-weighted multivariable analysis by additionally adjusting for the two covariates with the strongest association with OS (Eastern Cooperative Oncology Group (ECOG) performance status, C-reactive protein levels (CRP)).

Finally, we performed exploratory hypothesis generating subgroup analyses of the relative efficacy of the two treatment strategies according to 8 pre-specified clinical covariables: ECOG performance status, age, gender, Charleson Comorbidity Index (CCI), primary metastatic disease, objective response to 1st-line therapy, surgery of the primary tumor, and modality of 1st-line therapy (monotherapy vs doublet). Here, interaction p-values <0.10 were considered to indicate a potentially relevant interaction. The analysis code is available on reasonable request from FP.

3 Results

3.1 Cohort description, 1st-line therapy data, and crude outcome rates

One-hundred-and-sixty-six patients with a median age of 63 years [25th-75th percentile: 57-70] were included in the analysis (**Table 7**). The median Charleson Comorbidity Index (CCI, excluding 6 points for advanced malignancy) was 3 [2-4], and most patients (75%) had an ECOG performance status <2. Nearly half (n=70) of the cohort had a primary palliative treatment intent, while 38 patients (23%) underwent prior resection of their primary tumor and 38 patients (23%) underwent prior definitive chemoradiation.

The majority of patients were treated with a platinum agent and a fluoropyrimidine in 1st-line therapy, with only 44 patients (24%) being treated with a monotherapy. For computation of 1st-line treatment outcomes, we also included the n=21 patients who died during 1st-line therapy (n=187). Overall, 1st-line treatment duration was relatively short (median: 2.2 months), and the investigator-assessed objective response rate was 25% while the median OS from start of 1st-line therapy was 7.1 months (**Figure 8**).

Variable	**n (% miss.)**	**Overall (n=166)**	**ASC (n=74)**	**2L+ASC (n=92)**	**p**	**p_{IPTW*}**	**SMD**	**SMD_{IPTW}**
Demographics at baseline								
Age (years)	166 (0%)	63 [57-70]	65 [58-71]	62 [56-69]	0.053	0.637	0.34	0.09
Male Gender	166 (0%)	141 (85%)	60 (81%)	81 (88%)	0.213	0.768	0.19	0.07
Weight (kg)	160 (4%)	68 [60-76]	68 [59-74]	70 [60-77]	0.131	0.624	0.27	0.12
Charleson Comorbidity Index	166 (0%)	3 [2-4]	3 [2-4]	2 [1-4]	0.269	0.385	0.14	0.16
Performance status: ECOG 0	155 (7%)	57 (37%)	10 (15%)	47 (53%)	<0.0001	0.246	0.88	0.25
---ECOG 1	/	67 (43%)	38 (57%)	29 (33%)			0.49	0.14
---ECOG 2-3	/	31 (20%)	19 (28%)	12 (14%)			0.36	0.13
Center: Graz	166 (0%)	75 (45%)	41 (55%)	34 (37%)	0.049	0.676	0.37	0.04
---Salzburg	/	77 (46%)	29 (39%)	48 (52%)			0.26	0.15
---Innsbruck	/	14 (8%)	4 (5%)	10 (11%)			0.20	0.17

Tumor variables								
Location: Proximal esophagus	162 (2%)	42 (26%)	17 (24%)	25 (27%)	0.877	0.522	0.08	0.05
---Middle esophagus	/	47 (29%)	21 (30%)	26 (29%)			0.02	0.19
---Distal esophagus	/	73 (45%)	33 (47%)	40 (44%)			0.05	0.22
Tumor grade: G3-4	151 (9%)	82 (54%)	34 (49%)	48 (58%)	0.255	0.499	0.19	0.14
Primary treatment intent: Palliative	166 (0%)	70 (42%)	36 (49%)	34 (37%)	0.129	0.566	0.24	0.11
Primary metastatic disease	166 (0%)	48 (29%)	20 (27%)	28 (30%)	0.630	0.636	0.07	0.09
Prior resection of primary tumor	166 (0%)	38 (23%)	16 (22%)	22 (24%)	0.727	0.234	0.05	0.21
Prior definitive chemoradiation	166 (0%)	38 (23%)	15 (20%)	23 (25%)	0.929	0.493	0.02	0.18
1st line systemic therapy data								
Treatment with platinum	166 (0%)	133 (80%)	57 (77%)	76 (83%)	0.370	0.975	0.14	0.01
Treatment with fluoropyrimidine	166 (0%)	119 (72%)	52 (70%)	67 (73%)	0.716	0.763	0.06	0.06
Modality: Monotherapy	166 (0%)	39 (23%%)	20 (27%)	19 (21%)	0.226	0.931	0.15	0.03
---Doublet	/	110 (66%)	50 (68%)	60 (65%)			0.05	0.04
---Doublet+EGFRi	/	16 (10%)	4 (5%)	12 (13%)			0.30	0.10
---Triplet*	/	1 (<1%)	0 (0%)	1 (1%)			N/A*	N/A*
Objective response	159 (4%)	37 (23%)	13 (19%)	24 (26%)	0.284	0.960	0.17	0.01
Treatment duration (months)	166 (0%)	2.2 [1.4-3.7]	2.0 [1.0-3.3]	2.6 [1.5-4.2]	0.005	0.953	0.36	0.02
Laboratory parameters at baseline								
Haemoglobin (g/dL)	125 (25%)	10.6 [9.7-12.1]	10.6 [9.9-11.7]	10.7 [9.7-12.4]	0.824	0.648	0.08	0.09
Leukocyte count (G/L)	125 (25%)	5.8 [4.2-8.1]	5.8 [4.2-8.8]	5.7 [4.3-7.8]	0.628	0.846	0.02	0.04
Neutrophil count (G/L)	115 (31%)	4.0 [2.7-5.9]	4.0 [3.0-6.2]	4.1 [2.6-5.5]	0.563	0.790	0.01	0.05
Lymphocyte count (G/L)	115 (31%)	0.9 [0.6-1.4]	0.9 [0.6-1.3]	0.9 [0.6-1.4]	0.881	0.878	0.16	0.03
Platelet count (G/L)	124 (25%)	232 [172-310]	228 [163-291]	235 [177-314]	0.560	0.322	0.13	0.19
C-reactive protein (mg/dL)	124 (25%)	7 [2-17]	12 [3-37]	5 [2-10]	0.002	0.201	0.54	0.25

Albumin (g/dL)	57 (66%)	4.0 [3.6-4.3]	3.7 [3.2-4.1]	4.2 [3.8-4.5]	0.004	0.310	0.27	0.20
LDH (IU/L)	125 (25%)	192 [163-239]	186 [156-248]	197 [170-239]	0.246	0.377	0.19	0.13
Creatinine (mg/dL)	137 (17%)	0.8 [0.7-0.9]	0.8 [0.6-0.9]	0.8 [0.7-1.0]	0.128	0.276	0.35	0.19

Table 7: Baseline characteristics of the study population (n=166)

Distribution overall and by treatment group. Data are medians [25^{th}-75^{th} percentile] for continuous data, and absolute frequencies (column %) for count data. n (%miss.) reports the number of patients with fully observed records for the respective variable (% missing). *IPTW-weighted p-values were obtained from linear, logistic, ordinal logistic, and multinomial logistic regression models. Abbreviations: ASC – Active symptom control, 2L – 2^{nd}-line therapy, p – p-value, p_{IPTW} – p-value after IPTW weighting, IPTW – Inverse probability of treatment weight, SMD – Standardized mean difference, SMD_{IPTW} – Standardized mean difference after IPTW weighting, ECOG – Eastern Cooperative Oncology Group, EGFRi – Epidermal growth factor receptor inhibitor (e.g. Cetuximab), LDH – Lactate dehydrogenase, N/A – not applicable.

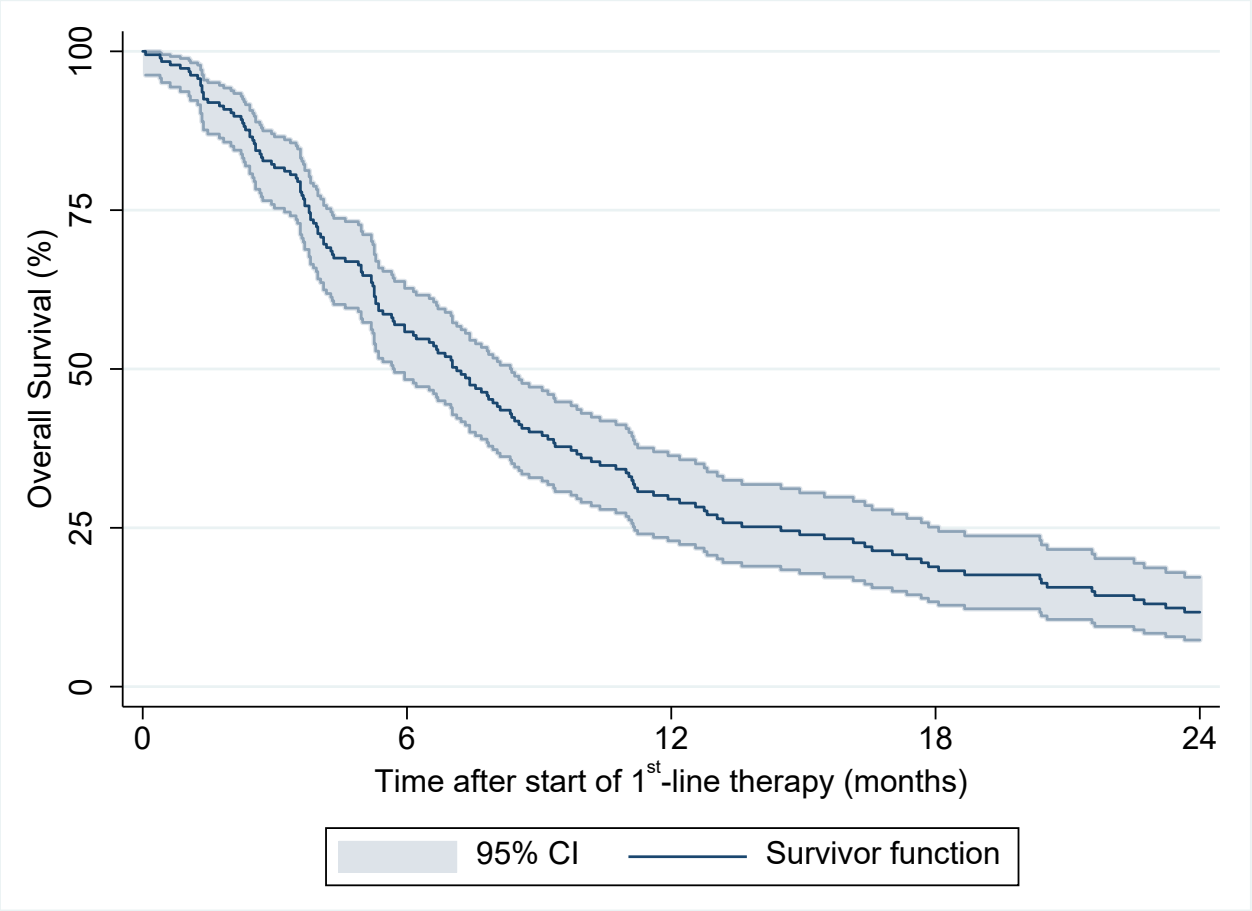

Figure 8: 1st-line therapy overall survival of the source cohort (n=187).

This cohort also includes the n=21 patients who died during 1st-line therapy and were thus not considered for the ASC vs. 2L+ASC analysis. Estimates were obtained with a Kaplan-Meier estimator.

3.2 Second-line therapy of advanced esophageal SCC – Unadjusted analysis

After progression on 1st-line therapy, seventy-four (45%) of patients were treated with ASC while 92 patients (55%) received additional 2nd-line therapy. The most frequent 2nd-line regimens were monotherapies (82%), including docetaxel (36%) and paclitaxel (18%). Small proportions of patients (7% and 4%) also received immune checkpoint inhibitors and EGFR inhibitors, respectively (**Table 8**).

The ORR of 2nd-line therapy was 13%, while median PFS and OS estimates were 2.2 and 4.7 months, respectively (**Figure 9**).

Variable	n (%)
2nd line aggressivity	
---Monotherapy	75 (82%)
---Combination therapy	17 (18%)
Agents used in 2nd line therapy	
---Taxanes	52 (57%)
---Fluoropyrimidines	19 (21%)
---Platinum agents	12 (13%)
---Vinca alkaloids	11 (12%)
---Irinotecan	9 (10%)
---Immune checkpoint inhibitors	6 (7%)
---EGFR inhibitors	4 (4%)
Most frequent 2nd line regimens	
---Docetaxel monotherapy	33 (36%)
---Paclitaxel monotherapy	17 (18%)
---Vinorelbine monotherapy	11 (12%)
---FOLFIRI	8 (9%)
---Platinum/5-FU	7 (8%)
2nd line treatment outcomes	
ORR, % (95% CI)	13% (6-19)
DCR, % (95% CI)	23% (15-33)
Median duration of treatment, months (p25-p75)	1.4 (0.5-2.5)
Median PFS (months, p25-p75)	2.2 (1.4-3.9)
Median OS (months, 95% CI)	4.7 (2.4-9.8)
Received 3rd line therapy	36 (39%)
Received 4th line therapy	9 (10%)

Table 8: Tabulation of 2nd-line therapy characteristics.

Abbreviations: EGFR – Epidermal growth factor receptor, ORR – Objective response rate, DCR, Disease control rate, 95%CI – 95% confidence interval, p25-p75 – 1st to 3rd quartile of the distribution of the respective variable, PFS – Progression-free survival, OS – Overall survival.

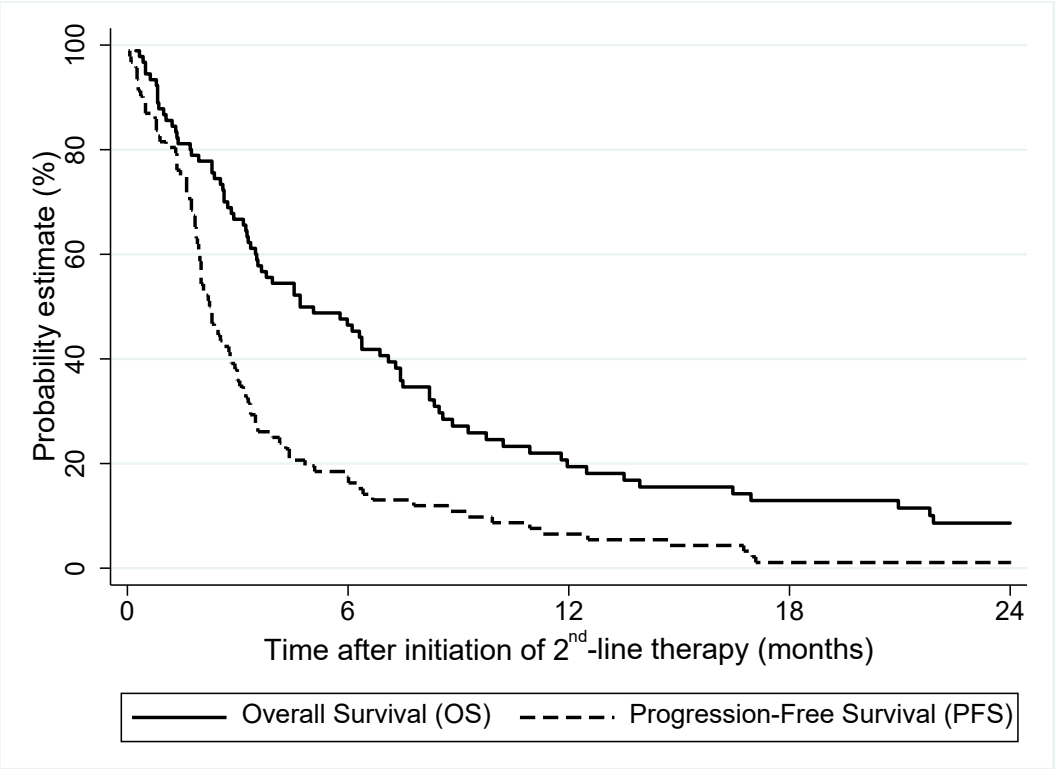

Figure 9: Overall and Progression-free survival of the n=92 patients who initiated 2nd-line therapy.

Estimates were obtained with Kaplan-Meier estimators, and the timescale starts at the date of the first 2nd-line treatment cycle.

In crude analysis of overall survival (starting from the baseline date, i.e. the date of administration of the last 1st-line cycle), patients who went on to receive 2nd-line therapy had a significantly more favourable OS experience than patients who were treated with ASC only. In detail, median OS estimates were 2.9 months in the ASC group, and 7.2 months in the 2L+ASC group, respectively (**Figure 10A**, log-rank p<0.0001, Hazard ratio (HR) from a univariable Cox model=0.49, 95%CI: 0.35-0.69, p<0.0001).

Because we observed strong evidence for a violation of the proportional hazards assumption (Schoenfeld test p=0.005, "converging curves" in Figure 1A), we also analysed the data with a Royston-Parmar model, yielding a HR of 0.29 (95%CI: 0.17-0.48, p<0.0001) and median predicted OS estimates of 2.7 months and 7.2 months in the ASC and 2L+ASC group, respectively (**Figure 11A**).

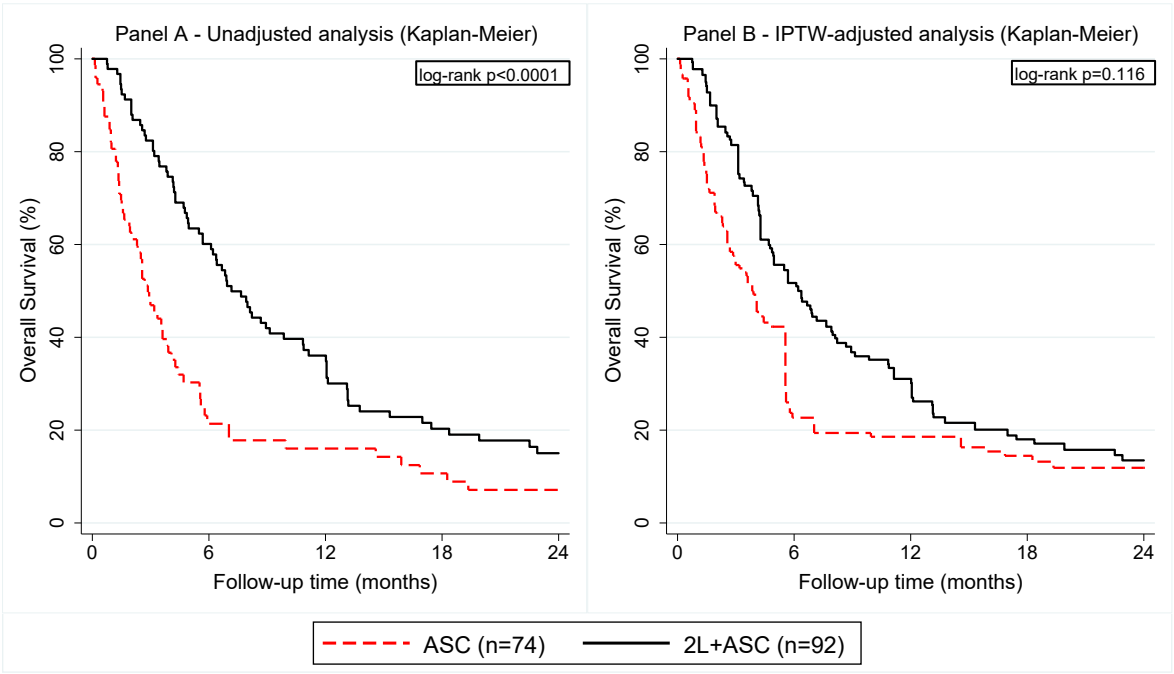

Figure 10: Kaplan-Meier analysis of Overall Survival by treatment group.

Panel A – Unadjusted analysis. Panel B – IPTW-adjusted analysis. Abbreviations: IPTW – Inverse probability of treatment weight, ASC – Active symptom control, 2L – 2nd-line therapy.

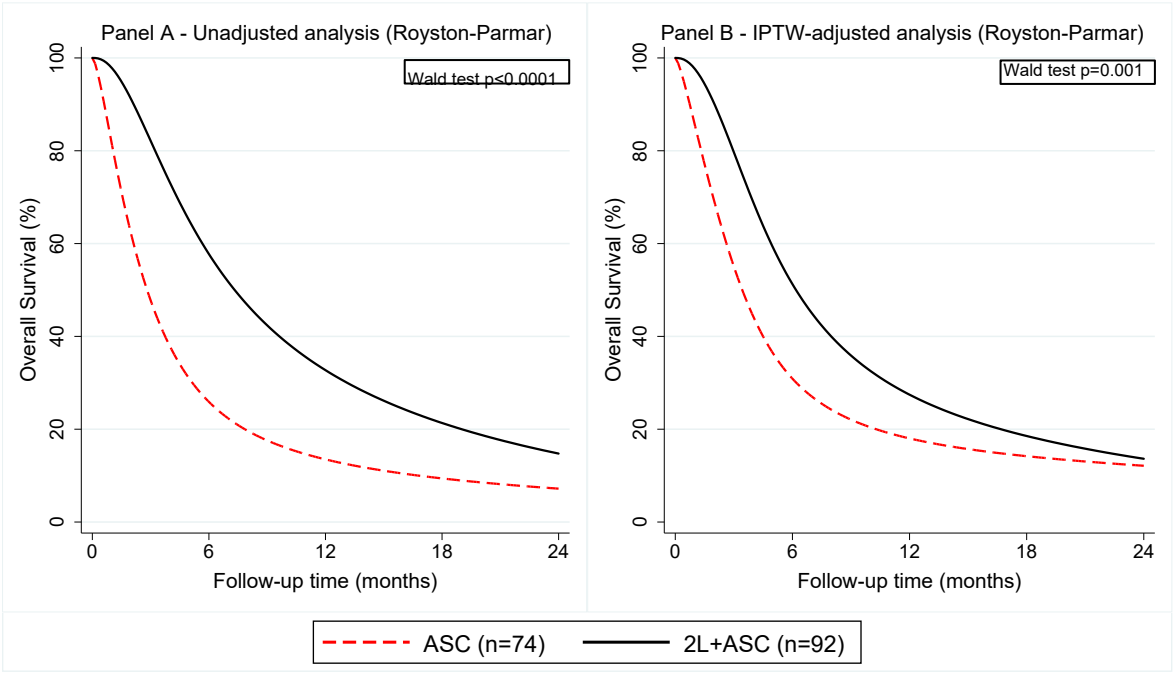

Figure 11: Royston-Parmar analysis of Overall Survival by treatment group.

Panel A – Unadjusted analysis. Panel B – IPTW-adjusted analysis. Abbreviations: IPTW – Inverse probability of treatment weight, ASC – Active symptom control, 2L – 2nd-line therapy.

3.3 Development of a propensity score

However, consistent with selection bias, patients in the 2L+ASC had a significantly higher prevalence of favourable prognostic factors (**Table 7**). Considering standardized mean differences (SMDs) ≥ 0.3 to indicate a potentially large magnitude of difference in the distribution of a variable between the two treatment groups, patients in the 2L+ASC group had, among others, better ECOG performance status (SMD for ECOG 0=0.88), a longer 1st-line treatment duration (SMD=0.36), and lower C-reactive protein (CRP, SMD=0.54) levels than patients who were treated with ASC alone. Given the association of these and other unevenly distributed variables with overall survival (**Table 9**), we obtained a propensity score (PS) from a multivariable logistic regression model (**Table 10**).

This propensity score covered the whole probability range (**Figure 12A**), and was transformed into an inverse probability of treatment weight (IPTW, **Figure 12B**). Re-weighting the data with this IPTW strongly reduced imbalances between the two treatment groups (**Table 7**).

In detail, none of the differences in baseline variables were statistically significant anymore, and SMDs were reduced (e.g. for age from 0.34 to 0.09). These balance diagnostics findings were considered to be indicative of adequate balance between the two treatment groups upon IPTW weighting.

Variable		**Univariable Hazard Ratio**	**95%CI**	**p**
Demographics at baseline				
Age (per 5 years increase)		1.01	0.93-1.10	0.861
Male Gender		1.10	0.68-1.78	0.708
Weight (per 5 kg increase)		0.94	0.88-1.01	0.087
Charleson Comorbidity Index (per 1 point increase)		1.01	0.92-1.11	0.841
Performance status: ECOG 0		Ref.	Ref.	Ref.
---ECOG 1		1.82	1.22-2.72	0.003
---ECOG 2-3		3.97	2.41-6.55	<0.0001
Center: Graz		Ref.	Ref.	Ref.
---Salzburg		0.95	0.67-1.35	0.786
---Innsbruck		0.88	0.47-1.68	0.705
Tumor variables				
Location: Proximal esophagus		Ref.	Ref.	Ref.

---Middle esophagus		1.19	0.75-1.89	0.452
---Distal esophagus		1.05	0.69-1.58	0.829
Tumor grade: G3-4		1.27	0.90-1.81	0.173
Primary treatment intent: Palliative		1.08	0.77-1.52	0.667
Primary metastatic disease		0.94	0.64-1.38	0.761
Prior resection of primary tumor		0.84	0.56-1.26	0.398
Prior definitive chemoradiation		1.04	0.68-1.58	0.860
1st line systemic therapy data				
Treatment with platinum		1.11	0.72-1.70	0.642
Treatment with fluoropyrimidine		1.10	0.76-1.60	0.616
Modality: Monotherapy		Ref.	Ref.	Ref.
---Doublet		1.02	0.68-1.54	0.912
---Doublet+EGFRi or Triplet		1.17	0.63-2.17	0.615
Objective response		0.62	0.41-0.93	0.022
Treatment duration (per 1 month increase)		0.89	0.83-0.96	0.003
Laboratory parameters at baseline				
Haemoglobin (per 1 g/dL increase)		0.91	0.81-1.02	0.100
Leukocyte count (per 1 G/L increase)		1.08	1.04-1.13	<0.0001
Neutrophil count (per 1 G/L increase)		1.08	1.04-1.13	<0.0001
Lymphocyte count (per 1 G/L increase)		0.85	0.67-1.08	0.186
Platelet count (per 50 G/L increase)		0.95	0.86-1.05	0.317
C-reactive protein (per doubling)		1.21	1.10-1.33	<0.0001
Albumin (per 1 g/dL increase)		1.00	0.99-1.01	0.757
LDH (per 100 IU/L increase)		1.08	1.01-1.16	0.028
Creatinine (per 1 mg/dL increase)		0.76	0.37-1.54	0.442

Table 9: Univariable predictors of overall survival in the study cohort (n=166).

Variable		**Multivariable Odds Ratio**	**95%CI**	**p**
Age (per 5 years increase)		0.73	0.55-0.96	0.024
Male Gender		1.83	0.50-6.60	0.359
Weight (per 5 kg increase)		1.05	0.88-1.26	0.601
Performance status: ECOG 0		Ref.	Ref.	Ref.
---ECOG 1		0.17	0.05-0.62	0.008
---ECOG 2-3		0.06	0.12-0.32	0.001
Center: Graz		Ref.	Ref.	Ref.
---Salzburg		3.22	0.66-15.80	0.147
---Innsbruck		8.61	1.45-51.31	0.018
Tumor grade: G3-4		2.17	0.84-5.63	0.109
Primary treatment intent: Palliative		0.90	0.33-2.49	0.837

1st-line treatment modality: Monotherapy		Ref.	Ref.	Ref.
---Doublet		0.71	0.19-2.63	0.601
---Doublet+EGFRi or Triplet		3.24	0.45-23.50	0.243
Objective response		0.90	0.29-2.84	0.862
Treatment duration (per 1 month increase)		1.18	0.95-1.46	0.139
Lymphocyte count (per 1 G/L increase)		0.97	0.40-2.35	0.939
C-reactive protein (per 10 mg/dL increase)		0.83	0.65-1.07	0.155
Albumin (per 1 g/dL increase)		1.00	0.96-1.03	0.799
LDH (per 100 IU/L increase)		1.07	0.85-1.34	0.581
Creatinine (per 1 mg/dL increase)		3.09	0.49-19.61	0.229

Table 10: A multivariable logistic regression model to predict the propensity score (i.e. the propensity score model).

Abbreviations: 95%CI – 95% Confidence interval, p – Wald test p-value, ECOG – Eastern Cooperative Oncology Group, Ref. Reference category, EGFRi – Epidermal growth factor receptor inhibitor, LDH – Lactate dehydrogenase.

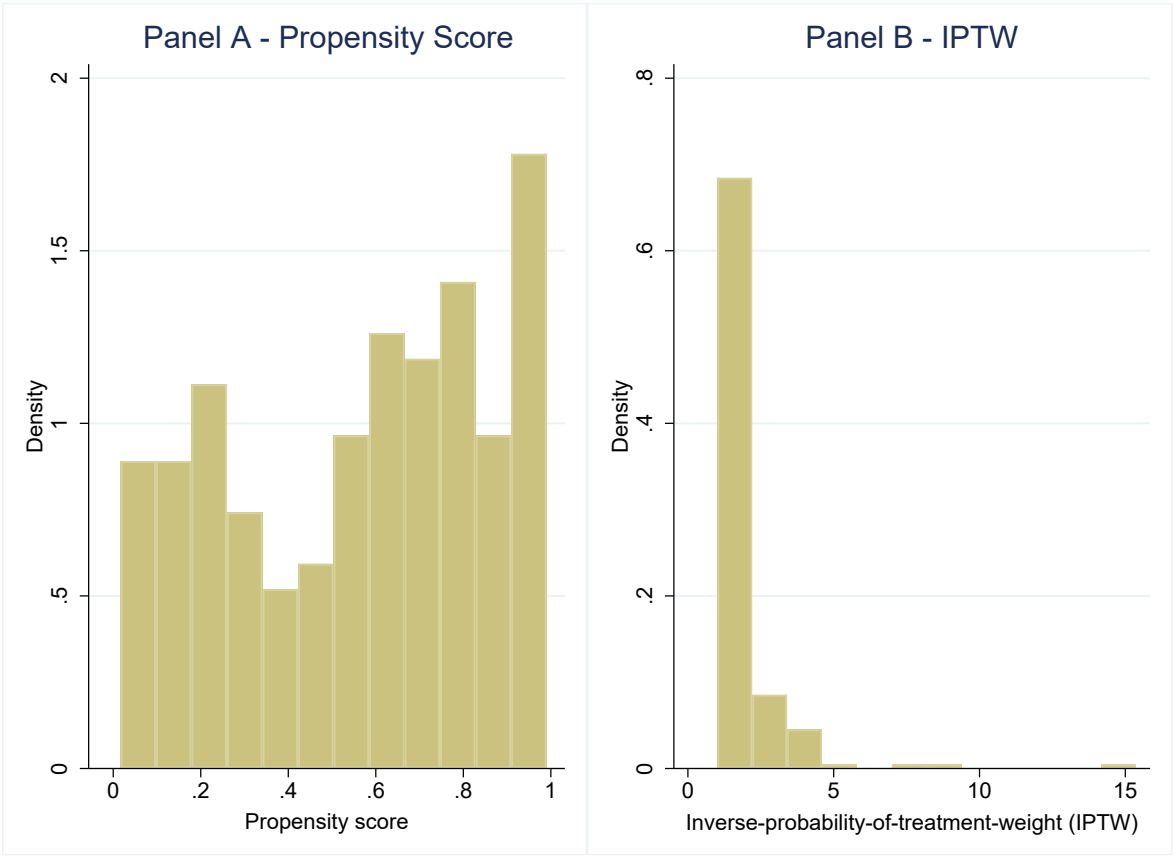

Figure 12: Histograms of the propensity score (Panel A) and the IPTW (Panel B).

Abbreviations: IPTW – Inverse probability of treatment weight.

3.4 Second-line therapy for advanced esophageal SCC – IPTW-adjusted analysis

Upon IPTW weighting and thus controlling for selection bias, the favourable association between 2nd-line therapy and longer overall survival weakened but prevailed. We again observed very strong evidence for a violation of the PH assumption (Schoenfeld-test after Cox model: p<0.0001, "converging curves"), and thus primarily analysed the data with the Royston-Parmar model (**Figure 11B**) but also provide Kaplan-Meier estimators for reference (**Figure 10B**).
In detail, median predicted OS estimates were 3.3 months in the ASC group and 6.1 months in the 2L+ASC group, with corresponding 12-month OS estimates of 18% and 28%, respectively (IPTW-adjusted HR=0.40, 95%CI: 0.24-0.69, p=0.001).

3.5 Sensitivity analyses

This association prevailed upon multivariable adjustment for the two strongest prognostic variables for OS, namely ECOG performance status and CRP levels (IPTW- and multivariably-adjusted HR for 2L+ASC within the Royston-Parmar model=0.45, 95%CI: 0.25-0.83, p=0.011, **Table 11**).
In terms of the violation of the proportional hazards assumption, our findings were consistent with a decreasing "effect" of 2nd-line therapy over time, with hazards of death between the two treatment groups approaching equality at around 10 months of follow-up (**Figure 13**).

In crude analysis of OS of the 92 patients receiving 2L+ASC, we observed a weak, "borderline" statistically significant association between taxane-based 2nd-line therapy and worse OS outcomes (HR for taxane-based (n=52) vs. non-taxane-based (n=40) 2nd-line therapy=1.54, 95%CI: 0.98-2.44, p=0.062, **Figure 14**), which prevailed after adjusting for ECOG performance status (Adjusted HR=1.58, 95%CI: 0.98-2.53, p=0.060).

Variable		Multivariable Hazard Ratio	95%CI	p
2nd-line therapy		0.45	0.25-0.83	0.011
Performance status: ECOG 0		Ref.	Ref.	Ref.
---ECOG 1		1.92	1.02-3.60	0.043
---ECOG 2-3		5.38	2.56-11.30	<0.0001
C-reactive protein (per doubling)		1.18	1.05-1.32	0.005

Table 11: IPTW- and multivariably-adjusted HR Royston-Parmar model for 2nd-line therapy and overall survival.

Abbreviations: 95%CI – 95% Confidence interval, p – Wald test p-value, ECOG – Eastern Cooperative Oncology Group, Ref. Reference category.

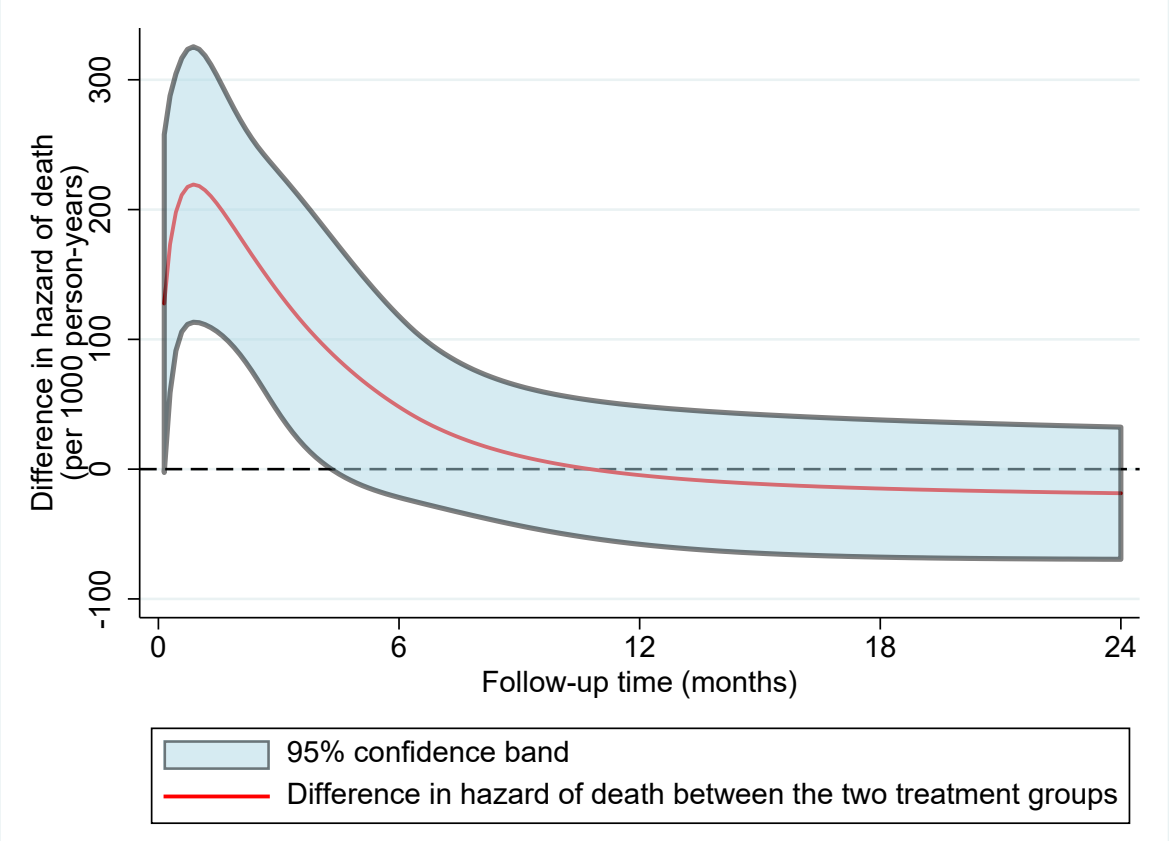

Figure 13: Time-dependent "effect" of 2nd-line therapy.

Data represent the difference (with 95% confidence bands) in the hazards of death (per 1000 person-years) between the 2L+ASC and ASC groups, as predicted from a Royston-Parmar model allowing for non-proportionality of hazards.

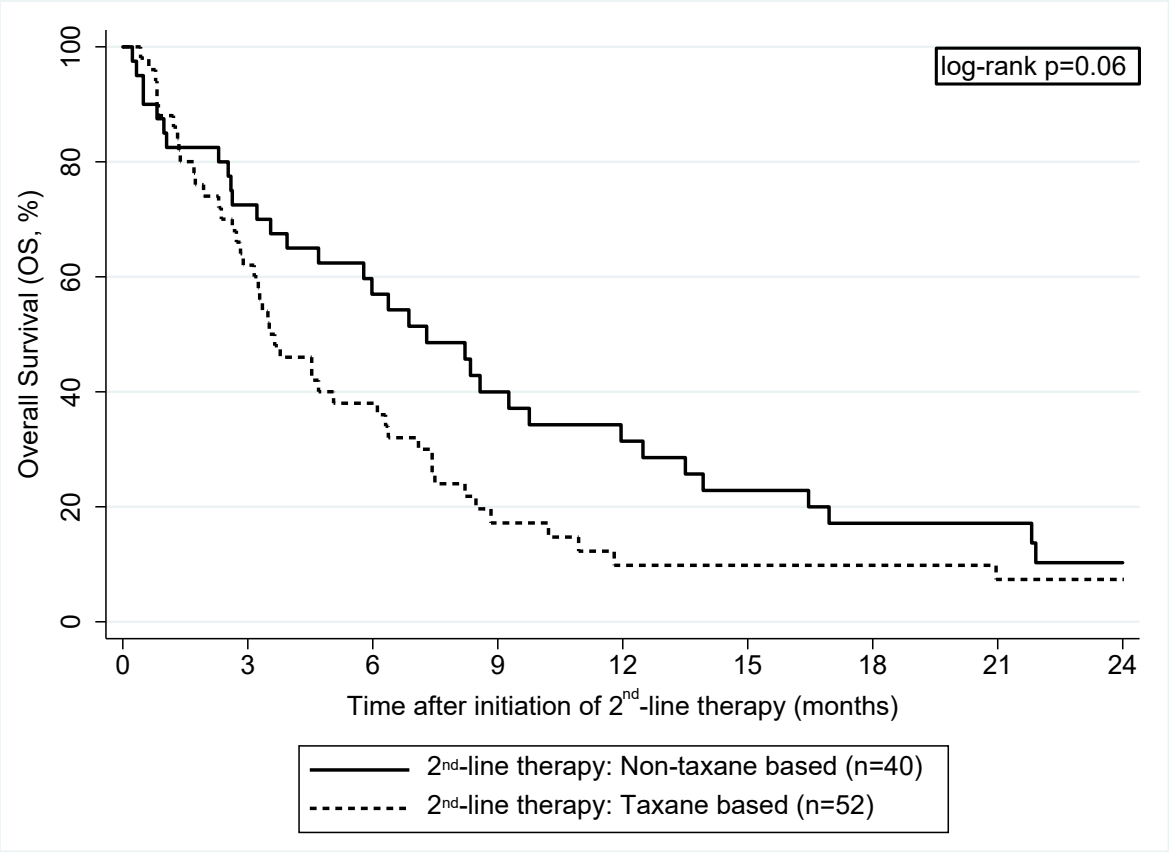

Figure 14: Overall and Progression-free survival of the n=92 patients who started 2nd-line therapy – Distribution by taxane therapy.

Curves were obtained with Kaplan-Meier estimators, and the timescale starts at the date of the first 2nd-line treatment cycle.

3.6 Exploratory subgroup analysis

The benefit of 2nd-line therapy appeared to be consistent across several clinical subgroups, including ECOG performance status (interaction p=0.950), age (p=0.929), gender (p=0.192), comorbidity (p=0.744), TNM cM status at diagnosis of disease (p=0.702), objective response to 1st-line therapy (p=0.260), surgery of the primary tumor (p=0.380), and aggressivity of 1st-line therapy (monotherapy vs doublet, p=0.704, **Figure 15**).

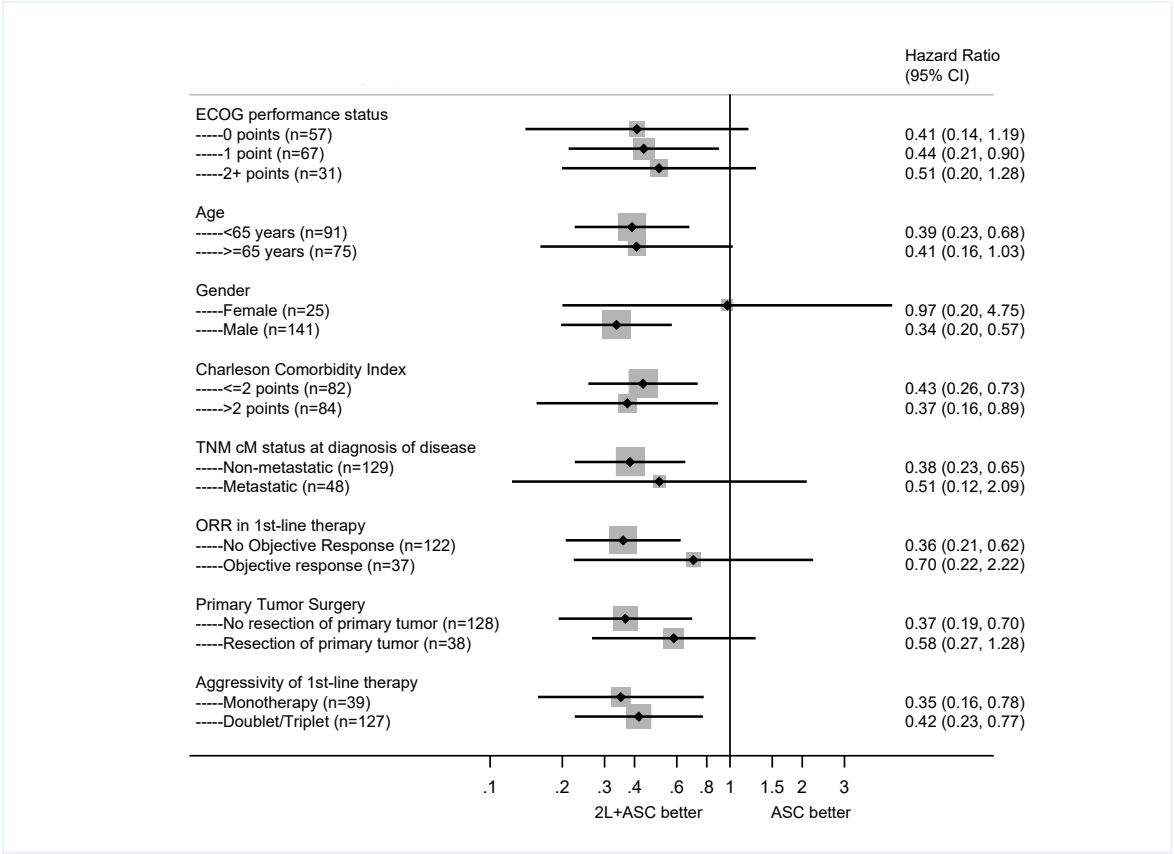

Figure 15: Hypothesis-generating, exploratory subgroup analysis of potential 2nd-line therapy benefit.

Black diamonds represent the hazard ratio for 2L+ASC within the respective subgroup, and black lines the associated 95% confidence intervals. The size of the grey boxes is proportional to the subgroups' weight (i.e. proportional to the subgroup sample size). Abbreviations: 95%CI – 95% Confidence interval, ECOG – Eastern Cooperative Oncology Group, TNM – Tumor Node Metastasis Classification, cM – Clinical metastasis status at diagnosis of disease, ORR – Investigator-assessed objective response rate, ASC – Active symptom control, 2L – 2nd-line therapy.

3.7 Evaluation of treatment associated adverse events

Table 12 shows the most frequent adverse events associated with 2LTX treatment. Most common toxic effects of treatment were anemia (61%), neutropenia (36%) and fatique (23%). However serve side effects were rare. In 16% hospitalization du to toxicity and in 54% a treatment cessation due to toxicity was reported. Fatal adverse events occurred in only 1%.

Toxicity of 2nd-line chemotherapy (n=92)	**n (% miss.)**	**Any grade**	**Grade 3 or 4**
Febrile neutropenia	91 (1%)	/	4 (4%)
Neutropenia	87 (5%)	31 (36%)	12 (14%)
Anemia	88 (4%)	54 (61%)	13 (15%)
Thrombocypenia	87 (5%)	19 (22%)	3 (3%)
PNP	90 (2%)	14 (16%)	1 (1%)
Diarrhoea	89 (3%)	10 (11%)	2 (2%)
Nausea	89 (3%)	11 (12%)	/
Allergic reaction	89 (3%)	3 (3%)	/
Fatigue	88 (4%)	20 (23%)	/
Treatment cessation due to Toxicity	92 (0%)	5 (54%)	/
Hospitalization due to Tox	90 (2%)	14 (16%)	/
Fatal adverse event	92 (0%)	1 (1%)	/

Table 12: Toxicity profile of 2nd-line therapy.

4 Discussion

Although incidence of ESCC is declining in western countries this cancer is still a global health burden. Unfortunately real world data is rare and often covers only Asian cohorts. In our study we provide data from three Austrian centers to face the lack of information in western countries.
Especially in palliative care, new treatment options are desperately needed. The median overall survival in our study is only 7.2 months from start of first line chemotherapy.

In the palliative first-line 42 of 187 patients in our study had a treatment-response (ORR= 0,25). However the treatment duration time was only 2.2 months and most of the patients showed progressive disease at time of the first response assessment.
After disease-progression in the first-line a treatment-decision between a palliative second-line chemotherapy plus active symptom control or active symptom control alone has to be made.
Studies evaluating palliative second-line are even more rare. Only several small phase II trials provide data for the usage of different agents and have implemented either paclitaxel, docetaxel or irinotecan mono or in combination, as well as vinorelbine in clinical routine.
A single arm phase II trial eveluated the response rate of vinorelbine. 46 Patients with metastatic ESCC were included. 16 patients previously underwent cisplatin-based first-line treatment. 6 percent of pretreated patients had a complete remission (CR) remission. The ORR was 15 percent. (9)
Other phase II trials using paclitaxel, docetaxel or irinotecan report response rates up to 45 percent for weekly paclitaxel. (8, 147, 149, 164)
It is important to mention, that these studies were designed as single arm interventional studies and therefore are not able to show evidence about second-line chemotherapy being superior to best supportive care. Further chemotherapy is accompanied by high toxicity rates and adverse events. Still, these findings have prompted physicians worldwide to consider systemic second line chemotherapy as an effective treatment strategy.

In our study around fifty percent of included patients who underwent first-line therapy and showed a progressive disease under this treatment were suitable for systemic second line therapy. This is in line with several previous reports.(8) The unadjusted primary outcome analysis pointed out a significantly improved overall survival for patients treated with

systemic second-line chemotherapy plus active symptom control compared with active symptom control only. Patients who underwent systemic therapy showed an overall survival of 7.2 months versus an overall survival of 2.9 months in ASC group (p<0,0001)
However these data have to be interpreted with caution. In prospective interventional studies randomization is the key for preventing biases. Due to the fact of retrospectively collected data a random treatment assignment was not possible. Patients with favorable prognostic factors are more likely to tolerate systemic therapy. As a matter of fact these patients are more often assigned to the intervention group. In our study, patients who underwent systemic second line had a significantly better ECOG performance status (p<0,0001), were younger (p=0,053), the duration of systemic first-line treatment was longer (p=0,005), as well as lower c reactive protein (p=0,002) and higher albumin levels (p=0,004). Since these are all known as good prognostic factors, the risk of overestimation of treatment effects and thus implementing a selection bias is high. (165-169)

To face this risk of bias we performed a propensity score analysis using inverse probability of treatment weighting (IPTW). The goal is to adjust for baseline imbalanced and favorable prognostic factors. This is achieved by mimicking randomization process.(161) In retrospective observational studies propensity score models are an effective and elegant way to reduce the effect of baseline confounding and therefore avoiding selection bias.(170, 171) This statistical method harbors great potential making basically non-comparable cohorts more comparable. Recently, a research published by our study group could demonstrate a benefit in overall survival for systemic second-line palliative chemotherapy over best supportive care in patients with biliary tract cancer by using a propensity score model. In fact these findings were recently confirmed by a prospective randomized phase III ABC-06 trial, underlining the potentials of these scores. (160, 172)
A Japanese retrospective study from Nomura et al. evaluated the benefit of chemotherapy of salvage chemotherapy in patients who were refractory to, or could not tolerate, chemotherapy with platinum, fluoruracil or taxanes. 283 Patients were included. 147 received best supportive care and 136 chemotherapy. Overall survival in BSC and Chemotherapy was 4.2 and 7.8 months, showing the superiority of chemotherapy. (173) This aligns well with our findings.

The survival benefit weakened after adjustment for potential baseline cofounders. In the unadjusted analysis OS in the ASC group was 2.9 months compared to 7.2 months in the

group receiving second-line and ASC. After using IPTW in a propensity score model the favourable association between 2LTX and OS prevailed but weakened. In ASC group median OS was 3.3 months versus 6.1 months in chemotherapy group. However these findings were still statistically significant.

In our analysis survival curves cross after one year of treatment. This indicates a weakening of survival benefit under second-line therapy over time. In fact, this underlines the possible interpretation of later lines of palliative treatment not improving long term survival but only delaying death. (160)
In facing a treatment decision especially the low treatment response rate of 13% and a median OS of 4.7 months after start of second-line, leading only to a modest survival benefit, should be discussed with the patient in detail.
In other retrospective studies slightly better OS were reported. In a study of Shirakawa et al. investigating the effects of docetaxel or paclitaxel in 163 patient with metastatic or recurrent esophageal squamous cell carcinoma who had a progressive disease under first-line systemic palliative chemotherapy with fluoropyrimidine and platinum, OS under therapy with paclitaxel was 6.1 months and 5.3 months with docetaxel.
Another retrospective study evaluated OS in 85 patients, who received a docetaxel-based second-line chemotherapy after treatment failure with platinum-based first-line. Median OS was 5.5 months.(174)
Abraham et al. reported data from 86 patients with advanced or metastatic ESCC either treated with taxane-based or non-taxane-based chemotherapy. OS in the taxane-based treatment group was 7.3 months and 5.1 months under non-taxane based therapy. (86) These different findings in OS benefit might be due to differences in baseline characteristics and inclusion criteria.

Interestingly in our study patients treated with non-taxane based chemotherapy experienced a longer OS than those with taxane-based regimes. This stands in contrast to the findings of Abraham et al. Mentionable is the fact, that in our study taxanes were mostly administered as monotherapy, whereas Abraham et al. looked at taxane-based combinations with carboplatin. (86)

For clinical practice it is important to identify markers with good predictive value. Based on these factors evaluation of treatment benefit of a second-line palliative chemotherapy could

be made individually. To face this issue we performed an exploratory propensity score adjusted subgroup analysis. Across several relevant clinical subgroups the favorable association between longer OS and second-line therapy was consistent. Even older patients aged 65 years or older and these patients with poorer ECOG performance status (≥1) seemed to benefit from the systemic therapy.

Limitations:

The following limitations of this study have to be considered:

The propensity score analysis tries to adjust differences in the baseline characteristics. These differences leading to a not random assignment.

1. Despite rigorous adjustment for differences of patients` baseline characteristics between the two study groups by the IPTW, a residual risk of confounding especially of unmeasured covariates cannot be fully excluded. (159)
2. No valid data looking at quality of life were available (due to the retrospective study design).
3. Imaging data for radiograph response assessment were not classified by central radiology review.
4. Information on dose density of the respective 2nd line treatment regimens were missing.
5. A potential risk of underreporting adverse events is possible because of the retrospective assessment from chart review.

Despite these limitations, this study provides valuable data to aid in treatment decision making in the management of patients with aESCC, which was refractory in first-line treatment.

5 Conclusion

This retrospective study provides efficacy data of patients with aESCC in a western cohort. Our findings support the view of palliative second-line chemotherapy prolonging life and being superior to active symptom control in terms of survival. For fit patients systemic second-line therapy with established agents (paclitaxel, docetaxel, irinotecan, vinorelbine) is standard of care. However decision whether chemotherapy is useful or not should be taken individually. These findings are promising. However, further research is needed to evaluate and confirm the results of this study.

6 Literature

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