

Oesophageal Cancer Management guidelines for Uganda

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Introduction

In Uganda, Oesophageal cancer is the third commonest malignancy in men and the fourth commonest in women, with an age standardized incidence rate of 13 - 14 per 100,000 of the population^{1,2}. It remains a challenging tumour to treat with many patients presenting with advanced disease^{3,4}. The currently accepted most appropriate approach to the management of Oesophageal cancer and that deemed available and accessible in Uganda is outlined in this document. Members of the Uganda Cancer Working Group have compiled it.

Presenting Clinical Features

There are early but few indicative warning symptoms indicative of the development of Oesophageal cancer. They should be treated as suspicious and merit serious assessment, with full history, physical examination and referral for possible investigations. They include, persistent heartburn/reflux, belching, cough, ear pain and unexplained persistent chest pain^{5,6,7,8}. The late symptoms and signs which are the more usual presentation of advanced disease include progressive dysphagia, choking sensation, anorexia, weight loss, drooling of saliva, odynophagia. and symptoms of metastatic disease e.g. Right upper chondrial pain^{3,5,6,9}

Diagnostic Investigations

The most appropriate investigations for diagnosis include barium swallow and upper gastrointestinal endoscopy. In early disease, double contrastbarium studies may demonstrate irregular mucosal pattern^{3,10}. In late disease, the barium swallow will typically show narrowing of the lumen of the oesophagus with restriction of barium flow, proximal dilatation and the classical 'shouldering' sign and a 'rat tail' appearance distally.

Upper Gastrointestinal Endoscopy¹¹ provides direct visualization of the oesophageal mucosa and allows biopsy of any suspicious areas, evaluation of anatomical extent of gross disease and assists in planning therapy. Abnormalities that indicate possible underlying malignancy include hyperemia, mucosal irregularity, ulceration and / or a frank mass with constriction of the oesophageal lumen. Balloon cytology (where available) allows mucosal samples to be taken in symptomatic patients where no mucosal irregularities are identified. Although barium swallow and upper GIT endoscopy are most appropriate, they are costly for the average Ugandan and only accessible in some public referral and private hospitals in the country.

Pathology

Minimum information^{12, 13, 14} required from biopsy report include:

- Dysplasia - mild, moderate or severe
- Histological subtype - e.g. squamous cell carcinoma, adenocarcinoma, or other more unusual subtypes e.g. carcinosarcoma, melanoma, Kaposi's sarcoma.
- Tumour grade - well, moderately and poorly differentiated.

And where possible (usually from operative specimens):

- Depth of penetration and involvement of adjacent structures: = Tumour (T) staging
- Lymph node involvement: = Nodal (N) staging
- Distance of tumour from resected margins.

Staging Investigations^{3, 15, 16, 17}

The staging system preferred is the UICC Staging system¹⁸ (see appendix I)

Information required to thoroughly stage the tumour is supplied by:

- Clinical evaluation - history and examination
- Chest physicians assessment / physiotherapy review if for surgery
- Baseline blood tests including full Haemogram, renal and liver function tests
- Barium swallow - to establish tumour length in cases where endoscopy is unable to pass, to assess any distortion of the axis of the oesophagus and to demonstrate any fistula formations
- Plain Chest Radiograph - to exclude distant metastases (especially lung)
- Abdominal Ultrasound scan - to exclude distant metastases (when CT is unavailable)
- Fiber optic bronchoscopy for upper / middle third lesions to exclude spread to adjacent structures
- Endoluminal ultrasound (where available) - to establish depth of invasion and lymph node involvement
- CT scans of the thorax and upper abdomen (when available)
- MRI (when available)
- PET Scan

Management of early stage disease^{3, 10}

Surgery

For patients who are appropriately staged, this remains the best chance of cure and should therefore always be considered. The criteria for a radical resection considers the following points: Good nutritional status, ECOG performance status 0,1 or 2 (see Appendix II), Adequate cardiac, pulmonary and renal function and tumour <3cm in length (the absolute maximum being 5cm).The other factors considered are that there are no signs of local spread to adjacent structures, and no signs of distant metastases. It may be considered inappropriate if the patient is more than 60years old, but always case dependent.

Facilities should be available for appropriate post-operative care (this includes Intensive care, physiotherapy and hyper alimentation supplements). Keep the patient nil by mouth for 4 days (greatest risk of leakage), then start oral sips. The surgical approach will be decided by the Surgeon and is dependent on site of primary (see Appendix III).

Neoadjuvant Chemotherapy^{19, 20, 21, 22}

There is now evidence of chemo responsiveness in esophageal cancer. In the neoadjuvant setting, for patients with an operable tumour who are fit enough for chemotherapy (normal cardiac, renal and hepatic function) and who have the resources for financing the treatment, they should be referred to the oncologists for consideration of pre-operative chemotherapy with Cisplatin and 5-Fluorouracil. For criteria for referral and chemotherapy details, (appendix IV).

Chemoradiotherapy^{23, 24, 25}

Patients who are unsuitable for surgery e.g. due to high anesthetic surgical risk from poor cardiac or respiratory function, but suitable for radiotherapy given with curative intent and who fulfill the same criteria for chemotherapy as stated above (adequate renal, liver, bone marrow

and cardiac function; and who have resources) consideration should be made for chemo radiotherapy as the best treatment option 3. Appendix V gives details of criteria for referral and chemo radiotherapy.

Radiotherapy^{26, 27, 28, 29, 30}

When patients are unsuitable for surgery, they may be suitable for radiotherapy alone given with curative intent. This will be with a 6-week course of external beam radiotherapy, treatment given on a daily basis. (Appendix VI).

Management of advanced disease / Palliative care^{26, 27, 28, 29, 30}

For patients with metastatic or locally advanced disease where cure is deemed impossible, palliation of symptoms is the priority. Symptoms frequently needing treatment include dysphasia and Odynophagia. the approach to each is outlined here under:

Dysphagia

This is one of the main symptoms of advanced oesophageal carcinoma. Dysphagia refers to difficulty in swallowing. Dysphagia is initially to solids when the oesophageal lumen is reduced to 12 mm or less progressing to dysphagia to liquids, and possibly total obstruction with pooling and drooling of saliva³⁰ (see appendix VII for dysphagia scoring system). Aspiration of pooled oesophageal contents can lead to choking and possibly aspiration pneumonia.

Management options for dysphagia include:

- Bougie dilatation alone or used prior to stenting
- Stenting³¹ with expandable metal mesh stent, Celestine tube or 'Mulago' tube or
- Palliative radiotherapy³²
- Pharmacological measures

(Appendix VIII)

Mulago tube (Oesophageal intubation³³)

This is a modified Celestine tube and requires a general anesthetic and laparotomy for insertion. Many patients develop significant reflux symptoms after insertion and are thus given the following advice:

- Eat small frequent meals.
- Remain upright for at least 1 hour after eating
- When sleeping, raise the head end of the bed
- Avoid heavy physical work, which may increase the intra-abdominal pressure. Distal migration of the tube is a recognized complication of this tube insertion^{30, 34}

Palliative Radiotherapy³⁵

This is delivered with external beam radiotherapy. The dose and fractionation will depend on the performance status of the patient, prognosis and length of field to be irradiated (Appendix VI).

The use of Brachytherapy treatment with endoluminal sources may become available as a treatment option in the future in Uganda³⁶.

Pharmacological measures

The above surgical, radio therapeutic and intubation interventions are important and are aimed at maintaining the oesophageal lumen, to maintain swallowing of food. In addition some drug measures can help. Dexamethasone (7-day trial) 4-12 mg in the morning, with either Nystatin 100,000 units/ ml, 1-2 ml tds, or Ketoconazole 200 mg daily for 7 days.

Oral drugs may not be possible when there is total obstruction of the lumen.

Odynophagia – Painful swallowing

Discomfort or pain may be felt retrosternally, in the neck or between the shoulder blades

together with dysphagia. It ranges from mild to moderate or severe pain. Management options maintain oesophageal lumen as above and WHO analgesic ladder for somatic pain^{37, 38, 39, 40} (See Appendix IX)

Reflux - with or without heartburn

Management options:

- Position patient upright to eat, and maintain position for at least 15 minutes (if no tube) after feeding Antacids e.g. magnesium trisilicate 10mls tds
- Dietary advice:
 - Frequent small meals
 - Position as above, with feeding assistant facing the patient so that they can see each other.
 - Food should be cooked until soft and mashed or mixed with soup.
 - Patient should be advised to eat slowly, and to take sips of water in between mouthfuls.

Drooling of saliva

Anticholinergic drugs can help relieve excessive salivation or drooling:

- Hyoscine Butyl bromide SC. 10 - 20 mg bd - tds
- Amitryptilline 12.5 mg od or bd orally
- Antihistaminic antiemetics e.g. Cyclizine 50 mg tds subcutaneously or orally.

Choking sensation

Choking sensation⁴¹ can be reduced by an antitussive e.g. oral morphine 5mg/5ml, 2.5 ml 4 hourly.

Anorexia

This is due to the local effects of dysphagia and odynophagia in addition to the systemic effects of advanced cancer⁴². Appetite can sometimes be improved by the use of low dose steroids, e.g Dexamethasone 2mg orally od or Prednisolone 10mg orally od. Insertion of a feeding gastrostomy tube or a percutaneous entero-gastrostomy (pEG) can assist in the nutritional supportive management of patients with severe dysphagia⁴³. It is also useful to build up the strength of patients prior to more intensive planned treatment such as surgery or higher dose radiotherapy.

Psychosocial and Spiritual aspects^{44, 45}

Palliative care aims to achieve the best quality of life for patients and their families with control of not only pain and other physical symptoms but also psychological, social and spiritual aspects of their health. Many aspects of palliative care are applicable early in the course of a patient's illness in conjunction with their anticancer treatment.

Psychosocial issues:

Anxiety

Both patient and relatives may be anxious that the patient will starve to death. Efforts should be taken as above to maintain the oesophageal lumen. Counseling includes distinguishing between eating for nutritional purposes and for pleasure. When the former goal is no longer possible, the patient can still chew their favourite food and spit it out. Acute anxiety and agitation in the last few hours of life may require sedation with diazepam.

Low Self Esteem

Drooling, dependency on others for feeding, food remaining on clothes, as well as loss of employment and other social issues may all contribute to low self-esteem. Independence should

be encouraged as much as possible, and occupational therapy can help in reassessment of skills such as those required for activities of daily living. Counseling can help the patient accept new levels of dependency without loss of self-esteem.

Sexuality

Prolonged illness, weakness and low self-esteem may all affect sexuality. Health workers should be aware of this, and avail opportunities for open, honest discussions for the patient and partner.

Spiritual issues:

Fear of Death

This is a common and natural part of life and the dying process. The patient and family may find comfort in prayer and referral for spiritual counseling from their religious leader of choice.

Conclusion

Following the above discussion, the mainstay of treatment is Surgery, Radiotherapy, and Chemotherapy, while we endeavor to explore the strategy of primary prevention from an understanding of the aetiology of this malignancy .. Update of these guidelines will be ongoing.

Appendix I - International 'Union against Cancer (UICC) Staging System Tumor, Node, Metastasis (TNM) System for Oesophageal Cancer

Primary tumor

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor invades lamina propria or submucosa
- T2: Tumor invades muscularis propria
- T3: Tumor invades adventitia
- T4: Tumor invades adjacent structures

Lymph node

- NX: Regional nodes cannot be assessed
- N0: No regional lymph node metastasis
- NI: Regional lymph node metastasis

Distant metastasis

- M0: No distant metastasis
- M1: Distant metastasis (including positive celiac nodes)

Tumor Stages for Oesophageal Cancer

- Stage 0: Tis N0 M0
- Stage I: T1 N0 M0
- Stage IIA: T1 N0 M0; T2 N0 M0
- Stage IIB: T1 N1 M0; T2 N1 M0
- Stage III: T3 N1 M0; T4 Any N M0
- Stage IV: Any T Any N M1

Appendix II- Eastern Cooperative Oncology Group (ECOG) Performance Status

- 0 Asymptomatic
- 1 Symptomatic; fully ambulatory
- 2 Symptomatic; in bed less than 50% of the day
- 3 Symptomatic; in bed more than 50% of the day, but not bedridden
- 4 Bedridden

Appendix III - Surgical Approach according to site

Site	Procedure
Cricoid	3 stage operation; laparotomy, thoracotomy and neck incision; generally results as good as when radiotherapy is used alone
Upper 1/3	2 stage operation; laparotomy and right thoracotomy approach; usually presents late so <10% respectable
Middle 1/3	Right thoracotomy approach; oesophagogastrectomy and pull-up; any problems with strictures / DU / scarring, needs jejunal or colonic interposition
Lower 1/3 sometimes	1/5 of the stomach respected in addition to the oesophageal cancer; splenectomy performed as well due to the proximity of splenic vessels

Appendix IV - Referral criteria for Neoadjuvant chemotherapy

Criteria for referral to the oncologists for consideration of neoadjuvant / pre-operative chemotherapy prior to undergoing attempted curative resection of oesophageal tumour: Tumour respectable with curative intent, as deemed by the appropriate surgeons. Should have completed the following tests: Endoscopy, Barium swallow, CT scan - when available, Histological Confirmation of cancer

No evidence of metastatic disease, as evidenced by normal results from the following tests:

Chest Radiograph, Ultrasound scan of the abdomen

Fitness for chemotherapy with adequate renal, liver, bone marrow and cardiac function with the following normal completed investigations: RFTs, LFTs, CBC and film comment ECG and echocardiogram.

Chemotherapy Regimen

Cisplatin: 80mg/m², IV over 4 hours with pre and post hydration, Day I, 5-Fluorouracil: 1g/m², IV bolus, Day 1-4

Adjuvants

Ondansetron 8mg orally bd for 2days with each dose of Cisplatin

Dexamethasone 8mg IV bolus and 8mg bd orally for 2 days

Metaclopramide 10mg IV bolus, then 10mg orally tds as required

This is repeated at 3 weeks for 2 cycles of treatment and then the patient should be scheduled for surgery at 3-6weeks after 2nd dose.

Appendix V - Chemoradiation

Criteria for referral the same as for neoadjuvant chemotherapy - see Appendix III

Radiotherapy dose - 50 Gy in 25 daily fractions of 2 Gy each

Concurrent chemotherapy

Cisplatin: 80mg/m², IV over 4 hrs with pre and post hydration, Day I & 28

5-Fluorouracil, 1g/m², IV bolus, Day 1-4 & 28-31

Adjuvants

Ondansetron 8mg orally bd for 2/7 with each dose of Cisplatin or Metaclopramide 10mg

IV bolus, then 10mg orally tds as required

Dexamethasone 8mg IV bolus and 8mg bd orally 2/7

Appendix VI- Radiotherapy Details

Radical/curative Radiotherapy

Criteria for curative radiotherapy for oesophageal tumour:

ECOG performance status 0,1 or 2

Non-metastatic disease

Localised tumour < 5cm in length

Squamous cell histology

Age < 70 years

Adequate nutritional/medical status

Dose and fractionation schedules

64Gy in 32 daily fractions of 2Gy each when radiotherapy given alone 40Gy

given by anterior and posterior fields

24Gy given by right and left laterals fields

Palliative Radiotherapy

Dose and fractionation depends on performance status / fitness of the patient, prognosis and length of field to be irradiated. Options include:

8Gy in a single fraction

20Gy in 5 daily fractions of 4Gy each

30Gy in 10 daily fractions of 3Gy each

Intraluminal Brachytherapy is also being considered as a potential future possible treatment.

Appendix VII - Dysphagia Scoring 2

0 Able to swallow all solids without difficulty

1 Difficulty with swallowing some hard solids or particular foods

2 Able to swallow a semi-solid or liquid diet only

3 Able to swallow a liquid diet only

4 Unable to swallow liquids or saliva

Appendix VIII - Therapy option according to site and severity of obstruction

Site	Severity	Treatment
Upper third	Grade 4	Radiotherapy
	Grade < 3	Dilation & stenting with or without radiotherapy
Middle third	Grade 4	Dilating & stenting if possible, otherwise Radiotherapy
	Grade < 3	Dilation & stenting with or without Radiotherapy
Lower third	Any grade	Stenting often with the Mulago tube with or without radiotherapy

Appendix IX - WHO Analgesic ladder

Step 1 Paracetamol tabs or syrup 1g tds and / or

Step 2 Codeine phosphate 30 mg tds or

Step 3 Liquid morphine 5 mg / 5 ml; Starting dose: 5 ml 4 hourly with 10 ml nocte if adult of normal weight (> 50 kg), if moderately to severely wasted, then start with 2.5 ml 4hrly with 5 ml nocte. If pain persists, the dose of morphine can be increased slowly to titrate with pain. Always prescribe a laxative together with opiates (Step 2 & 3), as they cause constipation, except if the patient has diarrhoea. E.g. bisacodyl 10mg nocte.

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