

MANAGEMENT OF OESOPHAGEAL CARCINOMA: A PRAGMATIC APPROACH FOR DEVELOPING COUNTRIES

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1. INTRODUCTION

Oesophageal carcinoma continues to have a poor prognosis world-wide⁽¹⁾. Despite improved diagnostic techniques and protocols, the majority of patients still present with advanced disease. The advent of TNM classification and disease staging revealed that prognosis correlates with the stage⁽²⁾. This article examines the evidence for current practices in the management of oesophageal carcinoma and suggests pragmatic solutions for the care of these patients in developing nations.

2. METHOD OF CONDUCTING LITERATURE REVIEW

Accessing the University of Toronto library system with a Ptolemy account, the Ovid Medline (R) database was searched using the Key words “Oesophageal” and “Carcinoma”; the search was limited to English language review articles. The latest review article obtained from this search cited a paper published in 2005. Ovid Medline (R) was searched again using the key words “oesophageal” and “carcinoma”; this search was limited to abstracts of all English language articles published between January 1st 2004 and February 1st 2007. Combined searches utilizing this search result and the key words “diagnosis” or “staging” or “treatment” were then launched using the same data base. Articles of interest were read in their entirety and cited articles were located using the Ovid Medline (R) name search.

3. EPIDEMIOLOGY

Early research revealed that most oesophageal carcinomas were of the squamous variety, however, more recent western literature indicates that the incidence of adenocarcinoma is rising^(3,4). The following risk factors for oesophageal carcinoma have been identified: Age, alcohol, smoking, high starch diet without fruit and vegetables, male sex, Barrett's oesophagus, black race (squamous cell carcinoma) and white race (adenocarcinoma)^(5,6). The incidence of squamous cell carcinoma in black males in the United States (US) is five times higher than that of white male: 18.6 per 100,000 and 3.0 per hundred thousand respectively⁽⁷⁾. Oesophageal cancer is the leading cancer amongst males in Kenya (90 % are squamous cell carcinomas and 10% are adenocarcinomas)⁽⁸⁾ and is ranked 2nd in Uganda⁽⁹⁾.

4. SURGICAL ANATOMY

The oesophagus is a muscular tubular structure approximately 25 centimeters long (in the average adult) extending from the hypopharynx to the stomach. The cervical portion extends from the lower border of the cricoid cartilage to the thoracic inlet. The thoracic portion may be divided into "thirds". The upper third extends from the thoracic inlet to the carina, the middle third extends from the carina mid-way to the gastro-oesophageal (GE) junction and the lower third extends from the midpoint between the GE junction and the carina to the GE junction. The esophageal wall is comprised of a mucosal layer, a muscular layer and an adventitia instead of a serosa.

A freely anastomosing network of lymphatics facilitates lengthwise tumour dissemination. The upper third drains to the cervical nodes, the middle third to the para-tracheal and para-oesophageal nodes, and the lower third to para-aortic and celiac axis nodes.

5. DIAGNOSIS

The typical African patient with squamous cell carcinoma of the oesophagus is a male aged between 50 and 60 years of age⁽⁸⁾. He usually has a history of excessive alcohol use or smoking. The patient with adenocarcinoma may have an additional history suggestive of reflux disease.

The majority of patients will present with a history of progressive dysphagia (about 6 months duration) and may have unintentional weight loss of more than 10 percent of their normal body weight. Although most patients will have an unremarkable physical examination, it is important to be on the "look-out" for features that may suggest metastatic disease: hepatomegally, supraclavicular lymphadenopathy, pleural effusions, voice changes and ascites.

There are several diagnostic protocols recommended in the literature. Most involve a combination of diagnostic modalities in one way or another. The ultimate aim is to provide a histological diagnosis and assign a stage to the disease as this facilitates treatment.

6. STAGING AND PROGNOSIS

Traditional diagnostic imaging methods continue to be useful in the management of patients. Barium swallows showing hold-up of barium, shouldering and proximal dilatation are very suggestive of carcinoma of the oesophagus and prompt the performance of flexible (or rigid) oesophagoscopy to obtain a histological diagnosis. Abdominal ultrasound can be quite useful at detecting hepatic metastases; however, CT scan is superior in this respect.

Investigations to stage oesophageal cancer reveal advanced disease with widespread metastasis in one third of cases. These reduce the need for explorative procedures where unresectable disease, such as liver metastasis, is found⁽¹⁰⁾.

Carcinoma of the oesophagus is staged using the TNM system; the various TNM designations are shown in table 1⁽¹¹⁾.

T PRIMARY TUMOUR	
Tis	Carcinoma in situ
T1	Invades lamina propria or submucosa
T2	Invades muscularis propria
T3	Invades periesophageal tissue
T4	Invades adjacent structures
N REGIONAL LYMPH NODES	
N0	No regional node involvement
N1	Regional node involvement
N1-4	More distant node involvement
M DISTANT METASTASIS	
M0	No distant metastasis
M1	Distant metastasis

Table 1. TNM designations

The corresponding stages of esophageal carcinoma are shown in table 2.

STAGE	TNM DESIGNATION
0	Tis N0 M0
I	T1 N0 M0
IIA	T2-3 N0 M0
IIB	T1-2 N1 M0
III	T3 N1 M0, T4 any N M0
IV	Any T Any N M1

Table 2. Disease Stage with corresponding TNM designation.

An elegant study by Wakelin et al showed that endoscopic ultrasound (EUS) was the most accurate modality at detecting early (T1 and T2) tumor (62% accuracy) and

locoregional nodal disease (72% accuracy), spiral CT scan was more accurate than EUS at detecting T3 and T4 tumors (accuracy; 94% and 88% respectively), laparoscopic ultrasound (Lap US) was more accurate than spiral CT scan at detecting distant abdominal metastasis (accuracy; 81% and 72% respectively) ⁽¹²⁾. Meta-Analysis has shown that positron emission tomography (PET) using the tracer Fluorine Fluorodeoxyglucose (FDG) is the most sensitive method of detecting distant hepatic metastases (sensitivity 90%). However its routine use in clinical practice is prohibited by its cost ⁽¹³⁾.

Fiber optic bronchoscopy has been suggested by some to be an important staging procedure in patients with tumour above the carina ⁽⁶⁾. Argyros found bronchoscopy to have a low yield in patients without pulmonary symptoms ⁽¹⁴⁾.

Magnetic resonance imaging (MRI) is similar to CT scan in its ability to detect hepatic metastases. It is better at determining tumour depth than CT, but inferior to it at detecting pulmonary metastases ⁽¹⁵⁾.

It becomes clear that to obtain the most accurate pre-operative stage, one should combine diagnostic modalities ⁽¹²⁾.

As disease stage increases, prognosis worsens ⁽¹⁶⁾. Although the TNM based staging system is predominantly used, it has been argued that the Dukes' staging system is simpler, clearer and more accurate ⁽²⁾. There continues to be pressure to modify the current TNM staging system so that it better predicts prognosis.

The number and extent of lymph node involvement by tumor have been shown to be independent predictors of prognosis ⁽¹⁷⁾. There are conflicting reports in the literature regarding tumor length as a prognostic predictor ^(18,19).

7. TREATMENT OPTIONS

It is generally accepted that patients with oesophageal carcinoma fall into three treatment categories: 1.surgery for cure (stage I and II), 2. palliative surgery (stage III) and 3. non-operative treatment (stage IV) ^(20,21). Some surgeons still operate on patients with stage IV disease ⁽²²⁾.

Curative resections should not be attempted on a patients with a FEV₁ of less than 1.25 and an ejection fraction of less than 40% as the risk of postoperative death from respiratory and cardiac failure, respectively, out-weigh the benefits derived from a curative resection.

The surgical outcomes of T3 tumours are particularly poor ⁽²³⁾. This has generated significant interest in adjuvant and neo-adjuvant treatment. In theory, neo-adjuvant chemo-radiotherapy can down-stage tumours. This might convert a palliative surgical prospect to a curative one ⁽²⁴⁾. Neo-adjuvant chemo-radiotherapy might enhance the

likelihood of R0 (complete resection of tumour with uninvolved margins at histology) resection⁽²⁵⁾. Smaller tumour length has been shown to be predictive of a greater response to chemo-radiotherapy⁽²⁶⁾. The toxicity of neo-adjuvant chemo-radiotherapy has been a concern, however, the postoperative quality of life in patients subjected to neo-adjuvant chemo-radiotherapy was found to be similar to those who had surgery alone⁽²⁷⁾.

In practice only 1 out of 7 RCTs conducted so far could detect any survival benefit for neo-adjuvant chemotherapy and only 1 out of 8 RCTs showed a positive survival impact of neo-adjuvant chemo-radiotherapy; adjuvant chemoradiotherapy does not improve survival⁽²⁰⁾. One meta-analysis of RCTs of preoperative chemo-radiotherapy demonstrated improvement in 3 year mortality rates over surgery alone, however they concluded that further RCTs were required to substantiate their findings⁽²⁸⁾. A RCT carried out since this meta-analysis revealed no survival benefits conferred by neo-adjuvant chemo-radiotherapy⁽²⁹⁾.

There is some evidence to suggest that definitive radiotherapy may be as effective as surgery for Stage I squamous cell carcinoma⁽³⁰⁾ and that definitive chemo-radiotherapy (i.e. chemo-radiotherapy without surgery) may be as effective as surgery alone for stage III squamous cell carcinoma and may even be considered as alternative treatment^(31,32).

The accepted standard of care for stage I disease is surgical excision of tumour (oesophagectomy) accompanied by a 2 or 3 field lymph node dissection. The same standard of care assigned to stage I disease is applied to stage II disease. For stage III disease, neo-adjuvant chemo-radiotherapy has been added to the standard of care for stage I and II disease. Chemotherapy remains the main stay of treatment for stage IV disease.

8. SURGICAL APPROACH

There are several surgical approaches, the choice of approach depends on factors such as tumour site and surgeon experience and training.

8.1. Left Thoraco-Abdominal Approach

Primarily used for tumours at the oesophago-gastric junction (OGJ).

8.2. Abdominal and right chest (Ivor Lewis/ Two stage)

This approach is best suited for lesions of the mid and distal esophagus (i.e lesions below the carina). A laparotomy is the first phase of the procedure; the main objective here is an adequate abdominal nodal dissection and adequate mobilization of the stomach. The abdomen is closed and a right posterolateral thoracotomy is performed; an appropriate thoracic node dissection is carried out together with tumour excision. Finally the oesophago-gastric anastomosis is carried out in the chest.

8.3. Abdominal, right chest and neck (McKeown/ Three stage)

This approach is appropriate for tumors above the carina. The initial steps are the same as those for the two stage procedure except that the chest is closed after tumour mobilization and the patient is returned to the supine position for completion of the anastomosis in the neck.

8.4. Trans-hiatal oesophagectomy (Orringer)

This technique avoids the need for a thoractomy and the anastomosis is in the neck. It is useful for patients with marginal respiratory status and is designed primarily for tumours of the lower third of the oesophagus. Formal nodal dissection is impossible and there is a risk of catastrophic mediastinal bleeding.

9. EXTENT OF LYMPH NODE DISSECTION AND TUMOUR RESECTION MARGINS

One may perform a 2 (figure 1) or 3 (figure 2) lymph node field dissection.

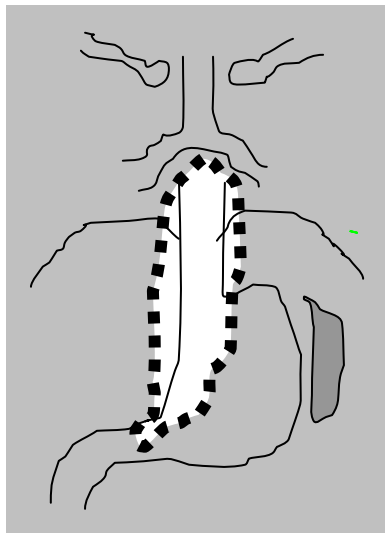


Figure 1

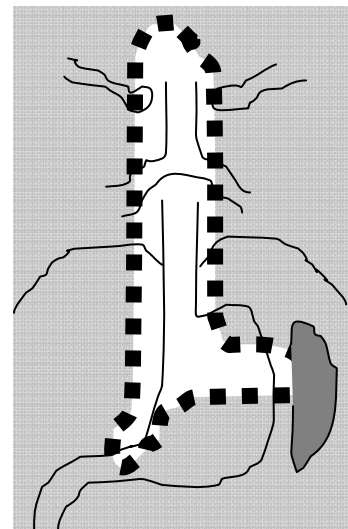


Figure 2

The trans-hiatal procedure essentially is a 1 field dissection and concern has arisen over its outcome. There is however, no evidence to suggest that a two stage procedure has a superior outcome (with respects to long term survival) over the THE⁽³³⁾. There is essentially no tangible evidence to suggest that a three field lymph node dissection is superior to a two field lymph node dissection⁽³⁴⁾.

Lam has shown that local recurrence at anastomotic sites can be prevented by resection margins of 10 cms⁽³⁵⁾. For curative resections, this will require a cervical division of the oesophagus in all patients and in lower third tumours and tumours of the OG junction, will necessitate a greater than 50% proximal gastrectomy. A greater than 50% gastrectomy compromises the length of stomach available for thoracic anastomosis and a colonic interposition will be required for lower third tumours.

10. PALIATIVE CARE

This is considered appropriate care for patients with stage IV disease. Dysphagia is one of the most distressing symptoms and satisfactory palliative care must address this complaint. Historically malignant oesophageal tumours have been dilated. Repeated dilatations are required and although the perforation rate is low, the median survival is shorter than for other forms of palliation⁽³⁶⁾. The advent of tube placement across malignant strictures greatly enhanced dysphagia management. Stents are a refinement of this idea and offer similar rates of dysphagia relief as their rigid predecessors but with fewer complications⁽³⁷⁾. Laser (NdYag) ablation results in similar mean survival as stenting, but the quality of life is inferior⁽³⁸⁾. Radiotherapy alone may be unsuccessful in relieving symptoms in up to 50% of patients⁽³⁹⁾. Feeding gastrostomies can be very efficacious at reducing the number of hospital admissions for re-hydration towards the end of a patient's life.

11. POSTOPERATIVE COMPLICATIONS AND COMPLICATIONS OF ADVANCED DISEASE

Post oesophagectomy patients are at risk of complications common to any postoperative patient. One of the most dreaded complications in post-oesophagectomy patients is an anastomotic leak. If the anastomosis is in the chest, this usually declares itself as an increase in drainage from the thoracostomy tube. The appropriate management is to immediately return the patient to theatre to repair the leak; some surgeons are utilizing self expanding stents with good results.

Locally advanced disease refers to tumour involvement of surrounding structures. Recurrent laryngeal nerve involvement results in voice changes, arterial involvement may lead to fatal haemorrhage. Air way (trachea or bronchus) invasion by tumour results in airway- oesophageal fistulae that may not be fatal immediately but most certainly increase patient morbidity. Fistulae patients treated with radiotherapy and surgical bypass were found to have significantly longer survivals than intubated patients⁽⁴⁰⁾ though at the price of a higher operative mortality. The optimal treatment for these fistulae, appears to be stenting.

12. MANAGEMENT IMPLICATIONS FOR DEVELOPING COUNTRIES

Oesophagectomy patients regularly spend the first 24 hours postoperatively in an ICU. It has been shown that adequate staffing of ICU correlates with patient outcome. When ICU nurses care for more than 2 patients during night shifts, there is a significantly higher patient complication rate⁽⁴¹⁾. There is evidence to suggest that higher (institutional) surgical volumes are associated with decreased operative mortality⁽⁴²⁾. It is clear that optimal staging of esophageal carcinoma enables health care providers to deliver the most appropriate mode of treatment.

Staging involves the use of expensive equipment that may not always be accessible to surgeons in developing countries⁽⁴³⁾. There are concerns about the quality of training in the use of EUS in developed nations and these concerns would simply be multiplied in developing nations⁽⁴⁴⁾. There are shortages of ICU nurses in developing countries and this will affect patient outcomes⁽⁴⁵⁾. Volume based referrals have been found to be

impractical in many regions of the United States of America ⁽⁴⁶⁾. This system of referral would most likely be even more impractical in many regions of Africa.

It is not unusual for patients in developing countries to be severely malnourished (with depressed serum albumin levels) at the time surgery is being contemplated. Fortunately, delays (of up to 6 weeks) in delivery of surgical care for carcinoma of the esophagus have not been shown to have any detrimental effect on survival ⁽⁴⁷⁾. In view of this finding, it would not be unreasonable to improve the patients preoperative nutritional status using parenteral nutrition or by giving the patient a feeding jejunostomy in a bid to decrease postoperative morbidity and mortality.

13. CONCLUSIONS

Although the median survival for stage I and II tumours is over 37 months, the median survival for advanced carcinoma of the oesophagus (Stage III and IV) remains short (10 months and 5 months respectively) despite the use of multimodal therapy ⁽⁴⁸⁾. Accurate staging remains vital as surgery for locally advanced (T3/T4) disease has a poor outcome and a high complication rate. Non surgical treatment may be more suitable for stage III disease. There is no tangible evidence that pre-operative chemo-radiotherapy improves outcome. Certain alterations to management protocols utilized in developed nations have to be made to develop protocols that are pragmatic for use in developing countries.

14. RECOMMENDATIONS FOR DEVELOPING COUNTRIES

- Patients, shown not to have evidence of metastatic disease either by physical examination, abdominal ultrasound or abdominal CT scan, should be encouraged to have a chest CT scan.
- Patients with a T3 or T4 tumour (on CT scan) should be advised to have non-operative palliative care, probably by a rigid plastic tube as these are more readily available than stents.
- Patients with a T1 or T2 tumour (on CT scan) should proceed to oesophagectomy via any method the surgeon is most familiar with.
- If a patient does not have evidence of metastasis and in the event that the patient cannot have a CT scan of the chest, he or she should be advised that there is about a 50% chance that they may have locally advanced disease. The operative mortality and expected outcome of locally advanced disease should be discussed with the patient. The patient and surgeon should then agree on a course of treatment.
- Patients with Stage IV disease should be palliated with a rigid tube (a stent would be better if available) as the cost of cisplatin based chemo-radiotherapy would most likely be prohibitive ⁽⁴⁹⁾.

- Patients with stage IV disease who are unable to have tube or stent placement (for whatever reason) should be given a feeding gastrostomy to avert repeated admissions for rehydration and to improve the quality of life.

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