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Practice Guideline: Disease Management

Evidence-Based Recommendations for the Management of Potentially Curable Esophageal Carcinoma

Effective Date: November 2015

CancerCare Manitoba Guideline
Disease Management – Esophageal Carcinoma
Developed by: Thoracic Disease Site Group

Preface

At CancerCare Manitoba (CCMB) the Clinical Practice Guidelines Initiative (CPGI) seeks to improve patient outcomes through the development, dissemination, implementation and evaluation of guidelines for the management of common clinical scenarios encountered by cancer patients throughout the province.

This clinical practice guideline was created through the efforts of a large interdisciplinary group from CCMB in collaboration with community and interprovincial partners. Members of the Thoracic Disease Site Group (DSG), the Department of Epidemiology and Cancer Registry, Pharmacy, and Department of Nursing at CCMB, along with the Departments of Pathology, Surgery, Radiology, Nuclear Medicine, Gastroenterology at the University of Manitoba, have participated in its development.

The Thoracic DSG will review and update this document every three years, unless emerging evidence from scientific research, or practice issues requiring urgent resolution dictate a need for immediate change in content.

Purpose

This document is intended as a guide to facilitate a common approach to the clinical management of potentially curable esophageal carcinoma.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, oncologists, surgeons, nurses, radiation therapists, pharmacists, psychosocial oncology caregivers and dieticians at CCMB, and Community Oncology Program sites (Community Cancer Program Network (CCPN) sites, Uniting Primary Care and Oncology (UPCON) clinics and Winnipeg Regional Health Authority (WRHA) Community Oncology sites).

Disclaimer

This guideline document should be viewed as an evidence-based practice tool, and as such, it does not represent an exhaustive text on the subject of esophageal carcinoma. Clinicians are advised to use it in their practice concomitantly with information from other evidence-based sources.

Use of this guideline in the clinical setting should not preclude use of the practitioner's independent clinical judgment, nor should it replace consultation with the appropriate oncology specialist when indicated (example: medical oncologist, radiation oncologist, family practitioner in oncology (FPO), hematologist, nurse practitioner/clinical nurse specialist, pharmacist, psychosocial oncology professional and dietician).

It is the responsibility of the practitioner to develop an individualized disease or symptom management plan for each patient under his/her care, and ideally this should take place within the context of a multidisciplinary team. The needs and preferences of the patient and the family should always be reflected in the plan of care.

Contents

Guideline Recommendations

Diagnosis, Staging and Staging Investigations

FDG-PET/CT

FDG-PET/CT imaging is recommended as a standard investigation for all patients undergoing radical treatment of thoracic esophageal and gastroesophageal junction (GEJ) cancers. This includes surgery and chemoradiotherapy. The primary purpose of this investigation is to assess for distant metastases.
Level of Evidence Ia

The role of FDG-PET/CT after preoperative therapy in the setting of neoadjuvant therapy is currently undefined.

EUS

1. EUS is a useful diagnostic tool to assess primary tumour and locoregional nodal involvement in the work-up of esophageal and GEJ carcinoma.
2. EUS should primarily be used when locoregional staging would significantly change treatment decisions, e.g., neoadjuvant therapy versus upfront surgery for locoregional tumours, or diagnosis of inoperable cases where esophageal biopsy is not diagnostic.

Surgical Considerations

Esophagectomy should be conducted in high volume centres that perform 15 or more esophageal resections per year. *Level of Evidence IIb*

Regardless of surgical technique, esophagectomy should strive for complete resection of the tumour with grossly clear (≥ 5 cm proximal and distal) margins and resection or sampling of ≥ 15 locoregional lymph nodes.

Nutritional supplementation prior to esophagectomy may be necessary in the case of an obstructing tumour. A variety of techniques may be employed such as temporary placement of esophageal stent, nasoenteric or jejunostomy feeding tubes. In general, placement of percutaneous gastrostomy tubes are discouraged as this may compromise viability of the stomach for future use as a conduit following esophagectomy.

Guideline Recommendations *Continued*

Treatment Options for Operable Esophageal Carcinoma

Neoadjuvant Preoperative and Perioperative Chemotherapy

Preoperative or perioperative chemotherapy is recommended for tumours of the thoracic esophagus and GEJ. The evidence is more robust for those with adenocarcinoma. *Level of Evidence Ia*

Preoperative chemotherapy can be recommended for treatment of thoracic esophageal cancer and GEJ cancer. However, there appears to be a greater effect size with perioperative chemotherapy; therefore, it is our recommended approach. *Level of Evidence Ib*

A greater benefit is suggested with chemoradiotherapy therefore, a decision between perioperative chemotherapy and neoadjuvant chemoradiotherapy should be made on a case-by-case basis. *Level of Evidence Ia*

Neoadjuvant Chemoradiotherapy

Preoperative combined concurrent chemoradiotherapy is recommended for potentially resectable stage II or III localized cancer of the thoracic esophagus and GEJ over local therapy alone. *Level of Evidence Ia*

Randomized trials comparing preoperative chemoradiation versus perioperative chemotherapy should be conducted.

Treatment Options for Inoperable Esophageal Carcinoma

Concomitant Chemoradiotherapy

Concomitant cisplatin-based chemotherapy and radical radiotherapy is recommended for the treatment of patients with unresectable/inoperable esophageal cancer. *Level of Evidence Ib*

Concomitant radiotherapy and chemotherapy is recommended over radiotherapy alone. Based on considerations of the current clinical practice pattern and the research evidence currently available, a cisplatin-based chemotherapy regimen is a reasonable chemotherapy regimen to use when concomitant radiotherapy and chemotherapy is used with no plan for surgery.

Radiotherapy

To define clinical target volume (CTV), 2-4 cm proximally and distally, and 1 cm radially to gross tumour volume (GTV) may be added. These margins may be modified at the discretion of the treating radiation oncologist(s).

The standard dose for radiotherapy is 4500-5000 cGy in 25/28 fractions in 5 to 5.5 weeks.

Brachytherapy

Intraluminal brachytherapy as boost to the primary tumour is **not** recommended. *Level of Evidence Ib*

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Disease Management Recommendations

Provincial Consensus Recommendations for the Management of Esophageal Carcinoma

I. Introduction

Esophageal carcinoma is an aggressive cancer for which control with current treatment modalities is limited. The overall 5-year survival is less than 10%. The incidence of adenocarcinoma is rising faster than any other malignancy. There were 112 cases in Manitoba in the years 2010 to 2012 with most patients presenting at an advanced stage of disease (64% stage III and higher).[1] Treatment options are limited by effectiveness, advanced stage of presentation and patient co-morbidities. Patients presenting with the disease often have a number of co-morbidities due to age, attendant medical problems and also to the disease process itself which often leads to severe nutritional impairments. This burden of morbidity can limit the therapeutic options.

The treatment of this disease has been on the whole disappointing except in those patients presenting with very early disease for whom complete resection is possible; however, even in these patients the outcome is not as good as can be expected in other malignancies. The management of patients with esophageal carcinoma relies on the application of imperfect imaging techniques and difficult and morbid treatment modalities. The evidence available for the management of this disease is conflicting, difficult to interpret and to apply in different clinical settings. There is variation in practice across the country and across the world; this reflects variability in disease presentation, the patient population and also the availability of treatment modalities. Aggressiveness of esophageal cancer, lack of precise preoperative staging and difficulty in interpreting the available evidence for the management of this highly virulent malignancy, justifies a continued and ongoing search for optimal therapy.

In an effort to improve patient outcomes in our local practice environment we undertook a consensus building exercise in 2008 which brought together medical practitioners from across the province who are looking after this group of patients. At this meeting, a set of consensus statements were developed for the management of esophageal cancer within our province. As guidelines are considered living documents and must be kept abreast of the evidence, in 2014 a small interdisciplinary working group convened to consider evidence from an updated literature search and to finalize the recommendations from the 2008 consensus meeting.

These guideline recommendations are intended to spell out and act as a framework to what we believe is a reasonable and justifiable approach to this problem in Manitoba, taking into consideration local availability and expertise. This guideline focuses on the contentious issues in diagnosis, staging and treatment of patients for whom treatment for cure or significant prolongation of life is considered. This guideline does not address those for whom only palliation is appropriate and nor does it address the important psychosocial issues surrounding this disease.

References

1. Manitoba Cancer Registry, Personal Communication, October 6, 2014.

II. Scope of Guideline

Aim and Purpose

Development of this guideline was undertaken for the purpose of knowledge translation of the current standards in practice for treatment of potentially curable esophageal carcinoma in Manitoba. The management of distant metastatic disease is not addressed in this document. The overall aim is to improve the standard of care received by this patient population, through application of evidence-based interventions and promotion of best practices.

Clinical Questions

What specific role does the FDG-PET/CT imaging modality play in the management of patients with esophageal carcinoma?
What is the role of EUS in staging and management of esophageal carcinoma?
What is the role of surgery in operable esophageal carcinoma?
Is there a role for preoperative and perioperative chemotherapy in the management of thoracic esophageal and gastroesophageal junction cancers?
Is there a role for preoperative chemoradiotherapy in the management of thoracic esophageal cancer?
What is the role of radiation and chemotherapy in patients with: 1. Resectable esophageal carcinoma who decline surgery? 2. Unresectable disease?
What dose, fractionation and volume of radiation should be used to treat patients with resectable esophageal carcinoma who decline surgery or have unresectable disease?
Is there a role for intraluminal brachytherapy as boost to the primary tumour?

Development Panel

Development Panel	
Oncology Subspecialties CancerCare Manitoba/University of Manitoba	3 Radiation Oncologists, Thoracic DSG 1 Medical Oncologist, Thoracic DSG
Pathology University of Manitoba	1 Anatomical Pathologist
Surgery University of Manitoba	1 Thoracic Surgeon

Development Process

A multidisciplinary group of medical professionals organized a conference in 2008 to establish management consensus for adult patients with potentially curable esophageal carcinoma. Attendees were experts and practitioners from across the province as well as some external experts. Presentations included evidence-based recommendations, as well as local expertise. As guidelines are considered living documents and must be kept abreast of the evidence, in 2014 a small interdisciplinary working group convened to consider evidence from an updated literature search and to finalize the recommendations from the 2008 consensus meeting.

Patient Population and Healthcare Setting

The recommendations in this guideline are applicable to the care of adult (18 years or older; male or female) patients with potentially curable esophageal carcinoma. These recommendations are intended for use in both inpatient and outpatient settings.

End-Users

This guideline is written for use by clinicians providing care for the above mentioned patient population. Intended primarily for use by medical clinicians, the guideline may be of interest to trainees, allied healthcare staff, healthcare administrators, policy makers and possibly members of the general public.

III. Guideline Methodology

Clinical Research Question Development

The working group developed clinical questions with the guiding factor being "can this be done in Manitoba?"

Literature Search

An initial literature search was conducted in 2008 and later updated in November 2014. PubMed, EMBASE and www.guidelines.gov were systematically searched for clinical practice guidelines. Searches were limited to clinical practice guidelines, with humans and English as a limit.

An environmental scan of the following guideline development groups was also performed:, Cancer Care Ontario, Alberta Health Services, BC Cancer Agency, Saskatchewan Cancer Agency, National Comprehensive Cancer Network (NCCN), New Zealand Guidelines Group, Scottish Intercollegiate Guideline Network (SIGN), Cancer Australia and National Institute for Health and Care Excellence (NICE).

Primary evidence was searched *via* PubMed. Literature searches were limited to human studies and English. Contributors to this document conducted their own literature search for primary evidence.

2008 Esophageal Provincial Consensus Meeting

A Provincial Consensus Meeting was held in Winnipeg, Manitoba on February 7th, 2008. The agenda included presentations of the available evidence with particular weight given to Level I evidence when available. The conference was attended by all medical specialties dealing with this disease such as medical oncologists, radiation oncologists, primary care providers, family physicians, surgeons, radiologists, pathology and allied staff from CancerCare Manitoba. Physicians from Saskatchewan Cancer Agency also participated in developing the recommendations (*See Section XII for participants*).

2014 Working Group Meetings

In 2014 a small working group was formed to consider evidence from an updated literature search and finalize the recommendations from 2008. This guideline was developed in response to the consensus statements developed at the 2008 Esophageal Provincial Consensus Meeting. Using the consensus statements for guidance, working group members drafted each of the guideline sections. Each section was reviewed by the working group and revised according to consensus decisions (*See Section XII for members of the working group*).

Internal and External Review

Internal and external peer review were pursued, the results of which are appended to these guidelines. The internal review consisted of revision by the working group. An external review was conducted by a medical oncologist from the BC Cancer Agency; a general and thoracic surgeon from Brandon Regional Health Centre and a family physician in oncology from Boundary Trails Community Cancer Program (*See Section XII*). All participants

completed a full review of the guideline document and submitted a standardized practitioner feedback survey (adapted from Brouwers and colleagues).[1] Feedback was considered and discussed by the working group. Decisions to incorporate any changes into the guideline were consensus-based (acceptance, rejection, or acceptance with modifications).

Maintenance

At CancerCare Manitoba clinical practice guidelines are considered 'living' documents which require ongoing evaluation, review and update. Re-evaluation of this guideline is planned for 2017. The working group will revise and update the document as needed, with any critical new evidence brought forward before this scheduled review.

References

1. Brouwers MC, Graham ID, Hanna SE, et al. Clinicians' assessments of practice guidelines in oncology: the CAPGO survey. *Int J Technol Assess Health Care* 2004;20(4):421-6.

IV. Epidemiology of Esophageal Carcinoma

In Manitoba, an average of 56 cases of esophageal cancer and an average of 70 deaths due to esophageal cancer are reported annually (Figure 1).[1] Nationally, the overall incidence rate of esophageal cancer has remained stable in females since 2001; however, a significant 1.4% increase per year has been exhibited in males.[2] Annual mortality rates are 6.7 per 100,000 among males and 1.5 per 100,000 for females.[2] The poor prognosis for esophageal cancer is likely a result of late stage diagnosis, when treatment is less effective. The 2-year prevalence data indicates the poor survival for esophageal cancer (Table 1). Patients diagnosed the year before make up less than half of the total esophageal cancer patients in a given year. The 5-year prevalence shows a similar trend.[1]

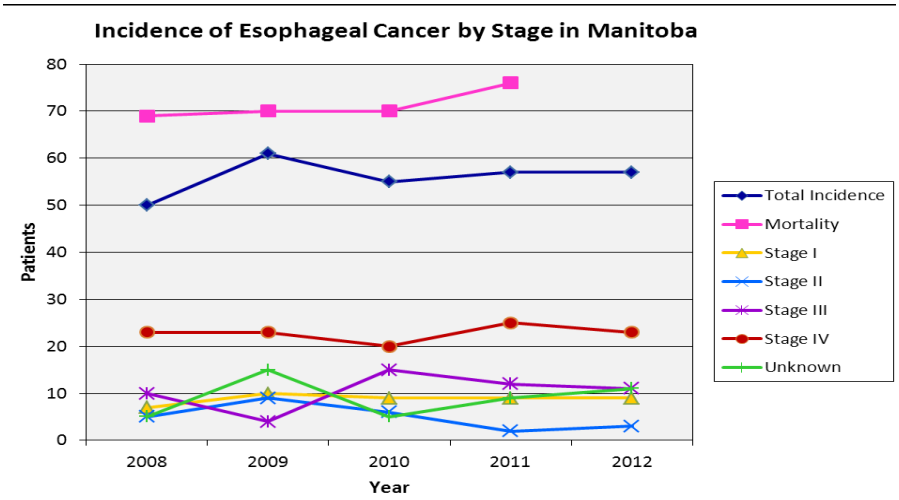

Figure 1. Incidence of esophageal cancer by stage and mortality in Manitoba from 2008 to 2012.[1]

Note: Different sources of information are used for cancer incidence and mortality; specifically, cancer incidence involves centralized coding by the Manitoba Cancer Registry using international cancer registry coding standards whereas mortality uses a distributed application of national/international death coding standards reported to the provincial Vital Statistics Department. As a result of these differences in methodology, cancer mortality may appear to exceed cancer incidence.

Table 1. Two-Year Prevalence of Esophageal Cancer in Manitoba[1]

Year	Year of Diagnosis	Patient Count	% of Total
2008	2007	16	38.10%
	2008	26	61.90%
	Total	**42**	**100.00%**
2009	2008	9	18.75%
	2009	39	81.25%
	Total	**48**	**100.00%**
2010	2009	20	40.00%
	2010	30	60.00%
	Total	**50**	**100.00%**
2011	2010	11	30.56%
	2011	25	69.44%
	Total	**36**	**100.00%**
2012	2011	10	22.73%
	2012	34	77.27%
	Total	**44**	**100.00%**

References

1. CancerCare Manitoba Epidemiology and Cancer Registry, Personal Communication, October 6, 2014.
2. Canadian Cancer Society's Steering Committee on Cancer Statistics. *Canadian Cancer Statistics 2014.* Toronto, ON. Canadian Cancer Society; 2014.

V. Pathology of Esophageal Carcinoma

A. Histology

The major histologic types of esophageal carcinoma are squamous cell carcinoma and adenocarcinoma, with adenocarcinoma being the more common type.

Squamous Cell Carcinoma

Subtypes:

- Verrucous (squamous) carcinoma
- Basaloid (squamous) carcinoma
- Spindle cell (squamous) carcinoma

Adenocarcinoma

Subtypes:

- Tubular
- Papillary
- Mucinous
- Singlet-ring

Neuroendocrine Carcinoma

Subtypes:

- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma

Less Common

- Adenoid cystic carcinoma
- Adenosquamous carcinoma
- Mucoepidermoid carcinoma
- Others

B. Pathology Reporting for Resection Specimens

For esophageal cancer resection specimens, pathology reporting confirms diagnosis and extent of the disease. The report should include all information required for pathological tumour stage (pT stage), as well as margin status. A synoptic reporting format is recommended as this will allow accurate communication of relevant information.

The Pathology Requisition

Information to be supplied on the pathology requisition by the operating surgeon:

- Endoscopic/surgical tumour location – from incisors or anatomic landmark
- Surgical orientation of the proximal and distal margins of the specimen with diagrams and labeling of the margins is often helpful
- Type of neoadjuvant therapy (as applicable)
- Biopsy pathology report number, if performed outside Winnipeg (pathologists can access previous reports within the city in the LIS)

The Pathology Report[1-3]

This information is crucial for further patient management and some features are particularly relevant for adjuvant therapy.

Key information that should be included in the pathology report:

- Margin status
- Lymph node status
- Depth of invasion
- Tumour location

Other information which should be reported:

- Specimen type
- Histological type
- Histological grade
- Vascular and perineural invasion
- Tumour regression grading (as applicable)
- Tumour size (greatest dimension)

Reporting Tumour Location

The pathology report should document tumour location precisely, including:

- Distance of tumour to proximal and distal margins
- Location of tumour center in relation to the gastroesophageal junction (GEJ), if the GEJ is identified in the specimen (*see section VI: Anatomical Subsites*)

Reporting Histological Grade

The pathology report should include the histological grade of the tumour:

- Grade 1 – Well differentiated
- Grade 2 – Moderately differentiated
- Grade 3 – Poorly differentiated
- Grade 4 – Undifferentiated

Reporting Depth of Invasion

The depth of tumour invasion should be documented in the pathology report in accordance with the 2010 TNM staging system (see Appendix I).

Reporting Lymph Node Involvement

The extent of lymph node involvement should be documented in the pathology report in accordance with the 2010 TNM staging system (see Appendix I).

NOTE: It is also important that the pathology report specifies the number of lymph nodes examined, as well as the number of nodes with tumour involvement.

Reporting Tumour Margins

Tumour margins should be documented in the pathology report, using the following descriptors:

Proximal and Distal Margins

- Cannot be assessed
- Uninvolved by invasive carcinoma
- Involved by invasive carcinoma
- High-grade dysplasia absent at proximal and/or distal margin
- High-grade dysplasia present at proximal and/or distal margin

Circumferential (Adventitial) Margins

- Cannot be assessed
- Uninvolved by invasive carcinoma
- Involved by invasive carcinoma

If all margins are negative for invasive carcinoma, the distance of invasive carcinoma from closest margin (in millimetres) should be documented in the pathology report.

Reporting Tumour Regression Grade

The extent of pathological response to preoperative neoadjuvant treatment should be documented in the pathology report using the criteria presented in Table 2.

Table 2. Tumour Regression Grade[4]

Description	Tumour Regression Grade
No viable cancer cells	0 (Complete response)
Single cells or small groups of cancer cells	1 (Moderate response)
Residual cancer outgrown by fibrosis	2 (Minimal response)
Minimal or no tumour kill; extensive residual cancer	3 (Poor response)

References

1. Chang F, Deere H, Mahadeva U, et al. Histopathologic examination and reporting of esophageal carcinomas following preoperative neoadjuvant therapy: practice guidelines and current issues. *Am J Clin Pathol* 2008;129(2):252-62.

2. Washington K, Berlin J, Branton P, et al. College of American Pathologists Protocol for the examination of specimens from patients with carcinoma of the esophagus. October 2013. Accessed from: http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2013/Esophagus_13protocol_3112.pdf

3. Bosman FT, Carneiro F, Hruban RH, et al (eds). WHO classification of tumours of the digestive system, 4th ed. IARC Press: Lyon, 2010.

4. Esophagus and esophagogastric junction. In Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer, 2010, pp. 103-52.

VI. Anatomical Subsites

The esophagus is a continuation of the pharynx, ending at the junction with the stomach. By endoscopic measurements it is 38 to 40 cm from the incisors to the GEJ in men and 36 to 38 cm in women. The total length from the cricopharyngeus to the GEJ is a median of 22 and 21 cm in men and women, respectively. A convenient division is that of the cervical portion, the thoracic portion and the abdominal portion, which are approximately 5 cm, 20 cm and 2 cm, respectively.

Tumours involving these sections differ in their incidence, presentation and histology. Treatment modalities also have to take into consideration the specific anatomical features in these regions; however, the similarities in thoracic esophageal carcinomas are such that they can be considered broadly equivalent with appropriate regard in specific situations to their anatomic site.

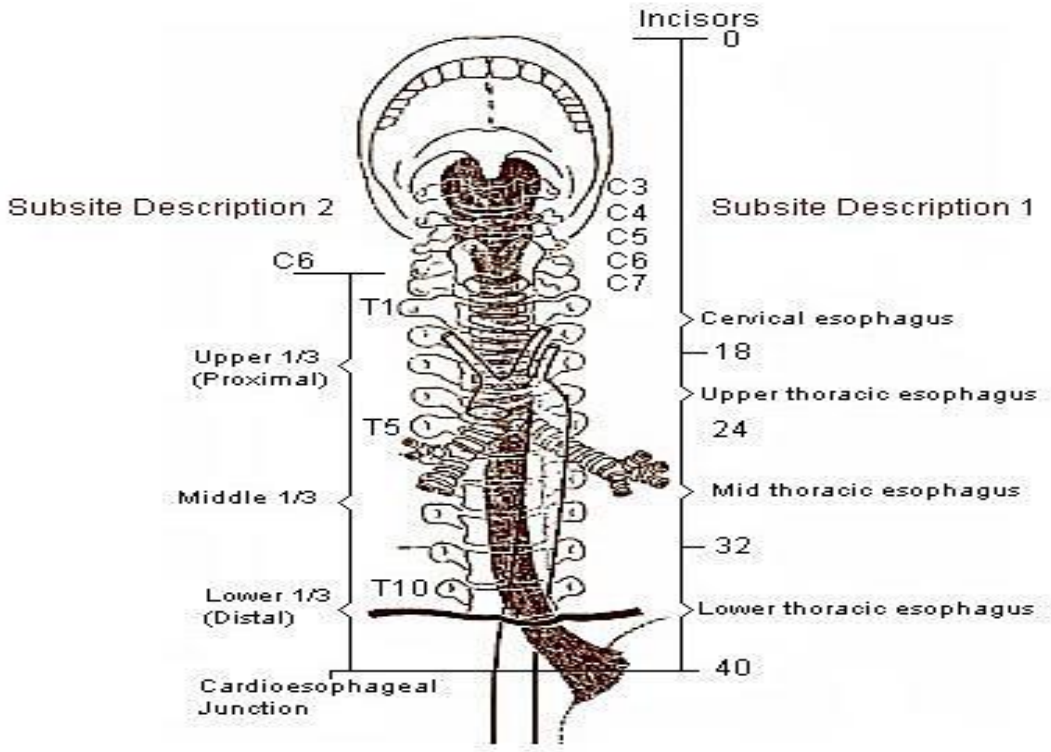

Figure 1. Anatomical subsites of the esophagus. Obtained from SEER Training Modules, *UGI Tract Cancer*. U. S. National Institutes of Health, National Cancer Institute. 16 May 2012 <http://training.seer.cancer.gov/ugi/anatomy/esophagus.html>.

Cervical Esophagus

The cervical esophagus is approximately 5 cm long and commences at the lower border of the cricoid cartilage and ends at the thoracic inlet (suprasternal notch), approximately 18 cm from the upper incisor teeth. Cervical or upper third esophageal carcinomas behave very differently in histology, presentation and treatment options.

Therefore, this subgroup is not discussed further in this document.

Thoracic Esophagus

The thoracic esophagus extends from the thoracic inlet to the diaphragmatic hiatus, and the abdominal portion from the diaphragmatic hiatus to the GEJ. The key anatomical landmarks are: the tracheal bifurcation and aortic arch, the diaphragmatic hiatus and the GEJ.

1. The upper thoracic portion extends from the thoracic inlet to the level of the tracheal bifurcation, at 24 cm from the upper incisors.
2. The mid and lower thoracic portion is the distal half of the esophagus between the tracheal bifurcation and the GEJ, and is 8 cm long. This portion also includes the abdominal esophagus which is below the diaphragm and is approximately 2 cm in length.

Gastroesophageal Junction (GEJ)

The incidence of adenocarcinoma of the esophagus and GEJ has markedly increased in the Western world in the last few decades.

If the epicenter of the tumour is in the lower thoracic esophagus, GEJ, or within the proximal 5 cm of the stomach that extends into the GEJ or esophagus, the tumour is classified as esophageal.[1] Conversely, if the epicenter of the tumour is in the stomach and greater than 5 cm distal to the GEJ, or is within 5 cm of the GEJ but does not extend into the GEJ or esophagus, it is classified as gastric.[1]

In cases where the tumour is equally located above and below the GEJ and/or is designated as being *at* the junction (anatomic center of the tumour), the histology determines the presumed origin where:

- Carcinomas of the squamous, small cell and undifferentiated types are classified as esophageal tumours
- Adenocarcinomas and signet-ring cell carcinomas are classified as gastric tumours

The Siewert classification of the GEJ organizes the subtypes of tumour based on the location of the tumour relative to the GEJ (Table 3).[2]

Table 3. The Siewert Classification of GEJ Tumours[2]

Type 1	Center is 1 to 5 cm above the GEJ
Type 2	Center is 1 cm above to 2 cm below the GEJ
Type 3	Center is 2 to 5 cm below the GEJ

References

1. Esophagus and esophagogastric junction. In Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer, 2010, pp. 103-52.

2. Rüdiger Siewert J, Feith M, Werner M, et al. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. *Ann Surg* 2000;232(3):353-61.

VII. Diagnosis, Staging and Staging Investigations

Accurate diagnosis and staging of esophageal cancer is crucial for appropriate treatment. This entails the description of the primary tumour, lymph nodes and metastasis component of the TNM staging system *(see Appendix 1)*. In clinical practice this includes a physical examination specifically looking for distant lymph node metastasis. Anatomic imaging includes a CT scan of the chest and abdomen, and upper gastrointestinal endoscopy for tissue diagnosis. In recent years, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) and endoscopic ultrasonography (EUS) have also been incorporated as staging investigations for esophageal cancer. Indications for these tests follow below.[1]

A. FDG-PET/CT

FDG-PET/CT is an imaging technique where malignancies avidly take up a radioactive tracer ^{18}F-fluorodeoxyglucose (FDG).[2] This gives a functional image of regions of increased metabolic activity, particularly neoplastic tissue. Combined with this metabolic evaluation, there is a CT scan which allows anatomical co-location of the lesion of interest.

Key Evidence

The sensitivity of FDG-PET/CT imaging for detection of primary esophageal tumours is 38% for stage T1 and 100% for stage T2-4 tumours. However, since other investigative methods are better and less expensive, PET scanning is not performed for primary tumour assessments.

In a systematic review evaluating three primary studies, PET exhibited superior sensitivity in detecting distant metastases when compared to CT or EUS.[3] Furthermore, another systematic review of twelve primary studies reported a sensitivity of 67% and specificity of 97% for PET, thus corroborating the evidence in a systematic review reported by Lacey and colleagues.[3,4] A primary study by Sihvo and colleagues illustrated the benefit of adding PET to CT and EUS.[5] The sensitivity of PET alone, PET plus CT, and PET plus CT and EUS was 53%, 64% and 74%, respectively.[5]

Numerous primary studies have established the significance of PET and PET/CT on the clinical management, prognostic stratification of patients with newly diagnosed esophageal cancer, prediction of regional and locoregional lymph nodes and improvement on the accuracy of pre-treatment staging compared to CT and EUS alone.[2,6-11]

Recommendations

1. FDG-PET/CT imaging is recommended as a standard investigation for all patients undergoing radical treatment of thoracic esophageal and GEJ cancers. This includes surgery and chemoradiotherapy. The primary purpose of this investigation is to assess for distant metastases. *Level of Evidence Ia*
2. The role of FDG-PET/CT after preoperative therapy in the setting of neoadjuvant therapy is currently undefined.

B. EUS

Prognosis of esophageal carcinoma is strongly associated with locoregional staging; therefore, imaging modalities such as EUS play a vital role in the diagnosis and staging of this disease. EUS is an imaging technique using ultrasound evaluation of a tumour and adjacent structures, which is integral to the initial staging of esophageal carcinoma and to a lesser extent, detection of disease recurrence.[12]

Key Evidence

EUS is felt to be the most accurate diagnostic modality to assess tumour depth, with sensitivities ranging from 81% to 92%, depending on the depth of tumour penetration.[13-18] EUS is less accurate for early-stage lesions, such as T1 or T2, compared to more advanced tumours. Another limitation is the presence of an obstructing tumour that may make passage of the EUS probe difficult. If accurate T stage is required for treatment planning purposes (i.e., whether or not a patient receives neoadjuvant therapy), EUS is recommended.

In addition to T staging, EUS may be performed in conjunction with fine needle aspiration (FNA) to assess nodal status. In the past, this was important to assess celiac node involvement, which was considered M1 disease. In the current AJCC staging classification for esophageal carcinoma, all lymph nodes from the level of the thoracic inlet to the celiac axis are considered locoregional and not metastatic.[19] Therefore, EUS and FNA should only be considered if identification of positivity would influence subsequent management.

Recommendations

1. EUS is a useful diagnostic tool to assess primary tumour and locoregional nodal involvement in the work-up of esophageal and GEJ carcinoma.
2. EUS should primarily be used when locoregional staging would significantly change treatment decisions, e.g., neoadjuvant therapy versus upfront surgery for locoregional tumours, or diagnosis of inoperable cases where esophageal biopsy is not diagnostic.

References

1. Bombardieri E & Crippa F. The increasing impact of PET in the diagnostic work-up of cancer patients. In: Freeman LM (Ed) *Nucl Med Ann* 2002. Philadelphia: Lippincott Williams & Wilkins, pp. 75-121.
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VIII. Surgical Considerations for Operable Esophageal Carcinoma

The treatment options for esophageal carcinoma are on the whole disappointing. The modalities are morbid and the outcomes are quite variable. This reflects the intensity of therapy and also the limitations imposed by the advanced stage of presentation and patient comorbidities.

Key Evidence

Surgical resection of esophageal cancer remains the standard therapy. In a recent prospective study, there was a 27% and 39% five-year disease free survival (DFS) and a median survival of 1.4 and 1.7 years, after transhiatal and transthoracic resection, respectively.[1] The study population had approximately 50% of patients in stage III.[1] There was a 3% thirty day mortality; however, mortality rates from a wider range of hospitals are closer to 10%.[1,2]

The suitability of surgery as the primary therapy is dependent on the resectability and operability. Resectability refers to the likely success of completely excising the tumour and adjacent lymph nodes. This is primarily a reflection of the tumour or disease process. Operability refers to the capacity of the patient to undergo the operation and reflects the burden of comorbidities in the patient.

Variables in surgery include the techniques of operation and hospital and surgeon volumes. Most studies have not yet shown a convincing superiority of one technique compared to the other; however, a clear determinant of outcomes is the surgical volume either in individual surgeons or hospitals. Individual surgeons performing more than 6 esophagectomies a year produce significantly less mortality.[3] This is also reflected in hospital volumes with more than 15 esophagectomies per year having a five-fold reduction in hospital mortality compared to those performing 6 or less.[3]

While undergoing preoperative treatment, any patient being considered for surgical resection of the esophagus should be closely monitored by both the treating oncologist(s) and the surgeon. Ongoing malnutrition due to an obstructing esophageal tumour is a common occurrence. A variety of treatment options exist regarding optimizing nutritional status. Close consultation with the treating surgeon is essential prior to any invasive procedure that may compromise future surgery. In general, placement of percutaneous gastrostomy tubes is discouraged as this may compromise viability of the stomach for use as a conduit following esophagectomy. Placement of an indwelling expandable esophageal stent may be used to palliate dysphagia, but should be removed prior to completion of neoadjuvant therapy as the presence of a stent may induce considerable inflammation of adjacent organs and increase the technical difficulty of operative resection.

While there is no clearly superior technique for esophagectomy, general surgical oncologic principles should be followed regardless of operative approach:

- Prior to committing to esophagectomy, careful exploration of the peritoneal/pleural cavity should be performed to rule out metastatic disease or unresectable tumour due to invasion of critical structures (e.g., heart, aorta, trachea).
- Gross surgical margins of at least 5 cm proximal and distal to the tumour should be obtained. Adequate circumferential margins should be obtained through meticulous sharp dissection with en bloc resection of surrounding tissue.

- For tumours of the thoracic esophagus and GEJ, locoregional lymph nodes in the upper abdomen (e.g., gastrohepatic/celiac region) and mediastinum (e.g., paraesophageal, subcranial, paratracheal) should be systematically sampled or dissected for accurate staging. The role of cervical lymph node dissection for tumours in the mid to lower esophagus (i.e., 3 field esophagectomy) is unclear.
- Following esophageal resection, intestinal continuity is re-established via construction of a conduit using stomach, colon or small intestine, with anastomosis to the remaining upper esophageal remnant.

Restaging for Surgery

Patients should have the appropriate restaging investigation prior to proceeding with surgery. Treatment response is best assessed by performing a CT scan of the chest and abdomen. The role of FDG-PET in this situation remains undefined.

Recommendations

1. Esophagectomy should be conducted in high volume centres that perform 15 or more esophageal resections per year. *Level of Evidence IIb*
2. Regardless of surgical technique, esophagectomy should strive for complete resection of the tumour with grossly clear (≥ 5 cm proximal and distal) margins and resection or sampling of ≥ 15 locoregional lymph nodes.
3. Nutritional supplementation prior to esophagectomy may be necessary in the case of an obstructing tumour. A variety of techniques may be employed such as temporary placement of nasoenteric or jejunostomy feeding tubes, or esophageal stent. In general, placement of percutaneous gastronomy tubes are discouraged as this may compromise viability of the stomach for future use as a conduit following esophagectomy.

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IX. Treatment Options for Operable Esophageal Carcinoma

A. Neoadjuvant Preoperative and Perioperative Chemotherapy

While there has been variation among individual randomized controlled trials (RCTs) examining a potential benefit to giving preoperative chemotherapy in addition to surgery, there has been agreement among multiple systematic reviews, which constitute a higher level of evidence (*Level Ia* instead of *Level Ib* for individual RCTs).

Key Evidence

Three meta-analyses have demonstrated a relative improvement in overall survival (OS) of 10-13% with the addition of preoperative chemotherapy (Table 4).[1-3] The literature-based meta-analysis by Sjoquist et al is an update on the earlier study by Gebski et al, whereas Thirion and colleagues used individual patient data from nine trials.[1-3] Both Gebski and Sjoquist provide subgroup analyses suggesting a clear benefit in patients with adenocarcinoma, but no statistically significant benefit to adding neoadjuvant chemotherapy for patients with squamous cell carcinoma.[2,3]

Thirion and colleagues also reported on DFS, complete resection and postoperative death.[1] Based on seven trials (n = 1849), the hazard ratio (HR) for DFS was 0.82 (95% confidence interval [CI], 0.74 to 0.91) favouring neoadjuvant chemotherapy. Complete resection (R0) was slightly, although statistically significant (p = 0.03), more common with the addition of neoadjuvant chemotherapy (67%) compared to surgery alone (62%). There was no difference in postoperative death at 6.7%.[1] The lack of increased postoperative or perioperative morbidity and mortality with neoadjuvant chemotherapy is further supported by a meta-analysis of seven trials.[4]

Finally, Sjoquist and colleagues performed an indirect comparison of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy.[2] There was a non-statistically significant trend towards greater benefit with chemoradiotherapy (HR, 0.88; 95% CI, 0.76 to 1.01; p = 0.07).

Table 4. Systematic Reviews Evaluating Preoperative Chemotherapy and Surgery versus Surgery Alone

Reference	# Trials	N	Hazard Ratio	95% CI	P-Value	Absolute OS benefit
Thirion et al (2007)[1]	9	2102	0.87	0.79-0.95	0.003	4% (5y)
Sjoquist et al (2011)[2]	10	1981	0.87 SCC – 0.92 AC – 0.83	0.79-0.96 0.81-1.04 0.71-0.95	0.005 0.18 0.01	5.1% (2y)
Gebski et al (2007)[3]	8	1724	0.90 SCC – 0.88 AC – 0.78	0.80-1.00 0.75-1.03 0.64-0.95	0.05 0.12 0.014	7% (2y)

Abbreviations: AC, adenocarcinoma; CI, confidence interval; N, number of patients; OS, overall survival; SCC, squamous cell carcinoma; 2y, 2-year; 5y, 5-year

For GEJ cancer, RCTs have focused on perioperative (preoperative plus postoperative) chemotherapy in addition to surgery. Two sizable RCTs have been completed suggesting a benefit to adding perioperative chemotherapy and therefore Level Ib evidence exists for two chemotherapy regimens.[5,6] Both trials include patients with distal esophageal cancer, GEJ cancer or gastric cancer. The results are summarized in Table 5.

Table 5. RCTs evaluating Perioperative Chemotherapy and Surgery versus Surgery Alone

Reference	N	Chemotherapy Regimen	5y OS	Hazard Ratio for Death	95% CI	P-Value
Ychou et al (2011)[5]	113 111	CF None	38% 24%	0.69	0.50-0.95	0.02
Cunningham et al (2006)[6]	250 253	ECF None	36% 23%	0.75	0.60-0.93	0.009

Abbreviations: CF, cisplatin/flurouracil; CI, confidence interval; ECF, epirubicin/cisplatin/5-fluorouracil; N, number of patients; OS, overall survival; 5y, 5-year

Based on the availability of evidence, the neoadjuvant preoperative and perioperative chemotherapy regimen of choice at CCMB is ECF (epirubicin, cisplatin, 5-fluorouracil) (Table 6).

Recommendations

1. Preoperative or perioperative chemotherapy is recommended for tumours of the thoracic esophagus and GEJ. The evidence is more robust for those with adenocarcinoma. *Level of Evidence Ia*
2. Preoperative chemotherapy can be recommended for treatment of thoracic esophageal cancer and GEJ cancer; however, there appears to be a greater effect size with perioperative chemotherapy; therefore, it is our recommended approach. *Level of Evidence Ib*
3. A greater benefit is suggested with chemoradiotherapy therefore, a decision between perioperative chemotherapy and neoadjuvant chemoradiotherapy should be made on a case-by-case basis. *Level of Evidence Ia*

Table 6. Chemotherapy Treatment Prescription for Operable Esophageal Carcinoma

1 cycle = 21 days; 3 cycles pre-operative and 3 cycles post-operative

Drug	Dose	CCMB Administration Guide
Epirubicin	50 mg/m^2 IV on Day 1	N/A
Cisplatin	60 mg/m^2 on Day 1	N/A
5-fluorouracil	200 mg/m^2/day	Continuous ambulatory infusion

B. Neoadjuvant Chemoradiotherapy

The poor long-term survival associated with surgery alone and the radiosensitizing effect of concurrent chemotherapy provided the impetus to evaluate preoperative chemoradiotherapy.

Key Evidence

At least seven trials have directly compared surgery with or without preoperative chemoradiotherapy for patients with potentially resectable esophageal carcinoma. Two studies demonstrate a significant survival benefit from combined modality therapy, both using a concurrent rather than sequential approach. Recently, there is a high level of evidence supporting the recommendation of preoperative chemoradiation as standard of care.

Gebski and colleagues evaluated ten randomized trials comparing preoperative chemoradiotherapy followed by surgery versus surgery alone.[3] Preoperative chemoradiotherapy displayed a 13% absolute benefit in survival at 2 years (HR, 0.81; 95% CI, 0.70 to 0.93; p = 0.002).

Recently, the Dutch CROSS trial clearly showed the benefit of preoperative chemoradiation in the management of esophageal cancer.[7] The investigators randomly assigned 363 patients with potentially resectable esophageal or GEJ cancer (86 squamous cell carcinoma; 273 adenocarcinoma; 4 other, majority distal esophageal - 11% GEJ) to preoperative chemoradiotherapy (weekly paclitaxel 50 mg/m^2 plus concurrent radiotherapy (41.4 Gy over 5 weeks)) or surgery alone. Grade 3 or higher hematologic toxicity and non-hematologic toxicity was reported in 7% of patients and less than 13% of patients, respectively, indicating preoperative chemoradiotherapy was well tolerated. No differences were seen in postoperative morbidity or mortality between the two groups. Chemoradiotherapy had a higher complete resection (R0) rate than surgery alone (92% versus 69%), and 29% of those treated with chemoradiotherapy had pathological complete response (pCR). Median OS was significantly better with preoperative chemoradiotherapy at the median follow-up of 32 months with a 3-year survival rate in 58% of patients compared to 44% in the surgery alone group (HR, 0.657; 95% CI, 0.495-0.871; p = 0.003).

Table 7. Systematic Reviews Evaluating Preoperative Chemoradiation and Surgery versus Surgery Alone

Systematic Review	# Trials	N	Hazard Ratio	95% CI	P-Value	Absolute OS benefit
Gebski et al (2007)[3]	10	1724	0.81	0.70-0.93	0.002	13% (2y)
Urschel et al (2003)[8]	9	1116	0.66	0.47-0.92	0.016	(3y)
Sjoquist et al (2011)[2]	12	1854	0.78	0.70-0.88	0.0001	8.7% (2y)

Abbreviations: CI, confidence interval; N, number of patients; OS, overall survival; 2y, 2-year; 3y, 3-year; 5y, 5-year

Table 8. Randomized Controlled Trials of Preoperative Chemoradiation and Surgery versus Surgery Alone

Trial	N	ChemoRT	3y OS	Hazard Ratio for Death	95% CI	P-Value
CROSS (2012)[7]	178 188	ChemoRT None	58% 44%	0.65	0.49-0.87	0.003

Abbreviations: ChemoRT, chemoradiation; CI, confidence interval; N, number of patients; OS, overall survival; 3y, 3-year

Recommendations

1. Preoperative combined concurrent chemoradiotherapy is recommended for potentially resectable stage II or III localized cancer of the thoracic esophagus and GEJ over local therapy alone. *Level of evidence Ia*
2. Randomized trials comparing preoperative chemoradiation versus perioperative chemotherapy should be conducted.

C. Radiation Therapy and Chemotherapy Dosing and Technical Details

Radiation Therapy

Dose Specifications

- Phase 1: Total radiation prescription dose 45-50.4 Gy given in 25-28 fractions of 1.8 Gy per fractions, 5 fractions/week, 1 treatment/day, starting on Day 1 of the first cycle of chemotherapy.
- Phase 2: (Gross Tumour Volume [GTV] only) Boost is not mandatory and up to the discretion of the radiation oncologist.

Prescription dose will be calculated with the heterogeneity correction turned on. Acceptable Planning Target Volume (PTV) dose range will be 95-107% with prescription dose.

Localization/Simulation/Immobilization

- Patient will be simulated in the supine position with arms above the head.
- 3D-CT scan or 4D-CT scan will be obtained in the treatment position with minimum thickness of 3 mm.
- Oral contrast will be given at the time of CT simulation to assist with delineation of GTV, normal esophagus and stomach.
- IV contrast may be used at the discretion of the radiation oncologist.

Target Volumes and Critical Structures Delineation

- **Gross Tumour Volume (GTV)** – defined as all known gross primary disease with circumferential full thickness esophageal wall and enlarged (> 1 cm) or PET-avid regional lymph nodes. The GTV will be determined using all available information (CT chest and abdomen, PET, endoscopy).
- **Clinical Target Volume (CTV)** – defined as GTV and uninvolved full thickness esophagus 2-4 cm proximal and distal form the GTV plus 0.5-1 cm in radial direction edited at the discretion of the radiation oncologist. Drainage nodal regions may be added at the discretion of radiation oncologist.
- **Planning Target Volume (PTV)** – defined as CTV plus minimum of 1 cm, 4D-CT scan-PTV margin = Internal Target Volume (ITV) + 0.5 cm. This expansion does not need to be uniform in all dimensions.

Critical Organs and Dose Constraints

Multiple photon beams will be used to optimize PTV while maintaining dose to Organs at Risk (OAR).

Dose volume histograms (DVH) will be generated for the following organs and the dose will be kept as low as possible. The following dose constraints will be applied:

- Lung – V20 Gy < 35%; Mean Lung Dose < 20 Gy
- Spinal cord – Maximum point dose ≤ 45 Gy; up to 50 Gy maximum point dose is acceptable

- Heart – V40 Gy < 30%; V30 Gy < 46%
- Liver – V30 Gy < 40%
- Kidneys – V20 Gy < 32%; V28 Gy < 20%; % Dose (D) Average < 18 Gy

Treatment Delivery

Radiation treatment will be delivered using Linear Accelerator with minimum photon energy of 6 MV.

Chemotherapy

Weekly paclitaxel (50 mg/m^2) plus carboplatin (Area Under the Curve [AUC] 2, based on renal function) for 5 weeks (with concurrent radiotherapy).

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X. Treatment Options for Inoperable Esophageal Carcinoma

Unresectable esophageal cancer is a heterogeneous group of diseases and different definitions are used. This group of diseases usually includes:

- Resectable disease which is inoperable due to comorbidities
- Resectable disease in patients who decline surgery
- Definitely unresectable tumours

A. Concomitant Chemoradiotherapy

Key Evidence

Radiation with chemotherapy remains the standard of care for this heterogeneous population of patients and this has been demonstrated in a series of Radiation Therapy Oncology Group (RTOG) phase II and phase III clinical trials.[1-3]

RTOG 8501 was a phase II trial conducted between 1985 and 1990 in which patients with stage I-III esophageal carcinoma were allocated (both randomized and non-randomized) to chemotherapy and radiation versus radiation alone.[1] The combined modality arm showed a 5-year survival of 14 to 26% (randomized arm: 26% (95% CI, 1 to 37), non-randomized arm: 14% (95% CI, 6 to 23)) versus 0% in the radiation alone arm. Unfortunately, the most common cause of treatment failure in both groups was persistent disease (37% in radiation alone and 25% in the combined modality arm). Side effects were more common in the combined modality arms.[1]

Cancer Care Ontario conducted a pooled analysis of 7 randomized trials with a total of 687 patients assessing the 1-year survival benefit for concomitant chemoradiotherapy compared with radiotherapy alone.[4] Results illustrate a 1-year odds ratio of 0.61 (95% CI, 0.44 to 0.84; $p < 0.00001$) and improved local control with an odds ratio of 0.52 (95% CI, 0.31 to 0.89; $p = 0.004$), in favour of concomitant chemoradiotherapy. Despite improved local control and survival benefit, concomitant chemoradiotherpy compared to radiotherapy alone, comes with a significant increase in adverse effects including life-threatening toxicities.

Recommendations

1. Concomitant cisplatin-based chemotherapy and radical radiotherapy is recommended for the treatment of patients with unresectable/inoperable esophageal cancer. *Level of Evidence Ib*

2. Concomitant radiotherapy and chemotherapy is recommended over radiotherapy alone. Based on considerations of the current clinical practice and pattern and the research evidence currently available, a cisplatin-based chemotherapy regimen is a reasonable chemotherapy regimen to use when concomitant radiotherapy and chemotherapy is used with no plan for surgery. *Level of Evidence Ib*

Clinical Considerations

Patients should be made aware of the increased acute toxicity associated with this approach. The decision to use concomitant radiotherapy and chemotherapy should only be made after careful consideration of the potential risks and benefits, and the patient's general condition.

B. Radiotherapy

Key Evidence

In an attempt to improve locoregional control, RTOG initiated a phase III trial in 1995.[3] Patients (n = 236) with stage I to III esophageal cancer were randomized to 50.5 Gy versus 64.8 Gy using the same chemotherapy (5-fluorouracil and cisplatinum) in both arms. With a median follow-up of 16.4 months, there was no significant difference in median survival (13.0 months; 95% CI, 10.5 to 19.1 versus 18.1 months; 95% CI, 15.4 to 23.1), 2-year survival (31% versus 40%), or locoregional failure (56% versus 52%) between the two arms.

Recommendations

1. To define CTV, 2-4 cm proximally and distally and 1 cm radially to GTV may be added. These margins may be modified at the discretion of the treating radiation oncologist(s).
2. The standard dose for radiotherapy is 4500-5000 cGy in 25/28 fractions in 5 to 5.5 weeks.

C. Brachytherapy

Key Evidence

Brachytherapy, when added to external beam radiation with chemotherapy in this group of patients, has led to increased mortality and morbidity. Severe treatment-related effects included a 12% incidence of esophageal fistulas.[2]

Recommendation

1. Intraluminal brachytherapy as boost to the primary tumour is not recommended. *Level of Evidence Ib*

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XI. Implementation and Dissemination

The value of guidelines truly lies in their implementation and use. For that purpose, consideration was given to implementation during the drafting of this guideline document.

CancerCare Resources

It was recognized that resources would be needed to distribute these guidelines to the community. For that purpose, the guideline will be accessible online through the CancerCare Manitoba website. Online availability will be preceded by an e-blast notification with the website embedded. Announcement of the guideline and updates will be through established provincial communication channels: Community Oncology Program to CCPN rural sites, UPCON clinics and WRHA Community Oncology Program sites. Use of the guideline in clinic will be through the online version.

Educational Events

Presentation of the guideline's recommendations will be made available at rounds and conferences: Thoracic Tumour DSG Conference rounds, CCMB Haematology/Oncology Regional Grand rounds, Allied Health rounds (Patient Services rounds), CCPN Community Cancer Care annual educational conference and at UPCON education and training events.

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Acknowledgements

We gratefully acknowledge the support of CancerCare Manitoba, the CancerCare Manitoba Foundation, the Provincial Oncology Clinical Practice Guidelines Initiative, and external reviewers.

XIII. Conflict of Interest

In accordance with the CCMB policy no. 01.001, “Conflict of Interest”, the authors of this guideline declare that no commercial support was received for their presentations at the 2008 Provincial Consensus meeting or during subsequent development of this guideline.

XIV. Appendices

Appendix 1

TNM Classification System

Letter	Description	Staging
T = Primary Tumour	Indicates the size of the primary tumour and the degree of spread into nearby tissues (local invasion)	***TX:*** Primary tumour cannot be assessed
		T0: No evidence of primary tumour
		Tis: High-grade dysplasia
		T1: Tumour invades lamina propria, muscularis mucosae, or submucosa • ***T1a:*** Tumour invades lamina propria or muscularis mucosae • ***T1b:*** Tumour invades submucosa
		T2: Tumour invades muscularis propria
		T3: Tumour invades adventitia
		T4: Tumour invades adjacent structures • ***T4a:*** Resectable tumour invading pleura, pericardium, or diaphragm • ***T4b:*** Unresectable tumour invading other adjacent structures, such as aorta, trachea or vertebral body
N = Regional Lymph Nodes	Indicates whether or not the cancer has spread to nearby lymph nodes, the size of the nodes that contain cancer and how many lymph nodes contain cancer	***NX:*** Regional lymph nodes cannot be assessed
		N0: No regional lymph node metastasis
		N1: Metastasis in 1-2 regional lymph nodes
		N2: Metastasis in 3-6 regional lymph nodes
		N3: Metastasis in ≥ 7 regional lymph nodes
M = Metastasis	Indicates whether or not cancerhas spread (metastasized) todistant organs	***M0:*** No distant metastasis
		M1: Distant metastasis

Esophagus and esophagogastric junction. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 103-11

Appendix 2

Definitions	
Adenocarcinoma	A type of cancerous tumour that forms in mucus-secreting glands throughout the body.
American Joint Committee on Cancer (AJCC) Staging System	A classification system developed to report the extent of cancer progression.
Brachytherapy	A form of radiotherapy which involves placing radioactive substances (isotopes) directly into, or very close to, the tumour.
Clinical Practice Guidelines	Systematically developed statements, informed by research evidence, values and local/regional context to assist provider and patient decisions about appropriate health care for specific clinical circumstances.
Computed Tomography (CT) imaging	An imaging procedure using X-Ray equipment to scan areas of the body in an aim to detect abnormal growths, help diagnose tumours, provide information about the extent or stage of disease, guide biopsy procedures and monitor for recurrence.
Disease Site Group (DSG)	Interdisciplinary working group with specific expertise of the disease-site. This group is responsible for clinical practice guideline development and aftercare.
Dysphagia	Difficulty swallowing.
Effect Size	A statistical measure quantifying the magnitude of treatment effect.
En Bloc Resection	A surgical procedure involving complete removal of the entire primary tumour.
Esophagectomy	A surgical technique involving complete or partial removal of the esophagus.
Endoscopic Ultrasound (EUS)	An imaging procedure combining endoscopy with ultrasound to obtain images of internal organs of the digestive tract in an aim provide information about the extent or stage of disease and guide biopsy procedures.
FDG-PET/CT	An imaging technique used to detect cancer utilizes positron emission tomography (PET) with a radioactive tracer, ^{18}fluorodeoxyglucose (FDG), integrated with computed tomography (CT). FDG is avidly taken up by neoplastic tissue due to the increased metabolic activity, giving an accurate anatomical localization of the tumour using the FDG-PET/CT scan.
Fine Needle Aspiration Biopsy (FNAB)	A diagnostic procedure in which a sample of cells is drawn for cytological examination during the investigation of lumps or masses.
Gy	The gray (Gy) is a unit of absorbed radiation dose.
Linear Accelerator (LINAC)	The most commonly used device to deliver high-energy external beam radiation treatments for patients with cancer.
Meta-Analysis	A quantitative statistical method used to contrast and combine results from different studies to increase the power of significant results and the precision of estimates
Multidisciplinary Team	A group consisting of members with specialized skills and expertise from different healthcare professions.
Neoplastic	Pertaining to the uncontrolled growth of an abnormal mass of tissue; tumour.
Radiosensitizing Effect	The resultant effect by which chemotherapy increases the sensitivity of tumour cells to radiation therapy.
Sensitivity	A statistical measure of the ability of a test to correctly classify positive results.
Specificity	A statistical measure of the ability of a test to correctly classify negative results.
Systematic Review	A literature review and critical assessment of the best available empirical evidence that meets pre-specified eligibility criteria to answer a given research question. Transparent procedures are used to identify, appraise, select and synthesize the results of this high quality research evidence.
TNM Staging	The most widely accepted cancer staging system used as a tool to stage different types of cancer based on the size and/or extent of the primary tumour (T), the spread to regional lymph nodes (N), and the presence of distant metastasis (M).

Appendix 3

Levels of Evidence	
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed, quasi- experimental study
III	Evidence obtained from well-designed, non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
British Committee for Standards in Haematology 2007 http://www.bcshguidelines.com	

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November 2015