Esophageal Cancer and Management of Localized Disease: A Review

Matthew Chan[a,°], MD; Rohit Paib[b], MD, FRCPC; Frank Wong[b], MD; John Hay[c], MD; Chir, MRCP, FRCR, Eric Yoshida[b], MD, MHSc, FRCPC
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° Corresponding author: matthew.chan02@bccancer.bc.ca
[a] Vancouver Fraser Medical Program, UBC Faculty of Medicine, Vancouver, BC; [b] Division of Gastroenterology, Department of Medicine, University of British Columbia; [c] Department of Radiation Oncology, British Columbia Cancer Agency Vancouver Centre, Vancouver, BC

abstract

Esophageal cancer is often diagnosed in its late stages, with a 5–year overall survival rate of approximately 28 % in British Columbia. It frequently presents as either squamous cell carcinoma or adenocarcinoma. The most common presenting complaint is dysphagia, typically characterized by a worsening tolerance to solid foods.

Esophagogastroduodenoscopy with biopsy is the gold standard for diagnosis. Useful staging investigations include computed tomography scan of the chest and abdomen, 18–fluoro–deoxyglucose–positron emission tomography scan, and endoscopic ultrasound.

Esophageal cancer is a heterogeneous disease with no single optimal treatment algorithm. Esophagectomy has traditionally been the gold standard treatment in early–stage (Tis-T1) disease, but endoscopic treatment is also an option. Neoadjuvant chemoradiotherapy prior to definitive surgery should always be considered in more invasive (T2) disease, and it is recommended in late–stage (≥T3 or N+) disease. There is controversial evidence against the survival benefit and potential added morbidity of neoadjuvant chemoradiotherapy in the treatment of early esophageal cancer. Unresectable and cervical tumors should be treated with definitive chemoradiotherapy. The optimal treatment of adenocarcinomas of the distal esophagus and gastro–esophageal junction is under investigation, but it likely includes peri–operative chemotherapy.

Current research in esophageal cancer is investigating the use of early 18–fluoro–deoxyglucose–positron emission tomography scans to assess response to chemotherapy, which could have important implications in prognostication and treatment decisions.

introduction

Esophageal cancer is often diagnosed in its late stages with a 5–year overall survival rate of approximately 28 % in British Columbia.[1] This is largely due to the lack of a serosal barrier in the esophagus, allowing for easier locoregional spread. In this instance, eliminating the microscopic disease with neoadjuvant or adjuvant treatment is very important.

Esophageal cancer frequently presents as either squamous cell carcinoma (SCC) in the proximal two-thirds of the esophagus (often in patients with a significant alcohol or smoking history), or as adenocarcinoma in the gastro-esophageal (GE) junction or the distal third of the esophagus (often in patients with longstanding gastroesophageal reflux and Barrett's esophagus). The incidence of SCC has decreased significantly in recent years in North America, likely secondary to a decrease in cigarette smoking. Conversely, the incidence of adenocarcinoma has increased considerably, believed to be in part due to increased rates of obesity and reflux disease.[2]

There is no suitable screening test for SCC. Patients with Barrett's esophagus should undergo routine endoscopic screening to rule out mucosal dysplasia, which may require ablation or surgical resection.

Patients with esophageal cancer commonly present with dysphagia to solids that may progress to dysphagia to liquids, sometimes in a matter of months. The dysphagia occurs several seconds after initiating a swallow, often with a sensation of food "sticking" in the neck, chest, or upper abdomen.[3]

anatomical classification and lymphatic drainage

Esophageal cancers are classified by their distance from the central incisors: 15-18 cm for cervical tumors, 18-24 cm for upper thoracic tumors, 24-32 cm for middle thoracic tumors, and 32-40 cm for lower thoracic/GE junction tumors. Cervical tumors primarily drain cranially to the supraclavicular, cervical, and peri–esophageal lymph nodes. Thoracic tumors drain to the mediastinal lymph nodes. GE junction tumors drain caudally to the left gastric and celiac axis lymph nodes. Distant metastatic disease is most common in the liver, lungs, and bone.

diagnostic workup

Esophagogastroduodenoscopy with biopsy is the gold standard test for establishing the diagnosis. Staging options include computed tomography (CT) scan of the chest and abdomen, 18-fluoro-deoxyglucose-positron emission tomography (FDG-PET), and endoscopic ultrasound. CT scan is the most frequently used imaging modality; however, it has low sensitivity in detecting subcentimetre lymph node metastases (sensitivity 57 % for detecting regional node involvement), which is problematic as diagnosis relies largely on size and shape criteria.[4,5,6]

Because metabolic changes precede structural changes in metastatic lymph nodes, it was proposed that FDG-PET could be used with higher sensitivity in detecting cancer in normal-sized lymph nodes.[7] Despite this rationale however, the sensitivity of FDG-PET for regional lymph node disease is only about 51 %.[8] Its primary use has therefore been to rule out distant metastatic disease and to save patients the morbidity of an unnecessary major surgery (29 % avoided unnecessary resection in a study by Van Westreenen et al.).[9] Interestingly, FDG–PET has been shown to alter the radiation treatment fields approximately 50 % of the time.[10]

Endoscopic ultrasound is another staging option with high accuracy in local tumor (T) staging, but it has limited utility in lymph node staging. Its penetration depth is restricted to approximately 5 cm.[11,12] It is considered to be complementary to CT and FDG–PET. It can be useful in scenarios where both CT and FDG–PET are negative for nodal disease, and accurate T–staging is required to clarify a patient's eligibility for local resection (versus esophagectomy). If the primary tumor is in close proximity to an airway, bronchoscopy is often required to rule out invasion because airway involvement precludes radical resection.

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Table 1: Staging of esophageal cancer.[13]

TNM Staging		Stage Groupings			
Tis	High-grade dysplasia	Stage 0	Tis	N0	M0
T1a	Invades lamina propria/muscularis mucosae	Stage IA	T1	N0	M0
T1b	Invades submucosa	Stage IB	T2	N0	M0
T2	Invades muscularis propria	Stage IIA	T3	N0	M0
T3	Invades adventitia	Stage IIB	T1-2	N1	M0
T4a	Invades pleura, pericardium, diaphragm	Stage IIIA	T4a	N0	M0
			T3	N1	M0
T4b	Other adjacent structures (aorta, trachea)		T1-2	N2	M0
		Stage IIIB	T3	N2	M0
N1	Regional lymph nodes (1-2)	Stage IIIC	T4a	N1-2	M0
N2	Regional lymph nodes (3-6)		T4b	Any N	M0
N3	Regional lymph nodes (>6)		Any T	N3	M0
M1	Distant metastasis	Stage IV	Any T	Any N	M1

staging and prognostic factors

Tumor–Node–Metastasis (TNM) classification of malignant tumors and staging groups are shown in Table 1. The most important prognostic factor is the stage at diagnosis. Other prognostic factors include the tumor volume, the presence of lymphovascular invasion, the Eastern Cooperative Oncology Group (ECOG) score, and the response to neoadjuvant treatment.

management

Early Disease Management

Esophagectomy with gastric tube pull–up has traditionally been the gold standard treatment for Tis-T1N0M0 disease, but its associated morbidity and mortality has restricted its role to a minority of medically fit patients.[14] Endoscopic techniques including endoscopic mucosal resection are an alternative to those with Tis/T1a disease.

Locally–Invasive Disease Management

In cases of ≥T3 or N+ disease, neoadjuvant chemoradiation therapy (CRT) followed by esophagectomy is the recommended treatment. The advantage of neoadjuvant treatment was demonstrated by the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS).[15] In the CROSS study, 368 patients with resectable esophageal or GE junction tumors were randomly assigned to either surgery alone or CRT followed by surgery. CRT involved the weekly administration of carboplatin and paclitaxel and concurrent radiotherapy with 41.4 Gy in 23 fractions. Median overall survival was shown to be significantly better in the CRT–surgery group, at 49.4 months with CRT–surgery versus 24 months with surgery alone (p=0.003). The CRT-surgery group had higher radical resection rates (92 % CRT–surgery versus 69 % surgery alone) and achieved pathologic complete response in 29 % of resected cases, without additional post-operative morbidity compared to the group treated with surgery alone.

Controversy in Early Disease Management

The benefit of neoadjuvant CRT in early esophageal cancer remains less clear than in locally-invasive disease. The Federation

Francophone de Cancérologie Digestive (FFCD) 9901 phase III trial published its results in June 2014, comparing surgery alone versus CRT followed by surgery in patients with stage I or II esophageal cancer.[16] The authors of the trial found no difference in overall survival or disease–free survival between the two groups, and interestingly, they found a 3–fold higher thirty–day post–operative mortality rate in the CRT group (11.1 % versus 3.4 %, p=0.049). This is in contrast to previous studies, including the CROSS trial, which demonstrated a survival benefit with pre–operative CRT and no increase in post–operative mortality.[15] It has been noted that there were several differences between these two trials. In FFCD 9901, the patient population may have had poorer baseline health, and the patients predominantly had SCC, unlike CROSS, wherein 75 % of patients had adenocarcinoma. Furthermore, fluorouracil and cisplatin were used in FCCD 9901, whereas paclitaxel and carboplatin, which are thought to be better tolerated, were used in CROSS. Lastly, there were differences in radiation techniques between the two trials. In the case of T2 tumors, some physicians advocate for neoadjuvant CRT due to observations of significant under–staging of T2N0 patients in previous studies (>50 % in the Zhang 2012 study).[17]

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Unresectable and Cervical Tumors

For unresectable tumors (such as those involving the trachea or aorta) and cervical tumors (where resection would usually require laryngectomy), definitive CRT is recommended. In these cases, the standard of care is to deliver five weeks of radiation treatment (50 Gy in 25 fractions) with two concurrent cycles of fluorouracil and cisplatin during weeks 1 and 5 and two cycles post–RT. Definitive CRT became the standard of care for inoperable disease after the Radiation Therapy Oncology Group (RTOG) 85-01 trial, which compared concurrent CRT (50 Gy in 25 fractions and two cycles of concurrent and post–RT cisplatin and fluorouracil) against RT alone (64 Gy in 32 fractions). This trial closed prematurely when an interim analysis showed a significant survival benefit with CRT (5–year survival 27 % versus 0 %).[18]

Adenocarcinomas of Distal Esophagus and GE Junction

The best treatment option for adenocarcinoma of the distal esophagus and GE junction is unclear, and optimal management continues to be defined. The current recommended treatment is three cycles of pre–operative chemotherapy and three cycles of post–operative chemotherapy, with epirubicin, cisplatin and capecitabine (ECC) or epirubicin, cisplatin and infusional fluorouracil (ECF). This recommendation was guided by the results of the Medical Research Council Adjuvant Gastric Infusion Chemotherapy (MAGIC) trial, which evaluated peri–operative chemotherapy in resectable gastric cancer, 25 % of which were of the lower esophagus or GE junction.[19] In this study, 503 patients with at least stage Ib disease were randomly assigned either to surgery alone or to three cycles of pre–operative ECF, then surgery, followed by three cycles of post-operative ECF. Five–year overall survival favoured treatment with ECF compared to surgery alone (36 % versus 23 %, p=0.009). Of note is that the design of this trial has attracted criticism for its lack of detailed pre–operative local staging, for insufficient data regarding surgical technique, and for poor rates of commencement and completion of postoperative chemotherapy (only 42 % of patients completed all prescribed chemotherapy). The French Fédération Nationale des Centres de Lutte Contre le Cancer (FNLCC)/FFCD trial showed similar benefit with neoadjuvant chemotherapy.[20] The benefit of CRT over pre–operative chemotherapy alone is currently the topic of a multicenter randomized trial of preoperative therapy for gastric and GE junction adenocarcinoma by the National Cancer Institute of Canada (NCIC), the European Organization for Research and Treatment of Cancer (EORTC), and the Trans-Tasman Radiation Oncology Group (TROG) collaborative group.[21]

The benefit of neoadjuvant CRT in early esophageal cancer remains less clear than in locally-invasive disease.

future directions

Current research is investigating the use of early FDG-PET scans to assess response to chemotherapy. The MUNICON-II (Metabolic response evalUatioN for Individualisation of neoadjuvant Chemotherapy in Oesophageal and esophagogastric adeNocarcinoma) prospective study found that PET scans taken upon initiation of chemotherapy and two weeks later were predictive of the overall response to neoadjuvant chemotherapy in patients with locally advanced GE junction adenocarcinoma.[22] Specifically, those whose tumors showed a mean standardized uptake value (SUV) decreased by >35 % were defined as chemotherapy–responders and received an additional three months of chemotherapy, whereas non–responders (mean SUV decreased by <35 %) were referred for earlier surgery after receiving only a relatively short course of salvage CRT. After a median follow–up time of 38 months, the median overall survival had not yet been reached in the PET responders, whereas the median overall survival in the non–responders was 18.3 months. The MUNICON–II study confirmed the prognostic value of FDG–PET even as early as two weeks after starting chemotherapy. The Cancer and Leukemia Group B (CALGB) 80803 randomized phase II trial will further investigate the use of PET scans in patients with locally advanced esophageal or GE junction adenocarcinoma.[23] In that

study, patients will be randomized to treatment with either carboplatin/paclitaxel or modified FOLFOX6 (fluorouracil plus leucovorin and oxaliplatin) and undergo PET scan at day 36-42. PET responders will continue chemotherapy and undergo radiation treatment. Non-responders will cross over to the other chemotherapy regimen and undergo radiation treatment. The primary objective will be to induce a pathologic complete response rate of 20 % in PET non-responders in either treatment arm.

conclusion

The optimal management of esophageal cancer remains to be defined. The intent of this review was to present some of the trials that have influenced current recommendations. A number of trials that were not discussed had conflicting results. Esophageal cancer is heterogeneous in its presentation, and there is no single treatment algorithm that can be applied to every patient. It is apparent from the literature that SCC and adenocarcinoma behave and respond differently, yet they are often grouped together in clinical trials. There is also a lack of definitive evidence to support the 41.4 Gy radiation dose used in the CROSS trial as the optimal pre–operative dose. Additionally, there are no head–to–head trials comparing carboplatin versus cisplatin–based CRT. Many questions still exist in the management of esophageal cancer, but because most patients present with locally invasive disease, tri–modality therapy should always be a consideration.

The benefit of CRT over pre–operative chemotherapy alone is currently the topic of a multicenter randomized trial of preoperative therapy for gastric and GE junction adenocarcinoma by the National Cancer Institute of Canada (NCIC), the European Organization for Research and Treatment of Cancer (EORTC), and the Trans-Tasman Radiation Oncology Group (TROG) collaborative group.[21]

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