King's Research Portal

DOI:

[10.1016/S0140-6736\(17\)31462-9](https://doi.org/10.1016/S0140-6736(17)31462-9)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Lagergren, J., Smyth, E., Cunningham, D., & Lagergren, P. (2017). Oesophageal cancer. *Lancet*.
[https://doi.org/10.1016/S0140-6736\(17\)31462-9](https://doi.org/10.1016/S0140-6736(17)31462-9)

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Oesophageal cancer: Seminar

Authors: Jesper Lagergren (MD, PhD),^{1,2} Elizabeth Smyth (MB, BCh, MSc),³ David Cunningham (FRCP, FmedSc),³ and Pernilla Lagergren (RN, PhD).⁴

Affiliations: ¹ Division of Cancer Studies, King's College London and Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom.

² Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, 17176 Stockholm, Sweden.

³ The Royal Marsden NHS Foundation Trust, London and Surrey, United Kingdom.

⁴ Surgical Care Science, Department of Molecular medicine and Surgery, Karolinska University Hospital, 17176 Karolinska Institutet, Stockholm, Sweden.

Corresponding author: Professor Jesper Lagergren. Address: Department of Molecular medicine and Surgery, Karolinska Institutet. NS 67, 2nd Floor, 171 76 Stockholm, Sweden. Telephone: +46 (0)8-5177 6012. Fax: +46 (0)8-517 76280. E-mail: jesper.lagergren@ki.se.

Funding: The Swedish Research Council (839-2008-7496), Swedish Cancer Society (CAN 2015/460), Royal Marsden/Institute for Cancer Research (RM/ICR) National Institute for Health Research (NIHR) Biomedical Research Centre (BRC), and the Karolinska Institutet Distinguished Professor Award to Jesper Lagergren (D-02418/2010).

Summary

Oesophageal cancer is a clinically challenging disease requiring a multidisciplinary approach. The extensive treatment may be associated with serious limitations in health-related quality of life and yet still a poor prognosis. Recent decades have witnessed a gradual improvement in prognosis in many countries. Endoscopic procedures have increasingly been used in the treatment of premalignant and early oesophageal tumours. Neoadjuvant therapy with chemotherapy or chemoradiotherapy has supplemented surgery as standard treatment of locally advanced oesophageal cancer. Surgery has become more standardised and centralised. There are several therapeutic alternatives for palliative treatment. This review aims to provide insights into the current clinical management, on-going controversies and future needs in oesophageal cancer.

Introduction

Oesophageal cancer is the 9th most common cancer and the 6th most common cause of cancer death globally.¹ This cancer is associated with extensive treatment requirements, serious limitations in health-related quality of life (HRQOL) and poor prognosis. Curative treatment typically includes chemotherapy or chemoradiotherapy followed by extensive surgery, often resulting in morbidity and persistent reductions in HRQOL.² However, recent developments have helped improve prognosis and survivorship.

Clinical presentation, signs and symptoms

Most patients seek healthcare following a period of progressive dysphagia and involuntary weight loss. Older men are overrepresented in both main histological types, i.e. oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC). The average male-to-female ratio is 3-to-1 for OSCC and 6-to-1 for OAC, although this ratio varies greatly across geographical regions.^{3, 4} Many patients with OSCC have a history of heavy tobacco and alcohol use, while patients with OAC may be obese and have chronic gastro-oesophageal reflux disease.

Incidence and prognosis

Globally, OSCC is the most common histology, particularly in high-incidence areas in Eastern Asia and in Eastern and Southern Africa.^{1, 5, 6} In the highest-risk region (“oesophageal cancer belt”) from Northern Iran through the Central Asia to North-Central China, approximately 90% of cases are OSCCs.^{1, 5, 6} While the incidence of OSCC has decreased in many regions,

Europe, North America and Australia have witnessed a marked increase in the incidence of OAC during the last four decades, which appears to be sustained.⁷ Thus, the incidence of OAC has surpassed that of OSCC in many Western countries.

The prognosis varies between geographical areas, but population-based studies have shown an improvement in the overall 5-year survival from <5% in the 1960s to currently about 20% in some European countries, the United States and China.⁸⁻¹⁰ Prognostic factors include tumour stage, tumour sub-site and histology, patients' performance status and co-morbidities, and HRQOL.^{8, 11}

Pathophysiology, risk factors and prevention

Squamous cell carcinoma

The pathophysiological pathway of OSCC is typically initiated by carcinogenic compounds in direct contact with the oesophageal mucosa. Mechanical injury, e.g. from achalasia, radiation therapy or from swallowing hot beverages or lye, increases vulnerability to carcinogenic compounds. The main risk factors for OSCC are tobacco smoking (including swallowed toxins from cigarette smoke) and alcohol overconsumption, particularly when in combination.¹² Among dietary factors, fruit and vegetable intake is protective,¹³ while intake of red meat¹⁴ and very hot beverages are risk factors.¹⁵ Genetic factors are also involved; a pooled analysis of three genome-wide association studies found new susceptibility loci for OSCC.¹⁶ Tobacco smoking cessation is probably the single most effective primary preventive measure.¹⁷

Adenocarcinoma

The main pathophysiological pathway of OAC is likely to be chronic gastro-oesophageal reflux disease (reflux), causing metaplasia from the native squamous cell mucosa to a specialised columnar epithelium, entitled Barrett's oesophagus.¹⁸ Barrett's can progress to low-grade dysplasia, high-grade dysplasia, and invasive OAC.¹⁸ The main risk factors for OAC are reflux, obesity, and male sex, while *Helicobacter pylori*-infection and dietary intake of fruit and vegetables, and possibly also non-steroidal anti-inflammatory drugs, are protective.¹⁹ The increasing prevalence of reflux and obesity, combined with a decreasing prevalence of *Helicobacter pylori*-infection, probably contribute to the increasing incidence of OAC.¹⁹ Research has now identified risk loci for Barrett's oesophagus associated carcinogenesis.²⁰⁻²³ These findings could be used for research examining tailored prevention in individuals at high risk of OAC. There is presently limited scientific evidence supporting specific preventive measures in OAC,²⁴ but aspirin and antireflux therapy are being tested in a RCT of patients with Barrett's oesophagus (AspECT).

Genetics

Recent developments in high throughput genomic technologies have led to an improved understanding of molecular underpinnings of OSCC and OAC. The global cancer genome atlas project (TCGA) characterised 164 oesophageal cancers using multiple platforms, and OSCC and OAC demonstrated distinct profiles in copy number alterations, methylation patterns, and RNA and microRNA expression (Table 1).²⁵ In particular, OSCC was associated with a pattern of C>A substitutions, overrepresented in tobacco smokers, and further comprehensive molecular characterisation suggested that OSCC is more similar to squamous cell carcinoma of the head-and-neck than to OAC. Similarly, OAC demonstrated copy number, RNA and methylation patterns closer to gastric adenocarcinoma than OSCC. The

results of this study support treating OSCC and OAC as different disease entities, as the genomic, transcriptomic and epigenetic changes identified in each cancer reflect underlying divergent aetiologies and tissues of origin.²⁵

Considering the oncogenic drivers, the most commonly mutated genes in OSCC are TP53, NFE2L2, MLL2, ZNF750, NOTCH1 and TGFBR2, whereas for OAC these are TP53, CDKN2A, ARID1A, SMAD4 and ERBB2. Copy number changes also differ; for OSCC the most commonly identified copy number alterations amplifications in SOX2, TERT, FGFR1 and MDM1, with common deletions of RB1, whereas in OAC amplification of ERBB2, VEGFA, GATA6, CCNE1 and deletion of SMAD4 are more common. Combined pathway analysis suggests that OSCC and OAC have frequent alterations of cell cycle regulators such as CCND1, CCNE1, CDK6 or RB1 via distinct mechanisms. This suggests that cell cycle related tyrosine kinase inhibitors could be a therapeutic strategy. However, in contrast to gastric adenocarcinoma, no microsatellite unstable or Epstein-Barr driven cancers were found in the oesophageal TCGA cohort.²⁵

OAC has also been characterised into three distinct subgroups using whole genome sequencing based on 129 samples.²⁶ These subtypes were characterised by defects in homologous recombination repair, a T>G mutation pattern with a high mutational load or a C>A/T mutation pattern associated with an aging imprint. It is possible that each of these subtypes have differential sensitivity to targeted therapy, e.g. [poly ADP ribose polymerase](#) (PARP) inhibitors for homologous recombination repair subtype and immunotherapy for high mutational burden. However these findings require clinical validation.²⁶

Diagnostic investigations

Diagnosis

The presence of oesophageal cancer is determined by endoscopy (Figure 1) with biopsies for histopathological confirmation. Endoscopy also provides information of the tumour sub-location and local extent, and the presence and extent of Barrett's. After the diagnosis is established, computerised tomography of the neck, chest and abdomen assessing distant metastasis will guide whether treatment will follow a curative or palliative route.

Operability

Treatment recommendations rely on tumour stage and patient fitness. Tumour stage is currently based on the 7th edition of the TNM-classification, which introduced a more detailed assessment of number of metastatic lymph nodes. In the up-coming 8th edition, clinical, pathological and post neoadjuvant pathological staging will be separated, and the pT1-category will be separated into pT1a and pT1b.²⁷ Tumours with their epicentre >2cm below the oesophago-gastric junction (Siewert type III) are classified as gastric cancers, even if they involve the oesophagus. The Siewert classification is widely used to categorise tumours near the oesophago-gastric junction. Tumours with their epicentre 1–5 cm above this junction are categorised as type I, tumours within 1 cm above and 2 cm below this junction as type II, and tumours 2–5 cm below the junction are type III cancers.²⁸ In early lesions, endoscopic mucosal resection provides a good specimen for histopathological assessment. Staging measures for more advanced tumours include positron-emission tomography-computerised tomography (PET-CT) and endoscopic ultrasound,^{29, 30} Laparoscopy and bronchoscopy are indicated if there is suspicion of abdominal tumour spread and tumour overgrowth on bronchi, respectively.^{29, 31} Laparoscopy can also uncover

tumoural extension on the gastric part for junctional adenocarcinomas, identify co-morbidities (e.g. cirrhosis) and be used for placement of feeding tube if required.

There is limited evidence of the evaluation of physical fitness when considering treatment recommendations. However, biological age, co-morbidity, cardiopulmonary capacity, and nutritional status should be considered prior to consideration of extensive surgery, and patients should be assessed by an experienced anaesthetist.³² Consultation of cardiologists and dietitians, and a treadmill test and spirometry can add valuable information.^{33, 34} For older patients, oncogeriatric assessment may be helpful prior to initiating therapy.

Interestingly, HRQOL measures can predict fitness and prognosis.^{11, 35, 36} An on-going RCT is assessing the role of prehabilitation (including physical, nutritional psychological care) of patients before curative treatment.³⁷

Treatment recommendations

Multidisciplinary assessment and determination of a treatment plan has been shown to improve clinical decision-making in oesophageal cancer and should be mandatory.³⁸⁻⁴⁰

Ideally the multidisciplinary team includes expertise in pathology, radiology, endoscopy, medical oncology, radiotherapy, surgery, nursing, dietetics and other relevant specialists as needed, e.g. laryngologists, physiotherapists and social workers.⁴¹ Treatment plans depend on clinical tumour stage, sub-site and histology of the tumour, performance status, and co-morbidity. Finally, the team meeting provides an opportunity to follow-up treatment results and for recruiting patients to research studies.

Curative treatment

Endoscopic treatment

Endoscopic techniques, mainly radiofrequency ablation, endoscopic mucosal resection and endoscopic submucosal dissection, are increasingly used for the prevention and curative treatment of early oesophageal lesions.^{42, 43} Most research has examined Barrett's oesophagus and early OAC, but some studies also support ablation therapies in early OSCCs.^{44, 45} Endoscopic mucosal resection combined with radiofrequency ablation can successfully prevent cancer progression in patients with high-grade dysplasia, and are increasingly also used in patients with low-grade dysplasia, even if multifocal.⁴⁶⁻⁴⁹ Endoscopic removal for the small proportion of patients with early (T1) oesophageal cancer has increased during the last few years.⁴² Superficial oesophageal cancer can be successfully removed by means of endoscopic submucosal dissection in 90% (95% confidence interval [CI] 87-93%) of cases; the main complication is a 5% (95% CI 3-8%) risk of stenosis, which can be managed with endoscopic dilatation.⁵⁰ Compared to endoscopic mucosal resection, endoscopic submucosal dissection offers a higher rate of complete resection of early cancer (92.7% versus 52.7%) and a lower rate of local tumour recurrence (0.3% versus 11.5%).⁵¹ These organ-sparing procedures offer great HRQOL benefits compared to oesophagectomy, and clinical guidelines recommend endoscopic mucosal resection or endoscopic submucosal dissection rather than surgery for T1a OAC in specialised centres.³⁸ However, there remains a 5% and 17% risk of lymph node metastasis in intra-mucosal (T1a) cancer and submucosal cancer (T1b), respectively.⁴² Moreover, endoscopic therapy is associated with an increased risk of local tumour recurrence compared to surgery.⁵² Thus, patients with superficial submucosal infiltration (T1b) oesophagectomy optimises the prognosis, while in patients

unfit for surgery, endoscopic resection is a good alternative. The learning curve associated with these therapies indicates the need for centralisation.⁵³

Oncological treatment

In patients with locally advanced (T3-T4 or cN1-N3) oesophageal cancer, chemotherapy or chemoradiotherapy plus surgery is required in addition to surgery; the differential sensitivity of OSCC and OAC to radiotherapy leads some centres to vary in treatment approaches across these histological subtypes (Figure 2) (Table 2). Meta-analysis of 24 randomised trials suggests that both neoadjuvant chemotherapy and chemoradiotherapy improve overall survival for patients with operable oesophageal cancer (hazard ratio [HR] for chemotherapy 0.87, 95% CI 0.79-0.96; HR for chemoradiotherapy 0.78, 95% CI 0.70-0.88).⁵⁴ Neoadjuvant oncological treatment for very early tumours not suitable for local ablation is less well defined. One randomised clinical trial (RCT) demonstrated no difference for stage I and II tumours treated with neoadjuvant cisplatin and 5-fluorouracil chemoradiotherapy (45Gy in 25 fractions) compared to surgery alone.⁵⁵ Therefore it is recommended that patients with $\leq$ T2N0 tumours proceed directly to surgery, although reliably identifying these patients with pre-operative investigations can be challenging. For all patients undergoing neoadjuvant treatment, restaging is recommended before oesophagectomy.³⁸ Nutritional assessment is recommended as malnutrition is common, and if enteral feeding is required, jejunostomy placement is preferable to stenting for resectable cancer.^{38, 56}

Squamous cell carcinoma

In an RCT (OE02), 247 (of 802) patients with OSCC were randomised to surgery alone or neoadjuvant chemotherapy with 2 cycles of chemotherapy with cisplatin (80mg/m² x 96

hours) and fluorouracil ($1000 \text{ mg/m}^2 \times 96 \text{ hours}$) followed by surgery.⁵⁷ Long-term follow-up demonstrated an overall survival benefit for OSCC patients treated with chemotherapy (HR 0.86, 95% CI 0.71-1.05).⁵⁸ A more contemporary RCT (CROSS) evaluated a regimen of weekly chemotherapy (carboplatin with an area under the curve of 2 mg/ml/min and paclitaxel 50 mg/m^2) for 5 weeks in conjunction with concurrent radiotherapy (41.4 Gy in 23 fractions five days/week).⁵⁹ Among 84 patients with OSCC (of 368), those treated with surgery alone had a median survival of 21.1 months compared to 81.6 months in the chemoradiotherapy group (HR=0.48, 95% CI 0.28-0.83).⁶⁰ These results have led to the adoption of the CROSS regimen as a standard of care for many OSCC patients undergoing oesophagectomy. However, OSCC may not always require surgery as several RCTs have demonstrated similar survival when comparing definitive chemoradiotherapy with neoadjuvant chemoradiotherapy and surgery, especially in patients with a response to chemoradiotherapy.^{61, 62} However, there are no trial results which directly compare the watch and wait versus immediate surgery approaches, but research in this area is on-going. Because local recurrence rates are higher with a non-surgical approach, close surveillance and salvage surgery, when indicated, are recommended as this may provide survival comparable to planned chemoradiation and oesophagectomy.⁶³

Adenocarcinoma

Neoadjuvant chemotherapy: OACs are less radiosensitive than OSCCs and all operable OAC patients with potentially curable cancer should be considered for neoadjuvant chemotherapy or chemoradiotherapy followed by surgery. Standard chemotherapy is cisplatin-fluoropyrimidine-based, which improved the survival in three RCTs (OE02, MAGIC and FNCLCC/FFCD).^{57, 58, 64, 65} In OE02, 802 oesophageal cancer patients (n=533 OAC) were

randomised to 2 cycles of chemotherapy with cisplatin and fluorouracil plus surgery or surgery alone, showing a 5% increase in 5-year survival for OAC patients treated with chemotherapy.⁵⁸ Another RCT (OE05) compared 2 cycles of neoadjuvant cisplatin and fluorouracil with 4 cycles of epirubicin, cisplatin and capecitabine (ECX) for resectable OAC, and although more intensive chemotherapy was associated with an improved pathological tumour response, the survival was similar.⁶⁶ Therefore, whenever neoadjuvant chemotherapy alone is preferred, doublet chemotherapy is recommended.

Perioperative chemotherapy: Perioperative chemotherapy is an alternative approach for OAC. Two RCTs (FNCLCC/FFCD, including 75% [n=58/503] OAC; and MAGIC, including 26% [n=164/224] OAC) randomised patients to perioperative cisplatin plus fluorouracil or epirubicin plus cisplatin and fluorouracil (ECF) regimens, respectively, and both trials reported a 13-14% improved 5-year survival.^{64, 65} Post-operative chemotherapy was a component in these trials, and patients with adequate performance status following surgery should therefore also be treated in the adjuvant setting. Perioperative chemotherapy may give the opportunity to treat patients who have derived the most benefit from chemotherapy in the neoadjuvant setting with further treatment following surgery. Metabolic imaging using a reduction in 18-F-fluoro-deoxy-glucose uptake in the primary tumour with PET following one cycle of chemotherapy is predictive of overall survival in patients with resectable oesophageal or junctional adenocarcinoma.⁶⁷⁻⁶⁹ Although promising, evaluation of chemotherapy response using metabolic imaging such as PET requires validation in larger studies and is not recommended as standard practice.

Neoadjuvant chemoradiotherapy: Neoadjuvant chemoradiotherapy may also be considered for OAC patients.^{60, 70} The CROSS trial randomised 275 OAC (of 368) patients to

chemoradiotherapy followed by surgery or to surgery alone.⁶⁰ Survival was improved in the chemoradiotherapy group (HR=0.73, 95% CI 0.55–0.98), although the magnitude of this benefit was less than that achieved for OSCC and following adjustment the difference in survival for OACC was not statistically significant.⁶⁰ However, despite this, no significant interactions between treatment effect and histological subgroup were identified.⁶⁰

Neoadjuvant chemoradiotherapy should be restricted to patients with characteristics similar to those in CROSS, i.e. $\leq T3$ tumours which are $<5\text{cm}$ in width and $<8\text{cm}$ in length. Alternative chemoradiotherapy regimens include cisplatin and oxaliplatin plus fluoropyrimidines.⁷¹

There are no data directly comparing neoadjuvant chemoradiotherapy and neoadjuvant or perioperative chemotherapy, but consensus opinion is that both are valuable options, however significant ($\geq$ grade 3) toxicities such as neutropenia and nausea are less common with CROSS type chemoradiotherapy.^{59, 64, 72} Induction chemotherapy followed by chemoradiotherapy has not improved survival in several small trials and therefore remains an investigational approach.^{73, 74} Randomised trials comparing neoadjuvant chemotherapy to chemoradiotherapy are currently ongoing (NCT01726452, NCT02509286).

Definitive chemoradiotherapy

Chemoradiotherapy is superior to radiotherapy for patients with OSCC or OAC who are not surgical candidates, including patients with cervical oesophageal tumours. The most frequently used definitive chemoradiotherapy regimen is cisplatin ($75\text{mg}/\text{m}^2$), 5-fluororacil ($1000\text{mg}/\text{m}^2$ infusion daily for 4 days), plus radiotherapy (50Gy). In an RCT, this chemoradiotherapy regimen offered a median survival of 12.5 months compared to 8.9

months for 64Gy radiotherapy alone.⁷⁵ Oxaliplatin-based definitive chemoradiotherapy is associated with comparable survival to cisplatin-based treatment, but with a different toxicity spectrum.⁷¹ Therefore, oxaliplatin or cisplatin are both evidence-based treatment choices in combination with radiotherapy in this setting. Notably, the radiation dose in CROSS (41.4Gy) is less than the standard radiation dose which is used in definitive chemoradiotherapy regimens. Intensification of radiotherapy to higher than standard doses did not improve local control or survival in one RCT (INT0123), and there are no RCTs supporting the use of brachytherapy in this setting.⁷⁶ However, intensification of radiotherapy dosing remains an area of active research as does development of a “watch and wait” strategy following chemoradiotherapy for both OAC and OSCC (NCT02741856, ISRCTN01483375, NCT01348217, NTR4834, NCT02551458).

Surgical treatment

Surgery remains a single modality treatment for early tumour stages, and for cT2N0 and T1a/T1b cancers after non-radical or failed endoscopic mucosal resection or endoscopic submucosal dissection,⁵⁵ but is combined with neoadjuvant therapy for locally advanced oesophageal cancer.⁷⁷ Oesophagectomy typically includes the removal of most of the oesophagus together with the cardia and lesser curve of the stomach (Figure 3). Some issues related to oesophagectomy deserve special attention.

Surgical approach

Tumour-free resection margins are prognostically important.^{78, 79} This can be accomplished through alternative approaches, including right-sided or left-sided thoraco-abdominal or transhiatal approaches using open or minimally invasive techniques.^{31, 80} Earlier studies

examining minimally invasive surgery showed a high risk of complications, possibly related to learning curve issues, while recent data show accelerated recovery, which has prompted its increased use.^{81, 82} On-going RCTs are comparing postoperative outcomes following minimally invasive procedures and open surgery, where HRQOL is a key outcome (ISRCTN59036820, [NCT01544790](#), NTRTC2452). Transhiatal and minimally invasive surgery seem to be associated with fewer pulmonary complications compared to thoraco-abdominal approaches.^{83, 84} There are no major differences in survival between any of the established approaches.^{31, 80, 82, 85, 86} Standardisation of the surgical approach might be a more important prognostic factor than selecting one specific procedure over another.⁸⁷ Alternatively, providing the surgeon has sufficient experience of various surgical approaches, the approach can be tailored depending on tumour and patient characteristics. However, the learning curve for surgeons associated with the adoption of new approaches should be taken into account.⁸⁸

Volume

Annual hospital and surgeon volume of oesophagectomy influence short- and long-term mortality.⁸⁹ High-volume hospitals had lower overall mortality compared to low-volume hospitals (HR=0.82, 95% CI 0.75-0.90). A cohort study found that surgeon volume was a stronger prognostic factor than hospital volume after mutual adjustment.⁹⁰ Even experienced surgeons who start to perform oesophagectomies have a learning curve before the survival outcome for their patients is stabilised.⁸⁸ Taken together, available scientific evidence supports centralisation of oesophagectomy.

Lymphadenectomy

Research findings advocating extensive lymphadenectomy⁹¹ have been challenged in recent large cohort studies showing no association between the number of resected nodes and survival after adjusting for surgeon volume.^{92, 93} Recent data indicate that knowledge of location of lymph node metastasis allows for a tailored lymphadenectomy with good sampling for tumour staging and possibly better outcomes.^{94, 95} Moreover, extensive lymphadenectomy does not seem to have any adverse effect on patients' postoperative HRQOL.⁹⁶ Taken together, current evidence indicates that a moderate and tailored lymphadenectomy providing a sufficient assessment of the pathological tumour stage is adequate.

Survivorship

Patients who have undergone oesophagectomy face some specific survivorship issues, including poor HRQOL, eating difficulties and malnutrition, in addition to a limited chance of long-term survival. A recent meta-analysis showed long-lasting deterioration in several HRQOL aspects, including social functioning, role functioning and increased symptoms of fatigue, pain, cough, dry mouth and reflux.⁹⁷ Additionally, patients often experience major social and emotional changes, and they might have an increased risk of developing psychiatric disorders, which in turn decreases survival.⁹⁸

Some patient and tumour characteristics reduce postoperative HRQOL, including co-morbidity, advanced tumour stage (III-IV), proximal tumour location and OSCC histology.⁹⁹ Neoadjuvant therapy has a negative influence on HRQOL aspects during treatment, except for dysphagia which is usually relieved.^{100, 101} However, most patients recover in their HRQOL before surgery,¹⁰² and there is no difference in postoperative recovery between patients

receiving neoadjuvant therapy and those undergoing surgery alone.¹⁰³ A recent multi-centre study found a detrimental impact of definitive chemoradiotherapy for localised oesophageal cancer on most HRQOL aspects, but many of these changes usually resolved within 6 months of treatment,¹⁰⁴ and HRQOL recovery was faster than after oesophagectomy. Surgical technical factors, i.e., surgical approach, extent of lymphadenectomy, blood loss or operation time, seem to have little influence on postoperative HRQOL.^{96, 105, 106} Early postoperative complications, however, have profound negative effects both in the short and long term.¹⁰⁷ A recent population-based cohort study found that several HRQOL measures are strongly negatively affected up until 10 years after surgery, e.g. reflux, dysphagia and eating difficulties (Figure 4).¹⁰⁸

Weight loss and malnutrition, before, during and after treatment, are major concerns in most oesophageal cancer patients.¹⁰⁹ The surgical resection results in a loss of stomach reservoir and is associated with several functional and mechanical issues, and also malabsorption,¹¹⁰ which contribute to eating difficulties and weight loss. Approximately two thirds of patients lose over 10% of their preoperative weight and one in five patients may lose over 20% of their preoperative weight within 6 months of oesophagectomy.¹¹¹

Nutritional deficiencies, e.g. in vitamin B and folate, may require vitamin or mineral supplementation. It is recommended that patients are counselled by a dietician at the time of diagnosis for assessing the need for enteral nutrition during neoadjuvant therapy, e.g. by supplying the patient with a jejunostomy. There is also some evidence from RCTs showing shortened length of hospital stay and improved clinical outcomes of using jejunostomy in the postoperative period,¹¹² including continued use at home.¹¹³

Palliative treatment

Most patients diagnosed with oesophageal cancer are not eligible for curative therapy or will develop tumour recurrence despite curatively intended treatment.⁵⁸⁻⁶⁰ Advanced tumour stage at diagnosis (e.g. T4b and M1) suggests palliative treatment. There is limited evidence how to select patients for palliative regimen based on other conditions, but this should be based on a balanced evaluation of fitness as described above. Palliative therapy aims to control disease-related symptoms, preserve as good HRQOL as possible, and prolong survival. The median survival in patients with metastatic oesophageal cancer without treatment is only a few months.

Local treatment

Dysphagia is a predominant problem. Oesophageal stenting with self-expanding metallic stents usually offers rapid partial relief of dysphagia, and is superior to thermal and chemical ablative therapies, at least regarding side-effects and need for re-interventions.¹¹⁴ Survival is not related to whether or not the stent is covered.¹¹⁵ Intraluminal brachytherapy may provide a slight survival benefit and better longer term HRQOL compared to stenting.¹¹⁴ The optimal treatment for dysphagia might be stenting plus brachytherapy.¹¹⁴ Interestingly, a recent RCT of 160 patients indicated a longer median survival if the stent was loaded with radioactive seeds (177 versus 147 days, $p=0.0046$).¹¹⁶ However, if chemotherapy is planned it often provides relief of dysphagia obviating the need for local treatment. Dysphagia may also be palliated by external radiotherapy.

Systemic treatment

Chemotherapy improves survival compared to best supportive care alone,¹¹⁷ but the survival benefit is modest and must be weighed against the side-effects of chemotherapy. No randomised phase III trials exist relating to the palliative treatment of OSCC, and data are usually extrapolated from OAC studies. A thorough discussion with the patient and family should provide them with a realistic view of the expected advantages and disadvantages of chemotherapy. In patients with metastatic oesophageal cancer, trial-eligible patients with a good performance status (0-1) have a median survival with first line chemotherapy of <1 year.^{64, 118, 119} First-line chemotherapy usually includes platinum and fluoropyrimidine, and the addition of a third drug may be considered for fit patients. A non-inferiority RCT (REAL-2) demonstrated equivalence of cisplatin and oxaliplatin, and also comparable outcomes for infused 5-fluorouracil and capecitabine.¹²⁰ Triplet combinations include epirubicin or docetaxel as a third drug, which may improve tumour response, but also increase toxicity.^{64, 118} In particular, the original docetaxel, cisplatin, and 5-fluorouracil regimen is associated with high rates of neutropenia and RCTs have evaluated modifications of this regimen to ameliorate this toxicity. Furthermore, the role of anthracyclines in providing additional benefit has been challenged.^{121, 122} OAC patients should have their tumour tested for overexpression of the HER2 protein, and if high level HER2 expression is demonstrated the anti-HER2 monoclonal antibody trastuzumab could be used in conjunction with cisplatin-fluoropyrimidine chemotherapy. In an RCT (TOGA study), patients with HER2 IHC 3+ or IHC 2+ FISH positive treated with trastuzumab plus chemotherapy had a median survival of 16.0 months, compared to 11.8 months for patients treated with chemotherapy alone (HR 0.65, 95% CI 0.51-0.83).¹²³

Second-line chemotherapy may be considered for patients with maintained performance status (0-1); the average absolute survival benefit with cytotoxic chemotherapy is 6 weeks leading to a median overall survival of approximately 5 months.¹²⁴⁻¹²⁶ Appropriate drugs include docetaxel, paclitaxel and irinotecan. The anti-VEGFR2 monoclonal antibody ramucirumab provides equivalent benefit to cytotoxic chemotherapy for patients with metastatic OAC when used as a single second-line agent.¹²⁷ In combination with paclitaxel, ramucirumab is associated with a small gain in median survival (9.6 months compared to 7.4 months with paclitaxel alone; HR=0.81, 95% CI 0.68-0.96).¹²⁴

Emerging therapies

The aggressive nature of oesophageal cancer with early spread, rapid tumour recurrence and poor prognosis highlight the need for research examining novel medical therapies.¹²⁸ Recent efforts to molecularly characterise oesophageal cancer have identified subgroups of patients who might benefit from targeted therapies in future. However, with the exception of HER2 positive tumours, RCTs of targeted therapies, including those targeting the EGFR and MET pathways, have thus far not been successful.^{129, 130} Failure to use biomarker selection or inadequate validation of biomarkers may be responsible in part for these failures. However, co-amplification of receptor tyrosine kinases, intra-tumour heterogeneity of copy number alteration and mutations in oesophageal cancers also leads to attenuation of the clinical benefit for targeted therapy.^{26, 131, 132} Emerging targets of therapeutic interest in oesophageal cancer include dysregulation cell cycle regulators such as CDK6 which have been successfully targeted in breast cancer by palbociclib and ribocicib, and impaired DNA damage repair mechanisms which have been exploited in ovarian cancer using olaparib and rucaparib).¹³³⁻¹³⁶ Finally, immunotherapy using checkpoint inhibitors such as programmed

cell death protein 1 (anti-PD-1) antibodies has resulted in survival benefits for patients with some other cancers, and gastro-oesophageal cancer is an attractive target for immunology intervention due to its relatively high mutation burden.¹³⁷⁻¹⁴⁰ Results from early phase trials in oesophageal cancer have been encouraging with response rates to the anti-PD1 antibody pembrolizumab reported as 29% for OSCC and 40% for OAC in an RCT of 23 programmed death-ligand 1 positive patients.¹⁴¹ PD-L1 negative gastro-oesophageal cancer patients also respond to checkpoint inhibitor therapy; the radiological response rate was 12% in PD-L1 negative patients treated with the anti-PD-1 antibody nivolumab, and radiological response rates were incremented for both PD-L1 positive and negative patients when the anti-CTLA4 antibody ipilimumab was added to nivolumab therapy.¹⁴² The promise of personalised immunotherapy for solid tumours could also be realised for oesophageal cancer, as adoptive T cell transfer of mutation specific T-cells have now been associated with a sustained radiological response in epithelial tumours such as cholangiocarcinoma.¹⁴³ However, as autologous adoptive T-cell transfer requires considerable expertise, alternative forms of personalised immunotherapy such as CAR-T cells which have been successful in haematological malignancies may be more widely applicable.¹⁴⁴ CAR-T cells are in early development for gastrointestinal cancers, selection of the most safe and specific target antigen will be of key importance; targets currently being investigated relevant to oesophageal cancer include HER2, MUC1, CEA and EpCAM (www.clinicaltrials.gov/ct2/results?term=CAR-T+gastric&Search=Search).

Best supportive care

Rapidly progressive dysphagia needs to be dealt with promptly and almost independently of the general condition of the patient. In the rapidly deteriorating patient, oesophageal

stenting alone is recommended since it promptly secures a continuity passing the obstructing tumour and is usually a single therapy without need for follow-up.¹¹⁴ The malnutrition seen in palliative oesophageal cancer patients is typically worse than that of most other cancer patients and depending on the clinical scenario enteral support may be considered. Deterioration in HRQOL is often rapid, which stresses the urgency in planning for the end of life care, and discussing the future with the patient and family members; and making early contact with the relevant healthcare facilities, e.g. ambulant palliative care unit, hospice or hospitals providing end of life care. Also in the many patients who have undergone curatively intended treatment, but develop tumour recurrence, it is recommended that palliative and supportive care is planned as soon as recurrent disease is discovered. Well-designed clinical trials using standardised measures may help improve the best supportive care in oesophageal cancer patients.^{145, 146}

Controversies and uncertainties

Endoscopic treatment

Although early tumours (T1) are not often identified, it is important to evaluate when endoscopic (organ-sparing) treatment can be recommended above surgical resection. There is a need for more large-scale observational research and RCTs to determine the answer to this question.

Oncological treatment

There is a need to clarify the role of neoadjuvant chemotherapy versus chemoradiotherapy. Both are associated with tumour down-staging, but rates of complete tumour response are higher following chemoradiotherapy, particularly for patients with OSCC.^{57, 60, 64, 65} However,

for patients with OAC, there is concern that the low dose of systemic chemotherapy in neoadjuvant chemoradiotherapy regimens may negatively impact on systemic disease control. In the long-term follow-up of the CROSS trial, distant metastatic recurrence was reduced overall (HR 0.63, 95% CI 0.46-0.87), however this was not significantly not reduced after two years compared to the control arm.⁶⁰ For OAC patients at high risk of metastatic recurrence, a systemic approach may be preferred. RCTs are needed to clarify these issues.

Timing of surgery following neoadjuvant therapy

The tumour stage after neoadjuvant chemoradiotherapy seems to be a better predictor of long-term prognosis than clinical tumour stage at presentation.¹⁴⁷ Some recent studies indicate that an increase in the time latencies between completed neoadjuvant therapy and surgery from currently 4-6 weeks to over 12 weeks may improve the tumour response to neoadjuvant therapy in OSCC and OAC, which may increase the rate of radical resection.^{148,}
¹⁴⁹ The optimal interval between neoadjuvant therapy and surgery in relation to survival is being assessed in an RCT (NCT02415101).

Follow-up

There is limited evidence on how to optimise the follow-up of patients having undergone radical treatment for oesophageal cancer. Some studies indicate that HRQOL measures can be used to identify the need for prompt interventions following treatment and also to predict survival.^{35, 150-152} Future research on these topics can provide further evidence that might guide future decision-making regarding choice of therapy as well as tailored follow-up.

Outstanding research questions

Detection

Increased detection of premalignant lesions and early stage tumours would improve prognosis. However, general endoscopic screening might not be cost-effective or clinically feasible, or well-tolerated by individuals. Future alternatives might be screening of carefully selected absolute high-risk individuals (with a combination of risk factors) in combination with use of less invasive screening tools, e.g. Cytosponge or breath tests,^{153, 154} although more research is needed before these tools may be introduced in routine clinical practice.

Diagnostics

Many oesophageal cancer patients undergo extensive therapy despite having tumour dissemination that has remained undetected prior to treatment. These patients may never recover from surgery before death. Thus, there is a need to develop new diagnostic measures with improved specificity and sensitivity for a more accurate assessment of the clinical tumour stage, potentially by developing novel radiotracers.

Biomarkers

New biomarkers that can help predict treatment response and prognosis would be valuable. Beyond HER2, there are no biomarkers for treatment selection for patients with operable oesophageal cancer. In essence, optimisation and developments in existing therapeutic tools can further improve the survival in oesophageal cancer. However, novel strategies for early tumour detection and new treatment are required for breakthroughs in the prognosis.

Search strategy and selection criteria

We searched the databases PubMed, Cochrane Library, MEDLINE, and EMBASE. We used the search terms “(o)esophageal” or “(o)esophagus” in combination with the terms “cancer” or “neoplasm” or “adenocarcinoma” or “squamous cell carcinoma”. We largely selected publications from the past 5 years. Review articles and book chapters are cited to provide readers with more details and more references than this seminar has room for.

References

1. Global Burden of Disease Cancer C, Fitzmaurice C, Dicker D, et al. The Global Burden of Cancer 2013. *JAMA oncology* 2015; **1**(4): 505-27.
2. Jacobs M, Macefield RC, Elbers RG, et al. Meta-analysis shows clinically relevant and long-lasting deterioration in health-related quality of life after esophageal cancer surgery. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2014; **23**(4): 1097-115.
3. Edgren G, Adami HO, Weiderpass E, Nyren O. A global assessment of the oesophageal adenocarcinoma epidemic. *Gut* 2013; **62**(10): 1406-14.
4. Xie SH, Lagergren J. A global assessment of the male predominance in esophageal adenocarcinoma. *Oncotarget* 2016; **7**(25): 38876-83.
5. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA: a cancer journal for clinicians* 2015; **65**(2): 87-108.
6. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. *Gut* 2015; **64**(3): 381-7.
7. Edgren G, Adami HO, Weiderpass Vainio E, Nyren O. A global assessment of the oesophageal adenocarcinoma epidemic. *Gut* 2013; **62**(10): 1406-14.
8. Gavin AT, Francisci S, Foschi R, et al. Oesophageal cancer survival in Europe: a EUROcare-4 study. *Cancer epidemiology* 2012; **36**(6): 505-12.
9. Njei B, McCarty TR, Birk JW. Trends in esophageal cancer survival in United States adults from 1973 to 2009: A SEER database analysis. *Journal of gastroenterology and hepatology* 2016; **31**(6): 1141-6.
10. Zeng H, Zheng R, Guo Y, et al. Cancer survival in China, 2003-2005: a population-based study. *International journal of cancer* 2015; **136**(8): 1921-30.
11. Chau I, Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. *J Clin Oncol* 2004; **22**(12): 2395-403.
12. Prabhu A, Obi KO, Rubenstein JH. The synergistic effects of alcohol and tobacco consumption on the risk of esophageal squamous cell carcinoma: a meta-analysis. *The American journal of gastroenterology* 2014; **109**(6): 822-7.
13. Liu J, Wang J, Leng Y, Lv C. Intake of fruit and vegetables and risk of esophageal squamous cell carcinoma: a meta-analysis of observational studies. *International journal of cancer* 2013; **133**(2): 473-85.

14. Qu X, Ben Q, Jiang Y. Consumption of red and processed meat and risk for esophageal squamous cell carcinoma based on a meta-analysis. *Annals of epidemiology* 2013; **23**(12): 762-70 e1.
15. Chen Y, Tong Y, Yang C, et al. Consumption of hot beverages and foods and the risk of esophageal cancer: a meta-analysis of observational studies. *BMC cancer* 2015; **15**: 449.
16. Wu C, Wang Z, Song X, et al. Joint analysis of three genome-wide association studies of esophageal squamous cell carcinoma in Chinese populations. *Nature genetics* 2014; **46**(9): 1001-6.
17. Bosetti C, Gallus S, Garavello W, La Vecchia C. Smoking cessation and the risk of oesophageal cancer: An overview of published studies. *Oral oncology* 2006; **42**(10): 957-64.
18. Spechler SJ, Souza RF. Barrett's esophagus. *The New England journal of medicine* 2014; **371**(9): 836-45.
19. Lagergren J, Lagergren P. Recent developments in esophageal adenocarcinoma. *CA: a cancer journal for clinicians* 2013; **63**(4): 232-48.
20. Buas MF, He Q, Johnson LG, et al. Germline variation in inflammation-related pathways and risk of Barrett's oesophagus and oesophageal adenocarcinoma. *Gut* 2016.
21. Ek WE, Lagergren K, Cook M, et al. Polymorphisms in genes in the androgen pathway and risk of Barrett's esophagus and esophageal adenocarcinoma. *International journal of cancer* 2016; **138**(5): 1146-52.
22. Lagergren K, Ek WE, Levine D, et al. Polymorphisms in Genes of Relevance for Oestrogen and Oxytocin Pathways and Risk of Barrett's Oesophagus and Oesophageal Adenocarcinoma: A Pooled Analysis from the BEACON Consortium. *PloS one* 2015; **10**(9): e0138738.
23. Gharahkhani P, Fitzgerald RC, Vaughan TL, et al. Genome-wide association studies in oesophageal adenocarcinoma and Barrett's oesophagus: a large-scale meta-analysis. *The lancet oncology* 2016; **17**(10): 1363-73.
24. Maret-Ouda J, El-Serag HB, Lagergren J. Opportunities for Preventing Esophageal Adenocarcinoma. *Cancer prevention research* 2016; **9**(11): 828-34.
25. Cancer Genome Atlas Research N, Analysis Working Group: Asan U, Agency BCC, et al. Integrated genomic characterization of oesophageal carcinoma. *Nature* 2017; **541**(7636): 169-75.
26. Secrier M, Li X, de Silva N, et al. Mutational signatures in esophageal adenocarcinoma define etiologically distinct subgroups with therapeutic relevance. *Nature genetics* 2016; **48**(10): 1131-41.
27. Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the Esophagus and Esophagogastric Junction: An Eighth Edition Staging Primer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2017; **12**(1): 36-42.
28. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. *The British journal of surgery* 1998; **85**(11): 1457-9.
29. Findlay JM, Bradley KM, Maile EJ, et al. Pragmatic staging of oesophageal cancer using decision theory involving selective endoscopic ultrasonography, PET and laparoscopy. *The British journal of surgery* 2015; **102**(12): 1488-99.
30. Chadwick G, Riley S, Hardwick RH, et al. Population-based cohort study of the management and survival of patients with early-stage oesophageal adenocarcinoma in England. *The British journal of surgery* 2016; **103**(5): 544-52.
31. Allum WH, Blazeby JM, Griffin SM, et al. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2011; **60**(11): 1449-72.
32. Carney A, Dickinson M. Anesthesia for esophagectomy. *Anesthesiology clinics* 2015; **33**(1): 143-63.
33. Wright CD, Kucharczuk JC, O'Brien SM, Grab JD, Allen MS, Society of Thoracic Surgeons General Thoracic Surgery D. Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. *The Journal of thoracic and cardiovascular surgery* 2009; **137**(3): 587-95; discussion 96.

34. Yoshida N, Baba Y, Shigaki H, et al. Preoperative Nutritional Assessment by Controlling Nutritional Status (CONUT) is Useful to estimate Postoperative Morbidity After Esophagectomy for Esophageal Cancer. *World journal of surgery* 2016; **40**(8): 1910-7.
35. Djarv T, Metcalfe C, Avery KN, Lagergren P, Blazeby JM. Prognostic value of changes in health-related quality of life scores during curative treatment for esophagogastric cancer. *J Clin Oncol* 2010; **28**(10): 1666-70.
36. Kidane B, Sulman J, Xu W, et al. Pretreatment quality-of-life score is a better discriminator of oesophageal cancer survival than performance status. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2016.
37. Le Roy B, Pereira B, Bouteloup C, et al. Effect of prehabilitation in gastro-oesophageal adenocarcinoma: study protocol of a multicentric, randomised, control trial-the PREHAB study. *BMJ open* 2016; **6**(12): e012876.
38. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; **27**(suppl 5): v50-v7.
39. van Hagen P, Spaander MC, van der Gaast A, et al. Impact of a multidisciplinary tumour board meeting for upper-GI malignancies on clinical decision making: a prospective cohort study. *International journal of clinical oncology* 2013; **18**(2): 214-9.
40. Schmidt HM, Roberts JM, Bodnar AM, et al. Thoracic multidisciplinary tumor board routinely impacts therapeutic plans in patients with lung and esophageal cancer: a prospective cohort study. *The Annals of thoracic surgery* 2015; **99**(5): 1719-24.
41. Boniface MM, Wani SB, Scheffter TE, et al. Multidisciplinary management for esophageal and gastric cancer. *Cancer management and research* 2016; **8**: 39-44.
42. Merkow RP, Bilimoria KY, Keswani RN, et al. Treatment trends, risk of lymph node metastasis, and outcomes for localized esophageal cancer. *Journal of the National Cancer Institute* 2014; **106**(7).
43. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *The New England journal of medicine* 2009; **360**(22): 2277-88.
44. He S, Bergman J, Zhang Y, et al. Endoscopic radiofrequency ablation for early esophageal squamous cell neoplasia: report of safety and effectiveness from a large prospective trial. *Endoscopy* 2015; **47**(5): 398-408.
45. Bergman JJ, Zhang YM, He S, et al. Outcomes from a prospective trial of endoscopic radiofrequency ablation of early squamous cell neoplasia of the esophagus. *Gastrointestinal endoscopy* 2011; **74**(6): 1181-90.
46. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. *Jama* 2014; **311**(12): 1209-17.
47. Hu Y, Puri V, Shami VM, Stukenborg GJ, Kozower BD. Comparative Effectiveness of Esophagectomy Versus Endoscopic Treatment for Esophageal High-grade Dysplasia. *Annals of surgery* 2016; **263**(4): 719-26.
48. Haidry RJ, Butt MA, Dunn JM, et al. Improvement over time in outcomes for patients undergoing endoscopic therapy for Barrett's oesophagus-related neoplasia: 6-year experience from the first 500 patients treated in the UK patient registry. *Gut* 2015; **64**(8): 1192-9.
49. Neuhaus H, Terheggen G, Rutz EM, Vieth M, Schumacher B. Endoscopic submucosal dissection plus radiofrequency ablation of neoplastic Barrett's esophagus. *Endoscopy* 2012; **44**(12): 1105-13.
50. Sun F, Yuan P, Chen T, Hu J. Efficacy and complication of endoscopic submucosal dissection for superficial esophageal carcinoma: a systematic review and meta-analysis. *Journal of cardiothoracic surgery* 2014; **9**: 78.
51. Guo HM, Zhang XQ, Chen M, Huang SL, Zou XP. Endoscopic submucosal dissection vs endoscopic mucosal resection for superficial esophageal cancer. *World J Gastroenterol* 2014; **20**(18): 5540-7.

52. Wu J, Pan YM, Wang TT, Gao DJ, Hu B. Endotherapy versus surgery for early neoplasia in Barrett's esophagus: a meta-analysis. *Gastrointestinal endoscopy* 2014; **79**(2): 233-41 e2.
53. Pasricha S, Cotton C, Hathorn KE, et al. Effects of the Learning Curve on Efficacy of Radiofrequency Ablation for Barrett's Esophagus. *Gastroenterology* 2015; **149**(4): 890-6 e2.
54. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *The lancet oncology* 2011; **12**(7): 681-92.
55. Mariette C, Dahan L, Mornex F, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. *J Clin Oncol* 2014; **32**(23): 2416-22.
56. Mariette C, Gronnier C, Duhamel A, et al. Self-expanding covered metallic stent as a bridge to surgery in esophageal cancer: impact on oncologic outcomes. *Journal of the American College of Surgeons* 2015; **220**(3): 287-96.
57. Medical Research Council Oesophageal Cancer Working G. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002; **359**(9319): 1727-33.
58. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009; **27**(30): 5062-7.
59. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *The New England journal of medicine* 2012; **366**(22): 2074-84.
60. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *The lancet oncology* 2015; **16**(9): 1090-8.
61. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005; **23**(10): 2310-7.
62. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol* 2007; **25**(10): 1160-8.
63. Markar S, Gronnier C, Duhamel A, et al. Salvage Surgery After Chemoradiotherapy in the Management of Esophageal Cancer: Is It a Viable Therapeutic Option? *J Clin Oncol* 2015; **33**(33): 3866-73.
64. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *The New England journal of medicine* 2006; **355**(1): 11-20.
65. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011; **29**(13): 1715-21.
66. Alderson D, Langley R, Nankivell M, et. a. Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: Results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072). *ASCO Meeting Abstracts* 2015; **33**(15 suppl): 4002.
67. Ott K, Fink U, Becker K, et al. Prediction of response to preoperative chemotherapy in gastric carcinoma by metabolic imaging: results of a prospective trial. *J Clin Oncol* 2003; **21**(24): 4604-10.
68. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *The lancet oncology* 2007; **8**(9): 797-805.
69. Ott K, Weber WA, Lordick F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. *J Clin Oncol* 2006; **24**(29): 4692-8.

70. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *The New England journal of medicine* 1996; **335**(7): 462-7.
71. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. *The lancet oncology* 2014; **15**(3): 305-14.
72. Van Laethem JL, Carneiro F, Ducreux M, et al. The multidisciplinary management of gastro-oesophageal junction tumours: European Society of Digestive Oncology (ESDO): Expert discussion and report from the 16th ESMO World Congress on Gastrointestinal Cancer, Barcelona. *Dig Liver Dis* 2016; **48**(11): 1283-9.
73. Klevebro F, Alexandersson von Döbeln G, Wang N, et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. *Ann Oncol* 2016; **27**(4): 660-7.
74. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009; **27**(6): 851-6.
75. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *The New England journal of medicine* 1992; **326**(24): 1593-8.
76. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002; **20**(5): 1167-74.
77. Pasquali S, Yim G, Vohra RS, et al. Survival After Neoadjuvant and Adjuvant Treatments Compared to Surgery Alone for Resectable Esophageal Carcinoma: A Network Meta-analysis. *Annals of surgery* 2016.
78. Markar SR, Gronnier C, Duhamel A, et al. Significance of Microscopically Incomplete Resection Margin After Esophagectomy for Esophageal Cancer. *Annals of surgery* 2016; **263**(4): 712-8.
79. Chan DS, Reid TD, Howell I, Lewis WG. Systematic review and meta-analysis of the influence of circumferential resection margin involvement on survival in patients with operable oesophageal cancer. *The British journal of surgery* 2013; **100**(4): 456-64.
80. Lagarde SM, Vrouenraets BC, Stassen LP, van Lanschot JJ. Evidence-based surgical treatment of esophageal cancer: overview of high-quality studies. *The Annals of thoracic surgery* 2010; **89**(4): 1319-26.
81. Zhou C, Zhang L, Wang H, et al. Superiority of Minimally Invasive Oesophagectomy in Reducing In-Hospital Mortality of Patients with Resectable Oesophageal Cancer: A Meta-Analysis. *PloS one* 2015; **10**(7): e0132889.
82. Yerokun BA, Sun Z, Jeffrey Yang CF, et al. Minimally Invasive Versus Open Esophagectomy for Esophageal Cancer: A Population-Based Analysis. *The Annals of thoracic surgery* 2016; **102**(2): 416-23.
83. Biere SS, van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet* 2012; **379**(9829): 1887-92.
84. Briez N, Piessen G, Torres F, Lebuffe G, Triboulet JP, Mariette C. Effects of hybrid minimally invasive oesophagectomy on major postoperative pulmonary complications. *The British journal of surgery* 2012; **99**(11): 1547-53.
85. Davies AR, Sandhu H, Pillai A, et al. Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer. *The British journal of surgery* 2014; **101**(5): 511-7.
86. Hulscher JB, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *The New England journal of medicine* 2002; **347**(21): 1662-9.

87. Markar SR, Wiggins T, Ni M, et al. Assessment of the quality of surgery within randomised controlled trials for the treatment of gastro-oesophageal cancer: a systematic review. *The lancet oncology* 2015; **16**(1): e23-31.
88. Markar SR, Mackenzie H, Lagergren P, Hanna GB, Lagergren J. Surgical Proficiency Gain and Survival After Esophagectomy for Cancer. *J Clin Oncol* 2016; **34**(13): 1528-36.
89. Brusselsaers N, Mattsson F, Lagergren J. Hospital and surgeon volume in relation to long-term survival after oesophagectomy: systematic review and meta-analysis. *Gut* 2014; **63**(9): 1393-400.
90. Derogar M, Sadr-Azodi O, Johar A, Lagergren P, Lagergren J. Hospital and surgeon volume in relation to survival after esophageal cancer surgery in a population-based study. *J Clin Oncol* 2013; **31**(5): 551-7.
91. Rizk NP, Ishwaran H, Rice TW, et al. Optimum lymphadenectomy for esophageal cancer. *Annals of surgery* 2010; **251**(1): 46-50.
92. van der Schaaf M, Johar A, Wijnhoven B, Lagergren P, Lagergren J. Extent of lymph node removal during esophageal cancer surgery and survival. *Journal of the National Cancer Institute* 2015; **107**(5).
93. Lagergren J, Mattsson F, Zylstra J, et al. Extent of Lymphadenectomy and Prognosis After Esophageal Cancer Surgery. *JAMA surgery* 2015: 1-8.
94. Phillips AW, Lagarde SM, Navidi M, Disep B, Griffin SM. Impact of Extent of Lymphadenectomy on Survival, Post Neoadjuvant Chemotherapy and Transthoracic Esophagectomy. *Annals of surgery* 2016.
95. Anderegg MC, Lagarde SM, Jagadesham VP, et al. Prognostic Significance of the Location of Lymph Node Metastases in Patients With Adenocarcinoma of the Distal Esophagus or Gastroesophageal Junction. *Annals of surgery* 2016; **264**(5): 847-53.
96. Schandl A, Johar A, Lagergren J, Lagergren P. Lymphadenectomy and health-related quality of life after oesophageal cancer surgery: a nationwide, population-based cohort study. *BMJ open* 2016; **6**(8): e012624.
97. Jacobs M, Macefield RC, Elbers RG, et al. Meta-analysis shows clinically relevant and long-lasting deterioration in health-related quality of life after esophageal cancer surgery. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2014; **23**(4): 1155-76.
98. Wikman A, Ljung R, Johar A, Hellstadius Y, Lagergren J, Lagergren P. Psychiatric morbidity and survival after surgery for esophageal cancer: a population-based cohort study. *J Clin Oncol* 2015; **33**(5): 448-54.
99. Djarv T, Blazeby JM, Lagergren P. Predictors of postoperative quality of life after esophagectomy for cancer. *J Clin Oncol* 2009; **27**(12): 1963-8.
100. Sunde B, Ericson J, Kumagai K, et al. Relief of dysphagia during neoadjuvant treatment for cancer of the esophagus or gastroesophageal junction. *Dis Esophagus* 2016; **29**(5): 442-7.
101. Cools-Lartigue J, Jones D, Spicer J, et al. Management of Dysphagia in Esophageal Adenocarcinoma Patients Undergoing Neoadjuvant Chemotherapy: Can Invasive Tube Feeding be Avoided? *Annals of surgical oncology* 2015; **22**(6): 1858-65.
102. Blazeby JM, Sanford E, Falk SJ, Alderson D, Donovan JL. Health-related quality of life during neoadjuvant treatment and surgery for localized esophageal carcinoma. *Cancer* 2005; **103**(9): 1791-9.
103. Hauser C, Patett C, von Schoenfels W, et al. Does neoadjuvant treatment before oncologic esophagectomy affect the postoperative quality of life? A prospective, longitudinal outcome study. *Dis Esophagus* 2015; **28**(7): 652-9.
104. Rees J, Hurt CN, Gollins S, et al. Patient-reported outcomes during and after definitive chemoradiotherapy for oesophageal cancer. *British journal of cancer* 2015; **113**(4): 603-10.
105. van der Schaaf M, Rutegard M, Lagergren P. The influence of surgical factors on persisting symptoms 3 years after esophageal cancer surgery: a population-based study in Sweden. *Annals of surgical oncology* 2013; **20**(5): 1639-45.

106. Rutegard M, Lagergren J, Rouvelas I, Lindblad M, Blazeby JM, Lagergren P. Population-based study of surgical factors in relation to health-related quality of life after oesophageal cancer resection. *The British journal of surgery* 2008; **95**(5): 592-601.
107. Derogar M, Orsini N, Sadr-Azodi O, Lagergren P. Influence of major postoperative complications on health-related quality of life among long-term survivors of esophageal cancer surgery. *J Clin Oncol* 2012; **30**(14): 1615-9.
108. Schandl A, Lagergren J, Johar A, Lagergren P. Health-related quality of life 10 years after oesophageal cancer surgery. *Eur J Cancer* 2016; **69**: 43-50.
109. Anandavadivelan P, Lagergren P. Cachexia in patients with oesophageal cancer. *Nature reviews Clinical oncology* 2016; **13**(3): 185-98.
110. Heneghan HM, Zaborowski A, Fanning M, et al. Prospective Study of Malabsorption and Malnutrition After Esophageal and Gastric Cancer Surgery. *Annals of surgery* 2015; **262**(5): 803-7; discussion 7-8.
111. Martin L, Lagergren P. Long-term weight change after oesophageal cancer surgery. *The British journal of surgery* 2009; **96**(11): 1308-14.
112. Barlow R, Price P, Reid TD, et al. Prospective multicentre randomised controlled trial of early enteral nutrition for patients undergoing major upper gastrointestinal surgical resection. *Clinical nutrition* 2011; **30**(5): 560-6.
113. Bowrey DJ, Baker M, Halliday V, et al. A randomised controlled trial of six weeks of home enteral nutrition versus standard care after oesophagectomy or total gastrectomy for cancer: report on a pilot and feasibility study. *Trials* 2015; **16**: 531.
114. Dai Y, Li C, Xie Y, et al. Interventions for dysphagia in oesophageal cancer. *Cochrane database of systematic reviews (Online)* 2014; (10): CD005048.
115. Yang Z, Wu Q, Wang F, Ye X, Qi X, Fan D. A systematic review and meta-analysis of randomized trials and prospective studies comparing covered and bare self-expandable metal stents for the treatment of malignant obstruction in the digestive tract. *International journal of medical sciences* 2013; **10**(7): 825-35.
116. Zhu HD, Guo JH, Mao AW, et al. Conventional stents versus stents loaded with (125)iodine seeds for the treatment of unresectable oesophageal cancer: a multicentre, randomised phase 3 trial. *The lancet oncology* 2014; **15**(6): 612-9.
117. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. *Cochrane database of systematic reviews (Online)* 2010; (3): CD004064.
118. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24**(31): 4991-7.
119. Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008; **26**(9): 1435-42.
120. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *The New England journal of medicine* 2008; **358**(1): 36-46.
121. Shah MA, Janjigian YY, Stoller R, et al. Randomized Multicenter Phase II Study of Modified Docetaxel, Cisplatin, and Fluorouracil (DCF) Versus DCF Plus Growth Factor Support in Patients With Metastatic Gastric Adenocarcinoma: A Study of the US Gastric Cancer Consortium. *J Clin Oncol* 2015; **33**(33): 3874-9.
122. Van Cutsem E, Boni C, Tabernero J, et al. Docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer: a randomized phase II study. *Ann Oncol* 2015; **26**(1): 149-56.
123. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**(9742): 687-97.

124. Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *The lancet oncology* 2014; **15**(1): 78-86.
125. Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012; **30**(13): 1513-8.
126. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol* 2013; **31**(35): 4438-44.
127. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; **383**(9911): 31-9.
128. Gaur P, Hunt CR, Pandita TK. Emerging therapeutic targets in esophageal adenocarcinoma. *Oncotarget* 2016.
129. Waddell T, Chau I, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. *The lancet oncology* 2013; **14**(6): 481-9.
130. Lordick F, Kang YK, Chung HC, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *The lancet oncology* 2013; **14**(6): 490-9.
131. Pearson A, Smyth E, Babina IS, et al. High-Level Clonal FGFR Amplification and Response to FGFR Inhibition in a Translational Clinical Trial. *Cancer discovery* 2016; **6**(8): 838-51.
132. Murugaesu N, Wilson GA, Birkbak NJ, et al. Tracking the genomic evolution of esophageal adenocarcinoma through neoadjuvant chemotherapy. *Cancer discovery* 2015; **5**(8): 821-31.
133. Turner NC, Huang Bartlett C, Cristofanilli M. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. *The New England journal of medicine* 2015; **373**(17): 1672-3.
134. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *The New England journal of medicine* 2016; **375**(18): 1738-48.
135. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *The New England journal of medicine* 2012; **366**(15): 1382-92.
136. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *The lancet oncology* 2017; **18**(1): 75-87.
137. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *The New England journal of medicine* 2015; **373**(1): 23-34.
138. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *The New England journal of medicine* 2016.
139. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *The New England journal of medicine* 2015; **372**(26): 2521-32.
140. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. *Nature* 2013; **500**(7463): 415-21.
141. Doi T, Piha-Paul SA, Jalal SI, et al. Updated results for the advanced esophageal carcinoma cohort of the phase 1b KEYNOTE-028 study of pembrolizumab. *ASCO Meeting Abstracts* 2016; **34**(15 Suppl): 4046.
142. Janjigian YY, Bendell JC, Calvo E, et al. CheckMate-032: Phase I/II, open-label study of safety and activity of nivolumab (nivo) alone or with ipilimumab (ipi) in advanced and metastatic (A/M) gastric cancer (GC). *J Clin Oncol* 2016; **34** (15 Suppl): 4010.
143. Tran E, Turcotte S, Gros A, et al. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. *Science* 2014; **344**(6184): 641-5.

144. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *The New England journal of medicine* 2014; **371**(16): 1507-17.
145. Zafar SY, Currow DC, Cherny N, Strasser F, Fowler R, Abernethy AP. Consensus-based standards for best supportive care in clinical trials in advanced cancer. *The lancet oncology* 2012; **13**(2): e77-82.
146. Lee RT, Ramchandran K, Sanft T, Von Roenn J. Implementation of supportive care and best supportive care interventions in clinical trials enrolling patients with cancerdagger. *Ann Oncol* 2015; **26**(9): 1838-45.
147. Davies AR, Gossage JA, Zylstra J, et al. Tumor stage after neoadjuvant chemotherapy determines survival after surgery for adenocarcinoma of the esophagus and esophagogastric junction. *J Clin Oncol* 2014; **32**(27): 2983-90.
148. Shapiro J, van Hagen P, Lingsma HF, et al. Prolonged time to surgery after neoadjuvant chemoradiotherapy increases histopathological response without affecting survival in patients with esophageal or junctional cancer. *Annals of surgery* 2014; **260**(5): 807-13; discussion 13-4.
149. Haisley KR, Laird AE, Nabavizadeh N, et al. Association of Intervals Between Neoadjuvant Chemoradiation and Surgical Resection With Pathologic Complete Response and Survival in Patients With Esophageal Cancer. *JAMA surgery* 2016: e162743.
150. van Heijl M, Sprangers MA, de Boer AG, et al. Preoperative and early postoperative quality of life predict survival in potentially curable patients with esophageal cancer. *Annals of surgical oncology* 2010; **17**(1): 23-30.
151. Kidane B, Sulman J, Xu W, et al. Baseline measure of health-related quality of life (Functional Assessment of Cancer Therapy-Esophagus) is associated with overall survival in patients with esophageal cancer. *The Journal of thoracic and cardiovascular surgery* 2016; **151**(6): 1571-80.
152. Wikman A, Johar A, Lagergren P. Presence of symptom clusters in surgically treated patients with esophageal cancer: implications for survival. *Cancer* 2014; **120**(2): 286-93.
153. Benaglia T, Sharples LD, Fitzgerald RC, Lyratzopoulos G. Health benefits and cost effectiveness of endoscopic and nonendoscopic cytosponge screening for Barrett's esophagus. *Gastroenterology* 2013; **144**(1): 62-73 e6.
154. Kumar S, Huang J, Abbassi-Ghadi N, et al. Mass Spectrometric Analysis of Exhaled Breath for the Identification of Volatile Organic Compound Biomarkers in Esophageal and Gastric Adenocarcinoma. *Annals of surgery* 2015; **262**(6): 981-90.

Table 1: Frequently dysregulated genes in oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC) as per Oesophageal Cancer Genome Atlas.

	OSCC	OAC
Receptor Tyrosine Kinases		
ERBB2	3%	32%
EGFR	19%	15%
VEGFA	3%	28%
KRAS	7%	14%
PIK3CA	13%	3%
FGFR1	12%	4%
Cell cycle regulators		
CDKN2A	76%	76%
CCND1	57%	15%
CDK6	16%	14%
CCNE1	4%	14%
RB	9%	0%
Proliferation and differentiation		
MYC	23%	32%
SMAD4	8%	24%
GATA4	1%	19%
GATA6	3%	21%
TP63/SOX2	48%	11%
Chromatin remodelling		
KDM6A	19%	4%
KMT2D	14%	1%

Red signifies activation of pathway, blue inactivation.
Dysregulation may occur via amplification, deletion, mutation or epigenetic modulation.

Table 2: Selected randomised clinical trials adjunctive therapy for operable oesophageal cancer.					
Trial acronym*	Tumour histology	Number of patients	Treatment	5 year survival in % Hazard ratio (95% confidence interval)	Median survival in months Hazard ratio (95% confidence interval)
Neoadjuvant chemotherapy					
OEO2	Squamous cell carcinoma 33.5% Adenocarcinoma 66.5%	802	Surgery (reference) Neoadjuvant chemotherapy	17 23	Not reported Not reported 0.83 (0.70-0.98)
Perioperative chemotherapy					
MAGIC	Adenocarcinoma 100% (Lower oesophageal/junctional 26%)	503	Surgery (reference) Perioperative chemotherapy	23 36	Not reported Not reported 0.75 (0.60-0.93)
FNCLCC- FFCD	Adenocarcinoma 100% (Lower oesophagus 11%; junctional 64%)	224	Surgery (reference) Perioperative chemotherapy	24 38	Not reported Not reported 0.69 (0.50-0.95)
Pre-operative chemoradiotherapy					
CROSS	Squamous cell carcinoma 26% Adenocarcinoma 74%	366	Surgery (reference) Neoadjuvant chemoradiotherapy	33 47 0.67 (0.51-0.87)	24 49 0.68 (0.53-0.88)