

Oesophageal cancer: an overview of a deadly disease

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Summary

Oesophageal cancer (OC) is one of the deadliest cancers in the world. Although it affects many people throughout East Africa, relatively little work has been done to fully understand this disease. This review addresses recent changes in the understanding of OC from a global perspective, with special attention given to OC in Kenya.

Epidemiology

Oesophageal cancer is the eighth most common cancer worldwide, and the sixth most common cause of death from cancer. From a worldwide perspective, one of the most striking features of oesophageal cancer is the extreme geographic variation in incidence. At a global level, a 20-fold difference is seen in official statistics between high-risk and low risk areas (1). This difference becomes even more striking when one looks at specific high-risk areas within certain countries. For example, while the incidence annually among women in North America is close to 2 cases per 100,000 population, the incidence among women in Iran has historically been estimated to be close to 100 times higher, and the annual death rate for OC in Linxian, People's Republic of China exceeds 100 deaths per 100,000 population (1,2). One therefore needs really to consider areas where OC is endemic separately from non-endemic areas. Those areas in which OC should be considered

endemic are listed in Table 1. It should be noted that even within these "hotspots" of OC, there is extreme variation within relatively short geographic distances (1-3).

The vast majority of oesophageal cancer consists of either oesophageal squamous cell carcinoma (OSCC), or adenocarcinoma (AC) (5). Other malignancies constituting less than 1% of total oesophageal malignancies include small cell carcinoma, melanoma, malignant mesenchymal tumours (including Kaposi's Sarcoma), and lymphomas. From a global perspective, OSCC accounts for approximately 80% of OC, and is clearly the predominant type in endemic areas (1,2,4,5). OSCC tends to occur more commonly among the black population (6), while AC is increasing among the white population in non-endemic areas (7). While OC in general tends to be a male dominated disease (male:female ratio of 5-7:1), a common finding in endemic areas is a more evenly distributed incidence between genders, with male:female ratios of 1-2:1 (1,4,5). In many western countries, AC is increasing rapidly, and the incidence has surpassed that of OSCC. In the USA, for example, AC overtook OSCC as the predominant type in the late 1980's and is now three times more common than OSCC, increasing at a rate of 5%-10% per year, making it the fastest growing cancer incidence rate in the country (7). One must bear in mind that the absolute numbers still remain relatively small compared to endemic areas. The overall incidence of OC continues to rise, with most of

the increase due to the rise of AC in non-endemic areas (8). Average age at diagnosis of OC tends to be in the 50's and 60's, with AC presenting in patients about 10 years older than in OSCC (9). However, in some endemic areas, this may vary considerably. White *et al* reported in 2002 that in an endemic area of Kenya, 11% of all patients with OC were 30 years of age or less (5).

Overall survival from OC remains low and varies somewhat between geographic locations, with 5 year survival in the USA approximately 16% ,while in Europe it is 10% (10,11). This difference is probably largely due to differences in stage at diagnosis.

There does not seem to be significant survival differences between endemic and non-endemic areas when differences in treatment options and availability are considered. While in China, the survival is essentially equal to that of the USA, survival in Africa tends to be lower. However, in a case series of surgically treated patients in East Africa, overall median survival of 24 months was reported (12,13). A great deal of debate centers around whether or not OSCC and AC have different survival patterns. Evidence can be found in the literature for increased survival with either OSCC or AC (14,15). It is a complex issue, however the truth may be more reflective of differences in regional access to health care and variable comorbidities than in actual survival differences between OSCC and AC.

Table 1: Geographic areas of endemic oesophageal cancer

China
Eastern Africa
Japan (males only)
Northern Italy
Northwestern France
Southern Africa
Southwestern Asia (particularly Iran, Kazakhstan, and Turkey)

Pathogenesis/ Risk Factors

While there are significant differences between AC and OSCC, there appears to be a common final pathway of progression from dysplasia

(mild, moderate and severe), to mucosal cancer to invasive carcinoma. While mild dysplasia seems to frequently spontaneously regress, the finding of moderate or severe dysplasia appears to be much more predictive of the development of frank carcinoma. The primary risk factor for the development of AC appears to be gastro-oesophageal reflux disease (GORD) with subsequent development of Barrett's oesophagus (BO) and Barrett's dysplasia. These and other risk factors for the development of OC are summarized in Table 2.

Clinical Presentation/ Diagnosis

For the majority of patients, OC is discovered in one of two ways. The first, and by far the most common course throughout the world, is for patients to present with symptoms usually indicative of advanced lesions. Secondly, patients may present with early lesions discovered through surveillance programs for patients with GORD, or after endoscopy for non-specific dyspepsia. These two presentations will be discussed separately.

Throughout most of the world, most patients present to health care personnel only after symptoms of OC develop. The nature of OC is such that symptoms generally do not develop until a significant portion of the oesophageal lumen is obstructed. Since intra-luminal growth is a relatively late phenomenon in the course of the disease, these patients present with advanced disease, often with large primary tumours, regional lymph node involvement, and distant metastases. The most common presenting symptoms are dysphagia and weight loss, both of which are late symptoms. Dysphagia has been reported to occur only after the tumour encroaches on 75%-90% of the oesophageal circumference (36). In the author's institution where 200-300 new cases of OC are seen annually-nearly all patients present with significant dysphagia. Endoscopic dilation is required in approximately 95% of cases simply to allow passage of the endoscope (personal data). Interestingly, most patients can accurately describe the level of their obstruction (upper,

mid, or lower oesophagus) based upon their symptoms. Odynophagia, vomiting, chest pain, and hematemesis are less common presenting symptoms (4,37). Cough productive of purulent sputum, particularly occurring immediately after oral intake, is highly suggestive of malignant tracheoesophageal fistula. Hoarseness of the voice is also a particularly ominous symptom, as this most often indicates recurrent laryngeal nerve involvement, or occasionally direct involvement of the larynx. A small percentage of relatively earlier lesions will present after food bolus obstruction of the oesophagus. After clearing of the obstruction (either spontaneously or via intervention), follow-up studies may reveal the presence of a non-obstructing oesophageal lesion which would not have otherwise been discovered.

With the rising incidence of AC in western countries, and the recognition of the association of GORD and Barrett's oesophagus, a new group of patients with early lesions discovered through screening or surveillance programs is emerging. These patients are generally found to have either Barrett's oesophagus or Barrett's dysplasia, and are then regularly followed with surveillance endoscopy. Several techniques have evolved for increasing sensitivity in finding early malignant or pre-malignant lesions. Chromoendoscopy involves endoscopic evaluation after staining with vital dyes such as Lugol's iodine, crystal violet, indigo carmine, and methylene blue. This technique has increased sensitivity and specificity to 89% and 86% respectively, for evaluation of Barrett's

Table 2: Risk factors associated with oesophageal cancer development (16)

Squamous Cell Carcinoma	Adenocarcinoma	Squamous cell carcinoma and adenocarcinoma
History of Head and Neck Cancer*	Gastro-oesophageal Reflux Disease* (RR = 2.5–40) (27,29)	History of breast cancer with radiation therapy*
Alcohol Consumption* (RR = 2.9–7.4)	Obesity (21,27-30)	Smoking* (OSCC RR = 10, AC RR = 1.5–4) (20,21,27)
Caustic injury to the oesophagus*	Eradication of <i>H. pylori</i> infection ^{†††}	Occupational exposure (possibly airborne contaminants) (32,33)
Achalasia cardia*		Socioeconomic status (possibly overcrowding, poor diet, common occupation) (17,28,34)
		Protective factors
Tylosis*		Effects of NSAIDS (20,24,27,35)
Plummer-Vinson syndrome*		
Family History of OC [†]		
Human Papillomavirus infection ^{††}		
Mycotoxin fumonisin ^{†††}		
Exposure/consumption of		
N-nitroso compounds and polycyclic aromatic hydrocarbons (20-23)		
Hot beverages		
Betel nut		
Dietary Deficiencies		
Vitamins C,E, riboflavin, zinc, Selenium (24,26)		
Fresh fruits and vegetables (17,20,21,27,28)		

* Indicates well-established risk factors with strong evidence for relationship with OC.

† In an area of high incidence in northern China, having more than one relative with oesophageal cancer increased the RR for OC to 1.9 (17).

†† Many contradictory studies exist. The only study to date looking at HPV in Kenya has shown no association with the development of OC (18).

††† Evidence to date for a specific correlation between the mycotoxin fumonisin (produced by the mold *Fusarium moniliforme*—a common contaminant of maize) and the development of OC is contradictory at best (19).

†††† *H. pylori* infection appears to be protective for AC (17,19), while a risk factor for OSCC. It has been suggested that the rising incidence of OC seen in western countries may in part be explained by the increasing treatment and eradication of *H. pylori* infection (31)

Table 3: Diagnostic/staging modalities for oesophageal cancer

Diagnosis	Use
Upper GI endoscopy with biopsy	Initial modalities of choice
Barium swallow	
Primary tumour Assessment (T Stage)	
CT scan	Tumour size and presence of invasion into surrounding tissue
MRI	Slightly superior to CT in detecting vascular invasion
Endoscopic Ultrasound	Depth of invasion
Bronchoscopy	Possible airway invasion for tumour above level of carina
Regional assessment (N Stage)	
CT scan	Evaluating regional lymph nodes
Endoscopic ultrasound	
Distant metastases (M Stage)	
CT scan	Metastases detection especially liver and brain
PET scan	Sensitive detection of distant metastases
Abdominal ultrasound	Helpful for abdominal spread
Fine needle aspiration	Cervical or supra-clavicular lymph nodes

oesophagus (38). Light-induced fluorescence endoscopy (LIFE) and narrow band imaging (NBI) are two additional endoscopic techniques for improving sensitivity in finding early lesions. NBI, or virtual chromoendoscopy, in particular, appears to be very promising in this regard without the use of additional reagents (39). Oesophageal capsule endoscopy also is being used for Barrett's screening and surveillance programs. One clear disadvantage of this technique is the inability to obtain biopsy samples for histologic confirmation (40). Optical coherence tomography (OCT) is also a technique with some promise in distinguishing neoplasia within Barrett's mucosa (41). Use of these techniques in early diagnosis of OSCC has not achieved widespread success, but have shown promise in a number of studies in high-risk populations (42,43).

Initial diagnostic evaluation tends to be either with barium swallow or upper endoscopy. The decision between these two modalities tends to be based upon regional availability of resources and referral patterns. Certainly, upper endoscopy is more reliable than contrast radiography, as small lesions can be missed on barium studies. Further, endoscopy allows for biopsy of suspicious lesions, permitting histologic confirmation of disease. In areas where OC is endemic, the clinical presentation of weight loss and dysphagia is nearly

pathognomonic for OC (4). This finding is virtually reproduced in the author's institution, with the exception of cases of oesophageal candidiasis related to AIDS, which may cause severe dysphagia and weight loss as well. Additional diagnostic modalities with their appropriate uses in staging assessment are summarized in Table 3.

Staging of oesophageal cancer

The TNM staging system incorporated in the manual for Staging of Cancer of the American Joint Committee on Cancer (44) is the most widely used system for classifying OC. This scheme classifies OC into stage 0 through stage IV based on tumour depth/penetration, nodal status, and presence of metastases. Superficial cancers are defined as tumours limited to the mucosa or submucosa (45). Mucosal lesions can be further subdivided into m1-m3 lesions. Tumours that are confined within the basement membrane are classified as m1 (described by some as "carcinoma-in-situ"). Lesions that invade into, but not through, the muscularis mucosa are considered m3. Lesions intermediate between these two would be considered m2. Submucosal lesions are similarly subdivided into sm1-sm3. The incidence of lymph node metastases in m1,

m2 and m3 lesions has been reported at 0%, 3.3%, and 12.2%, with sm1, sm2, and sm3 lesions yielding a positive lymph node rate of 26.5%, 35.8%, and 45.9%, respectively (46).

Management options

As described, historically patients have presented with OC only at late stages with advanced symptoms. In recent years, particularly in association with GORD and BO, a number of patients are being found with either pre-malignant dysplasia, or OC at a very early stage. For purposes of this discussion, management options will be discussed in the categories of superficial lesions and pre-malignant dysplasia, invasive lesions with curative intent, and treatment with palliative intent.

Superficial lesions/Pre-malignant dysplasia

Multiple options exist for superficial malignant lesions of the oesophagus, including oesophagectomy, a variety of ablative therapies, and endoscopic mucosal resection (EMR). In most cases, ablative therapies are considered for pre-malignant dysplasia, but not for superficial carcinomas. Oesophagectomy has been advocated for high grade dysplasia (HGD) and early cancers, while EMR has been used for all grades of dysplasia and early carcinomas. Ablative therapies and EMR are generally considered for one of two reasons. First, given the relatively low risk of lymphatic spread with very early lesions, and the ability to completely remove or ablate the lesion endoscopically, the inherent morbidity and mortality associated with oesophagectomy may be avoided without compromising appropriate oncologic treatment principles and survival advantage. Second, individual patients often have associated comorbidity making treatment without the risk of oesophagectomy very attractive.

Currently, a number of different ablative therapies are available (47). The goal in all of these therapies is to achieve tissue destruction to various levels of the mucosa or submucosa.

After ablative therapy, patients are generally maintained on effective acid suppression therapy while allowing normal healing of the damaged tissue. Descriptions of a number of ablative techniques as well as their relative advantages and disadvantages are summarized in Table 4.

Endoscopic Mucosal Resection (EMR) is a technique whereby portions of the oesophageal mucosa and submucosa can be removed via the endoscope. Therefore, unlike the ablative techniques, tissue is retrieved during EMR for histologic examination. Several different specific techniques exist. However, all of them have the general principle of submucosal injection of saline (with or without epinephrine or dye) to delineate a submucosal plane and facilitate resection. The involved mucosa, and varying degrees of submucosa, are then resected using electrosurgical techniques.

Newer variations of EMR, such as endoscopic submucosal dissection, have allowed the resection of progressively larger and deeper lesions. These techniques have been frequently pioneered and further developed by Japanese endoscopists (53). Although EMR was initially considered only in cases of pre-malignant lesions, or very superficial malignant lesions (i.e. m1 lesions), the indications are becoming broader, and some authors are now advocating use of EMR for m3 and even sm1 lesions, provided they are less than 25 mm in diameter and have no evidence of lymphatic invasion (54). In appropriately selected patients, EMR can achieve complete local remission in more than 90% of cases of HGD and superficial cancers, although recurrence of malignancy may occur in approximately 25% of cases (55). Bleeding complications with EMR are more common (17%), but few require specific intervention, and stricture formation occurs in 6%-23% of cases (55).

Invasive lesions with curative intent

While radiation therapy alone, or in combination with chemotherapy has been used in some cases with a small number of long term survivors, in general, surgical resection is the mainstay of

Table 4: Ablative techniques for Barrett's oesophagus and dysplasia

Technique	Description	Advantages	Disadvantages
PDT (48)	Systemic administration of a chemical photosensitizer. Light is applied endoscopically to the area generating oxygen free radicals and toxic species leading to tissue destruction	High effectiveness in 54-87%	Complications of chest pain, cutaneous toxicity (30%), fever (33%), pleural effusions (33-75%), stricture (58%) High Cost
MPEC (49)	Utilizes thermal energy with an electrical circuit between two or more electrodes on a probe tip that is passed through an endoscope	Success rates of 75% Low cost Less serious complications	Low success with long lesions Complications of dysphagia, odynophagia, chest pain x 4days in 41%
Laser therapy (47)	A variety of different lasers. Utilizes the heat of laser directed at the lesion to destroy tissue	Less serious complications	High cost Subsquamous metaplasia (90%)
APC (50)	Involves passing a monopolar electric current through ionized argon gas delivered via an endoscopic probe	Less depth of injury Effective resolution of BO (38-98.6%)	Serious complications including stricture, bleeding, perforation, and death occur in up to 24% Subsquamous metaplasia (30%)
RFA (51)	Balloon-based bipolar electrode allows for circumferential destruction of the mucosa, without direct injury to the submucosa	Elimination of non-dysplastic BO (70%)	Relatively new technique without significant studies
Cryo-ablation (47,52)	Involves the delivery of liquid nitrogen via a low pressure spray to cause tissue destruction through induced apoptosis and cryonecrosis	Ablation of BO/HGD (82%) Lower cost Less serious complications	Multiple treatments required

PDT = Photodynamic Therapy, HGD = High Grade Dysplasia, MPEC = Multipolar Electrocoagulation, APC = Argon Plasma Coagulation, RFA = Radiofrequency Ablation

therapy in cases where pre-operative evaluation indicates that cure is possible and the patient is fit for surgery. The areas of controversy include the type and "radicality" of resection, the extent of surgical lymphadenectomy, and the addition of adjuvant therapy.

Type of Surgical Resection

The three main types of surgical resection being performed today include the trans-thoracic oesophagectomy (TTO), transhiatal oesophagectomy (THO) and more recently the minimally invasive oesophagectomy (MIO). The TTO procedure can be performed via either a right or left thoracotomy, although the right-sided thoracic approach is certainly more common and accepted. The classic Ivor Lewis TTO begins with a laparotomy for gastric mobilization, followed by right thoracotomy and tumour mobilization and resection.

Gastrointestinal continuity is restored by an anastomosis between the gastric fundus and the proximal oesophagus in the apex of the right chest. The three-field approach is a variant of the TTO and begins with a right thoracotomy for tumour and oesophageal mobilization. The chest is then closed and a laparotomy and left cervical incision is performed. The oesophagus is divided in the neck and the specimen is removed via the abdomen, with the anastomosis placed in the left neck. The THO, or so-called blunt oesophagectomy, involves a laparotomy and left cervical incision only. The thorax is never opened, and the tumour and oesophagus are mobilized and resected via blunt, transhiatal dissection. The gastro-oesophageal anastomosis is created in the left cervical position. The MIO has only recently emerged as an option and is going through significant evolution. However, in general, this approach involves thoracoscopic mobilization of the tumour and oesophagus,

followed by laparoscopic gastric mobilisation and transhiatal oesophagectomy, with a left neck incision and cervical anastomosis.

In general, oesophagectomy is a relatively morbid operation with high rates of complications and mortality, compared with other surgical procedures. The most common complications include pulmonary and cardiac complications, anastomotic leak and stricture formation. The rates of these complications vary significantly between series, but overall complication rates are approximately 50%, and are summarised in Table 5. In general, most series show a higher rate of anastomotic leak for cervical anastomoses compared with intra-thoracic anastomoses. However, this fact must be considered in light of the fact that the mortality for an intra-thoracic leak is much higher than that for a leak in the cervical position. It is largely for this reason that this author's personal practice is to place all oesophago-gastric anastomoses in the neck.

Table 5: Complications following oesophagectomy

Complication	Incidence (%)
Pulmonary complications	15-57
Cardiac complications	16-26
Anastomotic stricture	6-36
Anastomotic leak	4-16
Vocal chord paralysis	0-21
Wound infection	8-10
Chylothorax	1-10
Gastric necrosis	1-4

Mortality related to oesophagectomy has been decreasing in recent years, but remains significant, with most series reporting mortality rates of 5%-10% for patients resected for cure (57). Most advanced, high-volume surgical centres are now aiming for surgical mortality to be less than 5%. However, it is interesting to note that in the USA, a recent review of the Medicare database revealed a mortality rate that ranged from 8% in high-volume centers to

23% in institutions in which the procedure was not commonly performed (58).

Significant controversy exists in the surgical literature regarding the best surgical approach to OC. On the one hand is the "radical" philosophy advocating radical, en-bloc resection of OC, to include the primary tumour and the pericardium, thoracic duct, azygous vein, intercostal vessels, bilateral pleurae overlying the tumour, and a cuff of crura if the tumour is abutting. The associated two-field lymphadenectomy involves en-bloc resection of all nodal groups between the tracheal bifurcation superiorly and the celiac axis inferiorly (59). This approach was first proposed by Logan in 1963 (60), and further expanded upon by Skinner and colleagues in the early 1980's (61). On the other hand is the view that OC tends largely to be a systemic disease at the time of diagnosis, and thus surgical intervention should be considered primarily palliative. This view is championed by Orringer and other advocates of the transhiatal oesophagectomy (62). A considerable body of evidence exists in the literature to support either view. A relatively recent meta-analysis of a decade of studies comparing TTO with THO showed no difference in 5-year survival between the two approaches, but significantly higher morbidity and mortality with the TTO approach. One year later, the same authors published one of the few prospective, randomized studies comparing the two approaches, which included "radical" lymphadenectomy. This study showed no difference in mortality between TTO and THO, a statistically higher rate of morbidity with TTO, and a non-significant trend toward improved survival in the TTO group (64). It is likely that this debate will continue indefinitely and that surgical technique will continue to be largely influenced by regional training and practice patterns. It is this author's opinion that the choice of the operation should be tailored to the individual patient characteristics, such that TTO should clearly be considered for upper and mid thoracic lesions, while THO is an option for distal lesions.

Extent of Surgical Lymphadenectomy

The question of the appropriate extent of lymphadenectomy associated with oesophagectomy is related to, but separate from the question of surgical approach. While there are significant variations in definitions in today's literature, it is generally accepted that a "two-field" lymph node dissection involves resection of the nodes and peri-oesophageal tissue below the level of the carina and the lymph node stations around the celiac trunk. When superior mediastinal lymph node dissection is added to this, it is frequently referred to "extended or total two-field lymphadenectomy" (65). However, in Japanese literature, the addition of the superior mediastinal lymphadenectomy is often assumed. The term "three-field lymphadenectomy" implies the addition of bilateral cervical lymph node dissection. The rationale for this radical lymphadenectomy is based on the finding that up to one third of patients undergoing curative resection for OC will have occult cervical lymph node metastases (59). In relation to the primary tumour location, cervical node involvement is found in 60%, 20%, and 12.5% of upper, mid, and lower third tumours respectively (64). Once again, one can find ample evidence to support the view that a more extended lymphadenectomy improves survival (66), or that a more extended lymphadenectomy does not improve survival (62). One common argument against the evidence supporting improved survival in more extended lymphadenectomies is the observation of stage migration. This refers to the situation in which the additional dissection upstages a patient. Therefore, a patient who would have been staged at a lower stage (e.g. stage I or II) is upstaged to stage IV based on the cervical lymphadenectomy. By removing this patient from the early stage patients, it then improves observed survival in this group of patients. It would also appear that the additional dissection of the three-field lymphadenectomy does increase morbidity (67), although there are significant variations between surgical centers. Currently, three field lymphadenectomy is commonly performed in Japan, while few

western centers perform this procedure with regularity. Again, it appears that this debate will continue and that practice patterns will largely be determined by training patterns and personal choice.

Adjuvant Therapy

A great deal of interest has been expressed in recent years regarding adjuvant therapy in the treatment of OC. Focus has shifted to pre-operative (so-called neoadjuvant) chemotherapy and combined chemoradiation therapy since radiotherapy alone has not proved to be effective (68). Post-operative chemoradiation therapy has also not shown promise (69). A number of randomized studies have compared neoadjuvant chemotherapy and surgery to surgery alone (70,71). Of these studies, only the MRC trial (the largest of the trials) showed a statistically significant survival advantage with hazard ratio of 0.79 and 95% confidence interval of 0.67-0.93 (71). In a similar fashion, numerous randomized studies have compared neoadjuvant chemoradiation therapy and surgery and with surgery alone (70,72). Of these studies, only two have shown significant survival advantages with a hazard ratios of 0.58 and 95% CI 0.38-0.88 (72). In many of these studies, morbidity (up to 80%) and mortality (2%-8%) associated with adjuvant treatment has been significant (73). A number of different meta-analyses have been performed attempting to combine the results of these relatively small randomized series (74,75). In general, these meta-analyses have failed to show any significant improvement in survival with adjuvant treatment. However, one of the most recent studies has demonstrated significant improvement in survival for both neoadjuvant chemotherapy and chemoradiation therapy. This meta-analysis included several non-published studies which had not been included in previous analyses (76,77). One of these studies (77) showed a marked improvement in survival favoring neoadjuvant chemoradiation therapy and surgery over surgery alone. This meta-analysis reported a hazard ratio for all-cause mortality with neoadjuvant chemoradiation therapy and surgery versus surgery alone of

0.81 (95% CI 0.70-0.93; $p = 0.002$), corresponding to a 13% absolute difference in survival at two years. This result differed slightly for OSCC with hazard ratio of 0.84 (95% CI 0.71-0.99; $p = 0.04$), than for AC with a hazard ratio of 0.75 (95% CI 0.59-0.95; $p = 0.02$). The hazard ratio for neoadjuvant chemotherapy was 0.90 (95% CI 0.81-1.00; $p = 0.05$), which indicates a two-year absolute survival benefit of 7%. This benefit was significant for AC with a hazard ratio of 0.78 (95% CI 0.64-0.95; $p = 0.014$), was not statistically significant for OSCC (75). This result has led some to consider neoadjuvant treatment as the standard of care for OC (78). While it seems clear that patients who achieve a complete pathologic response to neoadjuvant therapy appear to have improved survival (79) and that neoadjuvant therapy may downstage patients and improve rates of complete surgical resection (80), it is not entirely clear what group of patients will ultimately benefit from neoadjuvant therapy. A recent study combined a meta-analysis of survival benefit with decision analysis evaluating relative risk for mortality and quality of life. This study demonstrated a very small increase in quality adjusted life years for neoadjuvant chemoradiation therapy and surgery compared with surgery alone, and concluded that surgery alone may be the preferred treatment in advanced OC (74). On a global basis, it appears that neoadjuvant therapy will likely become standard of care in resource rich areas (such as westernized countries where AC is more common), while surgical resection alone will remain the cornerstone of treatment for much of the world where OSCC predominates.

Treatment with palliative intent

Recognizing that less than one third of patients with OC are candidates for operative treatment with curative intent, it is obvious that palliation will be the goal in the majority of patients with OC (81). Palliation is defined as the easing of symptoms without curing the underlying disease. Since the majority of the serious symptoms related to incurable OC are related to oesophageal obstruction (i.e. dysphagia and weight loss), the goals of palliation are generally

directed toward overcoming oesophageal obstruction and improving dysphagia. Chest and abdominal pain are generally managed with narcotic and non-narcotic pain medications, while bleeding is particularly difficult to palliate without resection.

Virtually all of the ablative techniques previously described have been used for palliation of advanced OC (82-86). Additionally, chemotherapy, radiation therapy, brachytherapy, direct ethanol injection, endoscopic intubation or stenting, and palliative surgery have all been utilized in the treatment of OC not amenable to resection (87-92). The simple fact that so many options exist would certainly seem to imply that there is no clear consensus on the most effective palliative technique. However, several observations should be made. When one talks of palliative surgical treatment of oesophageal cancer, the most common situation is that of discovering that a tumour is unresectable or discovering the presence of metastases at the time of attempted surgical resection. The literature is in fact nearly absent of studies looking specifically at surgical palliation which was planned pre-operatively, with only one clear study in this area. This is due to the inherent difficulty in surgically treating OC with anything less than resection. Partial resection or debulking procedures are nearly always fraught with complications and mortality. It is this author's opinion that during surgical exploration for intended resection, if the surgeon does not feel reasonably sure that at minimum an R1 resection can be carried out (in which all gross disease is removed)—and preferably an RO resection (in which microscopic margins are negative), then no resection should be performed, and an alternate form of palliation should be pursued. Surgical bypass is difficult to perform due to the anatomic position of the oesophagus, and carries a very high rate of morbidity and mortality.

While chemotherapy alone has not been shown generally to provide significant palliation, chemoradiation therapy, or radiation therapy alone seems to provide temporary improvement in swallowing in appropriately selected patients. Radiotherapy has been utilized particularly in proximal oesophageal lesions, where other palliative treatments are

more difficult. All of the ablative techniques used for palliation have met with some success. However, common to all of these techniques is the need for re intervention, with dysphagia often recurring as soon as one month after treatment (94). In patients with non-curable OC, survival is measured in weeks and months, and so providing palliation with as few treatment sessions as possible is certainly preferable.

Endoscopic intubation or stenting has become more common in recent years, and is now the most common technique utilized for palliative treatment of advanced OC (91). In earlier years, stenting was performed with a variety of plastic, metal, or wooden prostheses. A nice review of the history of stenting is provided by Mitton and Ackroyd (91). Common to all of these prostheses was the difficulty in insertion often requiring general anesthesia and laparotomy. Additionally, these fairly rigid, smooth prostheses had a very significant rate of migration (95). The introduction of self-expanding metal stents (SEMS) in 1983 heralded the beginning of a new era in the use of stents (96). Since that time, the use of SEMS has virtually replaced rigid endoprotheses in much of the world. The procedure of inserting SEMS is generally performed with conscious sedation. Although fluoroscopy may be helpful in placement, it is certainly not required (97). Currently, SEMS with a plastic coating are most commonly used to reduce the incidence of tumour ingrowth through the interstices of the stent. Stent placement can be performed as an outpatient procedure, and combined with dilation, provides immediate improvement in dysphagia. Early or immediate complications

are generally related to dilation or misplacement and include perforation and airway compromise. Whereas oesophageal perforation is generally considered a surgical emergency, perforation of an unresectable malignancy can usually be treated effectively with placement of a coated SEMS (98). Later complications of SEMS include chest pain, stent migration, stent occlusion, and bleeding. Morbidity and mortality is clearly lower with SEMS than with rigid prostheses (99). While some have reported complications as high as 16%-45% and mortality rates as high as 9%, (99). Others have reported 5% late complications and 0% mortality with very good reduction in dysphagia until death (100).

Outcome/survival

On a global basis, overall 5-year survival of OC is significantly less than 10% (29,101). In the USA, the American Cancer Society estimated that there would be 11,260 new cases of OC in men, and 3,290 cases in women. In the same year they estimated that 10,730 men and 3,040 women would die of the disease, indicating very high case fatality (7). In the USA, 5-year survival estimates for OSCC has improved from 4.6% in 1974-1979 to 12.3% in 1992-1997, while AC has seen an improvement from 5.3% to 13.7% for the same time period (102). In patients undergoing potentially curative resection, overall 5-year disease-free, all-stage survival is approximately 30% with median survival of 21 months (64,103). This is, of course, highly dependent upon the stage of the disease at the time of diagnosis and treatment, and is summarised in Table 6.

Table 6: Survival following oesophagectomy for oesophageal cancer

Stage	5-year survival (%)	Median Survival
0	68-100	NR*
I	42-78	44-78 months
II	26-72	23-59 months
III	15-39	14-53 months
IV	0-27	7-20 months

*NR: Not Reported

Source: 59, 103,106

The most important prognostic factors for patients undergoing surgical resection for OC appears to be the ability to carry out an RO resection, and the presence (and absolute number) or absence of involved lymph nodes. There are, however, a number of other factors which have prognostic significance, and these are summarised in Table 7.

Table 7: Prognostic factors following oesophagectomy for oesophageal cancer

Weight loss before operation
Duration of symptoms
Tumor location (proximal tumors indicate worse prognosis)
Radicality of resection (i.e. RO vs. R1 vs. R2)
Pathologic Stage
Presence and absolute number of involved lymph nodes
Grade of differentiation
Neural invasion
Vascular invasion

Source: 103,104,107

Oesophageal cancer in Kenya

Relatively few published reports exist regarding the situation of OC in Kenya. The earliest published report is from a colonial officer in 1935 who reported several cases of OC (108). Nevill then reported 79 cases of OC from what is now Kenyatta National Hospital in Nairobi (109). Ahmed and Cook published several case-series from 1966 to 1971, with OC accounting for 25%-30% of all cancers (110,111). These reports indicated that in certain regions of central and west Kenya, OC ranked as the first or second most common cancer. In 1978, Gatei and colleagues reported OC as the fifth most common cancer nationwide, accounting for 5.4% of solid malignancies (112). This study reported an overall incidence for the country of 0.67 per 100,000 per year. This would imply that Kenya is an area of extremely low incidence of OC. Further, they reported the incidence of OC among the Kalenjin tribes at 0.2 per 100,000 per year. Unfortunately, these rates were based solely

on cases that were histologically confirmed at the central pathology laboratory in Nairobi and reported to the Kenya Cancer Registry. Since most of the hospitals did not have the resources to perform histological studies, these numbers clearly grossly underestimated the actual incidence. White et al reported their experience with OC in southwestern Rift Valley Province from 1989 to 1998 (5). In our series, OC was the most common malignancy for both men and women, accounting for 19% of all malignancies. The male to female ratio was 1.4 to 1 with OSCC accounting for 90% of cases. The median age at diagnosis was 54 for men and 56 for women. There was a significant proportion of patients presenting at a young age, with 11% of cases aged 30 years or less, with the youngest patient presenting at age 14. This is quite a striking finding which has not been reported in any other place world-wide. Even in areas of extremely high incidence of OC, such as Linxian, China, cancer cases in people aged 30 years or less are extremely rare, with a proportion of less than 1% (113). In western countries, such as the USA, this proportion is even lower at 0.18% (10).

More recently, Wakhisi et al. described the experience with OC at Moi Teaching and Referral Hospital in Eldoret (4). They described OC as the most common cancer in men, and the third most common malignancy in women. In this series, OC accounted for 13.8% of all malignancies, with OSCC accounting for 90% of cases. The male to female ratio was 1.5 to 1. The mean age at diagnosis was 59 years, with 10% of cases less than 40 years old. The youngest patient in the series was 20 years old. This series attempted to describe an incidence rate of more than 30 per 100,000 per year for men, with approximately half of that for women. However, it is very unclear how this incidence was calculated. Recognizing the inherent difficulty in establishing valid incidence rates (i.e. assuring that all cases are reported, and knowing the number of the total population at risk), it is probably wiser not to report incidence rates. Elsewhere in Kenya, the Nairobi Cancer Registry reported cancer cases registered during 2000-2002. They found that OC was the most common single site cancer among men at 10% of all malignancies, while it was third most

common (behind breast and uterus/cervix) accounting for 4.4% of all malignancies (114).

It is clear that OC is one of the most common cancers in Kenya. Whether or not specific geographic sites of very high incidence within the country exist is not clear at this point. What is clear to anyone who sees OC patients in Kenya with regularity is that the vast majority of patients are presenting at a very late stage. For most patients, surgical resection for cure is not an option due to either very late stage disease, very poor overall condition of the patient, or both. Very little has been done to identify patients at early stages of the disease, although at least one study has been reported looking at the feasibility of a screening program for OC in Kenya (115). At Tenwek Hospital, patients with OC undergo upper GI endoscopy, chest radiograph, abdominal ultrasound and HIV testing. Patients with upper oesophageal lesions also undergo bronchoscopy. The exclusion criteria for surgical resection are summarized in Table 8. Those found to have no contraindications for surgical resection (generally approximately 10% of all OC patients seen) are offered surgery with curative intent. The remaining 90% of patients are usually offered stenting with self-expanding metal stents. In general, it is difficult to arrange either adjuvant or primary chemotherapy or radiation therapy for the majority of OC patients in Kenya. Therefore, either surgical resection alone or stenting alone are the treatments most often available for patients with OC.

A great deal of work remains to be done regarding OC in Kenya. These projects include clarifying epidemiologic trends and patterns, examining potential risk factors and etiologies, further defining the role of screening programs and early intervention, clarifying the role of surgical and adjuvant treatment, and improving the availability of palliative care for the many cases of advanced OC which will surely continue to present to many health care workers throughout the country. There is a tendency to become somewhat fatalistic when dealing with this disease in our context. This has led some to question whether there is any hope at all for making progress regarding OC (12). However, with appropriate work and diligence, there

is tremendous potential to make significant contributions toward the understanding of this disease, and to provide preventative, curative, and palliative care to a very large number of people in need.

Table 8: Contraindications to oesophagectomy at Tenwek Hospital

Absolute	Contraindications
Distant Metastases	Age > 80 years
Tracheo-oesophageal fistula	Extreme cachexia/ malnutrition
Phrenic or recurrent laryngeal nerve palsy	Poor exercise tolerance
HIV positivity	
Relative Contraindications	

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