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Oesophageal cancer: Seminar

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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 meat[14] 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 an 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 OACC 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 ration [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-fluororuracil chemoradiotherapy (45Gy in 25 fractions) compared to surgery alone.[55] Therefore it is recommended that patients with ≤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/m^2 x 96 hours) and fluorouracil (1000 mg/m^2 x 96 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 2mg/ml/min and paclitaxel 50mg/m^2) for 5 weeks in conjunction with concurrent radiotherapy (41.4Gy 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. ≤T3 tumours which are <5cm in width and <8cm 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 (≥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 (75mg/m^2), 5-fluororacil (1000mg/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 lymphadenectomy[91] 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-fluororuacil 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-fluoruracil regimen is associated with high rates of neutropenia and RCTs have evaluated modifications of this regimen to ameliorate this toxicity. Furthermore, the role of anthracylines 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 immuno-oncology 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.

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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 acronyme*	**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)