Curative management of adenocarcinoma of the oesophagus and oesogastric junction — Current recommendations of the Belgian Working Group

J.-L. Van Laethem (Coordinator, ULB-Erasme,), F. Baert (Helig-Hart Ziekenhuis,Roeselaere) , M. Buset (ULB, St Pierre),B. de Hemptine (UZ Ghent), Th. De Ronde (UCL-Mont Godinne), P. Honoré (ULg, Sart Tilman), T. Lerut (KUL), P. Scaillet (UCL, St Luc) and E. Van Cutsem (KUL)

Clinical case

A 65 y.o. male with a long history of heartburn presents with dysphagia due to 3 cm bulging adenocarcinoma of the GE junction. Endosonographic evaluation reveals a T_3N_1 lesions.

Therapeutic option

- curative surgery with or without chemoradiation.

The incidence rate of oesophageal and junctional adenocarcinoma is dramatically rising over these 20 last years in Western countries and overall 5-year survival rate is approximately less than 25% for patients with locally advanced disease (stage T_3/T_4 - N_0/N_1-M_0).

For localized tumors (T_1/T_2 - N_0-N_1), the 5-year survival varies from 90% (T_1N_0) to 35-50 % (T_2-N_1) after curative surgery.

The above working group provides the following recommendations based on the experts' lectures (pro or contra multimodal approach), the recent literature and their own experience and practice in their relative centers :

1. An optimal preoperative staging aiming to determine the patient's operability and the resecability of the tumor is a key step for a better management of adenocarcinoma of the lower oesophagus or the oesogastric junction (OGJ). For both localizations,TNM classification is provided in table 1.
   Work-up should ideally include : upper GI endoscopy, endoscopic ultrasonography (EUS), barium swallow study, chest and abdominal CT-scan, bronchoscopy. A staging using (echo)laparoscopy could be proposed in stage III OGJ especially for detecting peritoneal micrometastases. PET-scan is an attractive and new procedure and might be recommended in staging when available. An evaluation of operability status is mandatory before resection and relies on cardiac, pulmonary and liver function assessment. Each patient should be ideally assessed and managed through a multidisciplinary team including a experienced surgeon, a gastroenterologist and/or medical oncologist and a radiotherapist.
2. Oesogastrectomy is considered as the standard for cure and should be ideally performed in centers of high expertise.
   Criteria of irresecability are :
   - clinical cT_4 stage in supracarinal tumors and in infracarinal tumors when there is a clear invasion of aorta on CT (> 90°) and/or EUS ;
   - distant metastases (peritoneal metastases seen at laparoscopy) ;
   - tumor progression under chemoradiotherapy.

   The recommended surgery is wide, en-bloc, peritumoral oesophagectomy with two field lymphadenectomy (left transthoracic approach). Transhiatal oesophagectomy is recommended only in patients with a higher operative risk and with tumor confined within the oesophageal wall.
   A total gastrectomy is advocated only if the tumor extends 5 cm aborally from the EGJ. In the other cases, a partial gastrectomy along the great curvature is performed with the gastric tube brought up into the apex of the chest or into the neck. A third field procedure, ie cervical lymphadenectomy is optional and investigational.
3. Preoperative (neoadjuvant) chemotherapy or rather chemoradiotherapy are not recommended before surgery for resectable tumors, due to insufficient data and discrepancies in staging and results from phase III randomized studies. However, despite an increased risk of postoperative mortality (ARDS, pneumopathia,...), the high rate of complete response observed in phase II studies ($\approx$ 25% of complete pathological response) opens attractive prospects in this field and can be proposed as induction therapy notably for T_4 and large T_3N^+ tumors ; in this setting, resection should be reconsidered unless clear tumor progression.
4. Due to the high rate of complete response after chemoradiation, exclusive chemoradiotherapy can be advocated as a valuable curative alternative to surgery in patients with non resecable tumors or at high operative risk (all stage), providing a 3 to 5-year survival around 25-30%.
5. Postoperative chemoradiation is usually not recommended due to a lack of significant benefit from the reported literature.

Table 1. — TNM classification (UICC 1997)

T- Primary tumor (**Lower third of the oesophagus**)
T0 : no evidence of primary tumor
T1 : tumor invades lamina propria or submucosa
T2 : « « muscularis propria
T3 : « « adventitia
T4 : « « adjacent structures

N- Regional Lymph Nodes
Nx : RLN not assessable
N0 : no RLN metastasis
N1 :RLN metastasis
Regional LN are the mediastinal and perigastric nodes , excluding coeliac nodes.

M- Distant Metastases
M0 : no distant metastases
M1 : ditant metastases
M1a : metastases in coeliac LN
M1b : other distant metastases

Stage grouping :

0 :	Tis	N0	M0
I :	T1	N0	M0
IIA :	T2-T3	N0	M0
IIB :	T1-T2	N0	M0
III :	T3-T4	N1(T4N0)	M0
IVA :	any T	any N	M1a
IVB :	any T	any N	M1b

T-Primary tumor (**CARDIA**)
T : idem supra

N- Regional Lymph Nodes

Nx :RLN not assessable
N0 : no RLN
N1 : metastases in 1 to 6 RLN
N2 : metastases in 7 to 15 RLN
N3 : metastasis in more than 15 RLN
Regional LN are the perigastric nodes,the nodes along the left gastric, the common hepatic, splenic ,and coeliac arteries, and the hepato-duodenal nodes.Other intraabdominal nodes (retropancreatic,mesenteric or paraaortic are distant metastasis)
M-Distant Metastases
M0 : no distant metastases
M1 :distant metastases
Stage grouping :

0	Tis	N0	M0
IA	T1	N0	M0
IB	T1	N1	M0
	T2	N0	M0
II	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
IIIA	T2-T3	N2-N1	M0
	T4	N0	M0
IIIB	T3	N2	M0
IV	any T	N3	M0-1

Remark : distinction between cancer of the lower third of the oesophagus and the cardia may be difficult in case of large and long tumors ; in undetermined accurate origin, involvement of coeliac nodes may be considered as regional.

Residual micro- or macroscopic (R_1 or R_2) disease is an indication of adjuvant chemoradiation ; a high number of positive lymph nodes could also be considered for an adjuvant therapy (chemotherapy or chemoradiation) but these indications should be discussed case by case.

6 Current chemotherapy based-regimens usually include cisplatinum and 5FU and the use of these drugs are recommended when chemoradiation or chemotherapy alone is indicated. Although a lot of new drugs are currently in development, in combinaison with other chemotherapeutic agents or radiation, such as docetaxel, paclitaxel, gemcitabine, vinorelbine, there is no clear proof that these experimental regimens are more active than the conventional ones and due to their possible high rate of toxicities, there should be assessed only within prospective controlled trials. It should be also noted that a

recent intergroup study (INT-0116) presented at the ASCO meeting (New Orleans May 2000), reports a significant benefit of an adjuvant combined radiation (45 Gy) and chemotherapy (5FU and leucovorin bolus) in resected (R0) adenocarcinoma of the stomach and OG junction (N+). The final publication of this study will possibly prompt us to recommend this strategy in oesogastric tumors.

7. Ablative endotherapy is attractive and provides promising results for highly selected cases but remains experimental. For patients unfit for surgery and presenting a superficial (high grade dysplasia or Tis-T_1 Sm using high frequency EUS, 20mHz) and single (< 20 mm) lesion of the oesophagus, endoscopic treatment could be reasonably advocated. Endoscopic mucosal resection (EMR) is the best option for a single well delineated lesion while photodynamic therapy (PDT) or Nd :Yag laser (due to the non availability of PDT in Belgium) is preferable in case of diffuse lesion (i.e. high grade dysplasia developed in Barrett's).
8. In summary the following therapeutic recommendations for each disease clinical stage are proposed :

Stage I (Tis-T_1-N_0) :
- *oesophagectomy* (+ two field lymphadenectomy)
- endoscopic treatment or (chemo)radiation (brachytherapy if patient unfit for surgery

Stage IIA (T_2-T_3-N_0) :
- *oesophagectomy*

IIB (T_1-T_2-N_1) :
- *oesophagectomy*
- chemoradiation if patient unfit for surgery

Stage III (T_3-T_4-N_1) :
- oesophagectomy (T_3-N_1)
- chemoradiation followed by surgery (unless tumor progression)
- exclusive chemoradiation

Stage IV (any T-N-M1) : M1b = organ : palliation of dysphagia-chemotherapy when good performance status

M1a = lymph node : induction therapy (chemo- and/or radiotherapy) then resection could be reconsidered if good response

REM. : for the tumors of oesogastric junction : oesogastrectomy is indicated in stage I, II and III. For stage III, induction therapy may be proposed before surgery.