GMCA GREATER MANCHESTER COMBINED AUTHORITY

NHS in Greater Manchester

Greater Manchester Cancer

Oesophago-gastric Pathway Board

Network Guidelines for the Management of Oesophageal and Gastric Cancer

- Chemotherapy and Radiotherapy

Contributors:

Dr Lubna Bhatt, Clinical Oncologist, The Christie NHS Foundation Trust

Dr Richard Hubner, Medical Oncologist, The Christie NHS Foundation Trust

Dr Was Mansoor, Medical Oncologist, The Christie NHS Foundation Trust

Dr Ganesh Radhakrishna, Clinical Oncologist, The Christie NHS Foundation Trust

Dr Hamid Sheikh, Clinical Oncologist, The Christie NHS Foundation Trust

Dr Tom Waddell, Medical Oncologist, The Christie NHS Foundation Trust

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1. CURATIVE INTENT - GASTRIC AND GASTRO-OESOPHAGEAL JUNCTION (GOJ) ADENOCARCINOMA

1.1 Gastric / GOJ Adenocarcinoma - Treatment Summary According to Stage

Stage	Recommendation	Comments
Surgical candidate – patient fit and appropriate disease distribution		
T1N0M0	Surgical Resection	EMR may be considered for T1a Perioperative chemotherapy may be considered for T1b
T2N0 or above	Perioperative chemotherapy; neoadjuvant FLOT x4 cycles + surgical resection + adjuvant FLOT x4 cycles (or ECX x3 cycles neoadjuvant/adjuvant)	As per FLOT4-AIO[1] or MAGIC[2] trials Surgery recommended within 4-6 weeks of completing neoadjuvant chemo Adjuvant chemo recommended within 12 weeks of surgery Chemo not recommended if presenting in gastric outlet obstruction or with uncontrolled bleeding
T2N0 or above and did **not** receive neoadjuvant chemo	Consider post-operative chemoradiotherapy (MacDonald regimen[6] – 45Gy in 25# with concurrent capecitabine) OR Consider adjuvant chemotherapy with FLOT/ECX if MacDonald not appropriate	Discussion and agreement of management plan via MDT is required prior to referral
Not surgical candidate – may be due to disease (e.g. nodal disease sites) or patient factors		
Type I / II GOJ	Consider definitive chemoradiotherapy (dCRT) if disease can be encompassed in radiotherapy field	Need <3cm of gastric extension PS 0-1
Gastric / Too extensive for dCRT / Poor PS	Consider palliative chemotherapy if deemed fit	

1.2 Perioperative chemotherapy

Patients with adenocarcinoma of the stomach and gastro-oesophageal junction (GOJ) with stage T2N0M0 or above that are deemed amenable to surgical resection should be considered for perioperative chemotherapy based on evidence from the FLOT4-AIO[1] and MRC ST02 (MAGIC)[2] trials. The recommended regimen is FLOT; docetaxel, oxaliplatin, and 5-flurouracil/leucovorin, 4 x 2-weekly cycles pre- and post-operatively assuming the patient remains of suitable performance status following recovery from surgery. The ECX (epirubicin, oxaliplatin, and capecitabine) regimen may also be considered if patients are unsuitable for FLOT. The ECX regimen is a modification of the ECF (epirubicin, oxaliplatin, and infusional 5-flurouracil) regimen used in the MAGIC trial based on data from the REAL2 trial[3] which demonstrated at least equivalent efficacy for ECX as compared to ECF and greater convenience in the advanced disease setting. The recommended time interval between completing neo-adjuvant (pre-operative) chemotherapy and undergoing surgery is 4-6 weeks, and adjuvant (post-operative) chemotherapy should be commenced within 12 weeks of surgery. Peri-operative chemotherapy may also be considered for patients with clinical stage T1bN0M0 disease on a case-by-case basis at MDT discussion. Peri-operative chemotherapy is not recommended for patients who have clinical features which make chemotherapy unsuitable such as gastric outlet obstruction or uncontrolled tumour bleeding.

Patients who undergo surgery for T2N0M0 or higher stage gastric or GOJ adenocarcinomas without neo-adjuvant chemotherapy may be considered for adjuvant chemotherapy[4-5]. In this instance 4 cycles of FLOT (or 3 cycles of ECX) is recommended. For gastric cancers, they may alternatively be considered for MacDonald regimen adjuvant chemoradiotherapy (see below). The decision regarding adjuvant therapy and most appropriate method should be discussed and agreed via the MDT.

1.3 Definitive chemoradiotherapy

For Sievert 1 or 2 adenocarcinoma of GOJ with <3cm of gastric extension, definitive chemoradiotherapy (CRT) may be considered for patients of good WHO PS (0-1) deemed unsuitable for surgical management.

1.4 Adjuvant chemoradiotherapy

Post-operative CRT (MacDonald's regimen[6]) can be considered in selected patients who did not receive neoadjuvant chemotherapy e.g. gastric outlet obstruction at presentation / upstaging at surgery. In selected cases, there may be a role for post-operative CRT in patients with microscopic positive longitudinal or circumferential resection margins. This should be discussed between the

medical and clinical oncology teams as appropriate. Patients should have WHO PS 0-1, adequate renal function, and have had an R0 or R1 resection (R2 excluded) with no measurable disease post-operatively.

Post-operative CRT regimen:

- Radiotherapy: 45Gy in 25 fractions treating 5 days per week
- Chemotherapy: induction capecitabine 1gm/m2 bd 14 days 3 weeks prior to start of RT, then capecitabine 1gm/m2 bd Mon-Fri 25 days during RT

2. CURATIVE INTENT – OESOPHAGEAL CARCINOMA

2.1 Oesophageal Squamous Cell Carcinoma - Treatment Summary According to Stage

Stage	Recommendation	Comments
Surgical candidate – patient fit and appropriate disease distribution		
T1N0M0	Surgical Resection	EMR may be considered for T1a dCRT may be considered for T1b
T2N0/1 or T3/4a N0/1	Trimodality therapy with neoadjuvant chemoradiotherapy (CRT) as per CROSS trial regimen[11] (Recommended) OR Definitive CRT (dCRT)[7-9] OR If tumour factors make CRT or dCRT inappropriate, consider perioperative chemotherapy as per FLOT-AIO/OE02/MAGIC and surgery.	For CRT: - Total disease length (including primary tumour and involved lymph nodes) ≤ 13 cm. Primary tumours should also be ≤10cm. where these parameters are exceeded, discussion with clinical oncologist should occur to judge if disease is encompassible within a tolerable radical radiation volume. - Need <3cm of gastric extension - PS 0-1 Surgery recommended within 6-10 weeks of CRT
Not surgical candidate – may be due to disease (e.g. nodal disease sites) or patient factors		
T1N0 or above	Consider definitive chemoradiotherapy (dCRT) if disease can be encompassed in radiotherapy field	Need <3cm of gastric extension GFR >40ml/min
Not fit for dCRT	Consider high dose palliative radiotherapy if disease can be encompassed in radiotherapy field	
Too extensive for RT	Consider palliative chemotherapy if deemed fit	

2.2 Oesophageal Adenocarcinoma - Treatment Summary According to Stage

Stage	Recommendation	Comments
Surgical candidate – patient fit and appropriate disease distribution		
T1N0M0	Surgical Resection	EMR may be considered for T1a Perioperative chemotherapy may be considered for T1b
T2N0 or above	Perioperative chemotherapy; neoadjuvant FLOT x4 cycles + surgical resection + adjuvant FLOT x4 cycles (or ECX x3 cycles neoadjuvant/adjuvant) OR Consider sequential trimodality CRT approach[10,11] (as for squamous cell carcinoma above) on a case-by-case basis	Surgery recommended within 4-6 weeks of completing neoadjuvant chemo Adjuvant chemo recommended within 12 weeks of surgery Chemo not recommended if presenting in gastric outlet obstruction or with uncontrolled bleeding
Not surgical candidate – may be due to disease (e.g. nodal disease sites) or patient factors		
T1N0 or above	Consider definitive chemoradiotherapy (dCRT) if disease can be encompassed in radiotherapy field	Need <3cm of gastric extension GFR >40ml/min
Not fit for dCRT	Consider high dose palliative radiotherapy if disease can be encompassed in radiotherapy field	
Too extensive for RT	Consider palliative chemotherapy if deemed fit	

2.3 Pre-operative chemoradiotherapy

The evidence base for neoadjuvant CRT is currently confined to improving outcomes in patients who are considered operable at time of initial staging. There is no current role in downstaging patients who are deemed inoperable. There is no role for radiotherapy alone in the pre-operative setting.

Squamous Cell Carcinoma

Neoadjuvant CRT should be routinely considered for any operable patient deemed fit for trimodality treatment with WHO PS0-1 and the following disease criteria[10, 11];

- T2 N0-1 or T3 –T4a N0-1
- Total disease length (including primary tumour and involved lymph nodes) ≤ 13 cm. Primary tumours should also be ≤10cm. where these parameters are exceeded, discussion with clinical oncologist should occur to judge if disease is encompassible within a tolerable radical radiation volume.

Mandatory staging required prior to neoadjuvant CRT;

- PET CT with reference measurements of tumour relative to the top of aortic arch and carina. Reference measurements required for nodes felt to be malignant
- EUS with reference measurements of tumour ab oral relative to the top of aortic arch and carina. Reference measurements required for nodes felt to be malignant
- Upper or middle third tumours: a bronchoscopy is required for all patients being considered for radiation therapy where the oesophageal tumours is encroaching, bulging and / or considered at risk of direct invasion in to the airway on any imaging modality
- Staging laparoscopy where tumour crosses diaphragm

Prior physiological testing with echocardiogram, pulmonary function tests, and CPEX is recommended, and there should be SMDT consensus that the patient has the required physiological fitness and limited co-morbidity. In addition, careful attention to feeding is required with a feeding jejunostomy sited before referral for trimodality therapy for those with higher grade of dysphagia (modified O'Rourke score 3 or above) or where felt required by specialist dietician at surgical centre.

Any patient considered of insufficient fitness for trimodality treatment should be considered for definitive CRT.

Trimodality treatment CRT regimen[10, 11]:

- Radiotherapy: 41.4Gy in 23 fractions treating 5 days per week
- Chemotherapy: Carboplatin AUC2 and Paclitaxel 50mg/m2 weekly days 2, 9, 16, 23 and 30.

Surgery should take place at no sooner than 6 weeks following completion of CRT but no later than 10 weeks. Re-staging CT imaging should take place around 4 weeks after completion, and should take place at surgical centre[7-11].

Adenocarcinoma

The benefit of neoadjuvant CRT over neoadjuvant chemotherapy alone in adenocarcinoma of the oesophagus is less well established, however if a patient meets the same criteria as for squamous cell carcinomas above than this option can be considered on a case-by-case basis.

Summary of published key Neoadjuvant Chemo and ChemoRT trials

Trial	Regimen	Median OS (months)	3Yr Survival Rate	pCR Rate	R0 Resection Rate
OeO5 (n= 897)	ECX x 4vs. PF x 2	26.1 vs. 23.4	42 vs. 39%	11 vs 3 %	66 vs60%
CROSS[11] (n=368)	Carbo/Taxol CRT + Sx vs Sx alone	48.6 vs 24	58% vs. 44% 5ys 47 vs 33%	29% CRT	92 vs. 69%
	SCC	81.6 vs 21.1	68.3%	49%	
	Adenoca	43.2 vs. 27.1	47%	23%	
FLOT[1] AdenoCa gastric and oesoph (44% gastric) (n= 716)	FLOT vs ECX	50 vs.35	45% vs. 36%	≤ T1=25vs. 15%	85% vs. 78%

Neoscope (randomised ph 2 adenoca only) n= 85) – advanced T3 N+ tumours	Carbo/Taxol CRT vs. Ox/Cap CRT	na		29.3vs 11.1%	80.5vs. 72.2%
NeoCRTEC5010 451 (SqCC only)	Cis/Vinorelbine and 40Gy in 20fractions +sx vs Sx alone	100.1 vs 66.5	69.1 vs58.9%	43.20%	98.4 vs 91.2%

OE05 www.thelancet.com/oncology Vol 18 September 2017
NeoSCOPE European Journal of Cancer 74 (2017) 38e46
NeoCRTEC JCO sept 2018. 36(27)

2.4 Definitive chemoradiotherapy

Definitive CRT (dCRT) can be considered for any oesophageal cancer, T1N0M0 or above, that can be encompassed within a radical radiotherapy field. For oesophageal squamous cell carcinoma, where trimodality therapy is not recommended due to tumour factors (e.g. sites of nodal disease) or patient related factors, dCRT is the recommended standard of care. For early stage squamous cancers (T1-T2N0) surgery alone (T1N0) or neoadjuvant chemotherapy/ surgery (T2N0) is an alternative option for patients deemed fit.

The required mandatory staging investigations are as for neo-adjuvant CRT (see above). Patients should have WHO PS 0-1, and a glomerular filtration rate (GFR) > 60ml/min is required for cisplatin-based chemotherapy but alternative chemotherapy regimens may allow dCRT in patients with GFR 60-40ml/min. Placement of a percutaneous gastrostomy tube (RIG), is recommended for patients with high grades of dysphagia or where felt necessary by specialist dietician.

Radiotherapy regimens for dCRT:

- 50Gy in 25 fractions treating 5 days per week
- 45-50.4Gy in 1.8Gy per fraction can be considered if gastric/small bowel tolerance is of concern and / or clinically indicated.
- 60-66Gy Gy in 30 fractions treating 5 days per week for tumours in cervical oesophagus or selected upper third cases

Chemotherapy regimens for dCRT

- Two cycles of cisplatin/capecitabine induction followed by radiotherapy and cisplatin/capecitabine week 1 and week 5.
- Weekly carboplatin/paclitaxel as per pre-operative regimen can be considered in patients where cisplatin/capecitabine is contraindicated e.g. history of ischaemic heart disease or suboptimal renal function (GFR 60-40ml/min).
- For 30 fraction radiotherapy regime, induction cisplatin/ capecitabine chemotherapy is allowed followed by 3-weekly cisplatin 80-100mg/m2 for 2-3 cycles concurrently.

2.5 High dose palliative radiotherapy

For patients who have localised disease encompassible within a radical radiotherapy volume, but who are deemed unsuitable for dCRT treatment, high dose radiotherapy to the local disease may be

considered. The suitability for dCRT or radiotherapy alone can only be decided after review by a clinical oncologist. A discussion should be conducted by a clinical oncologist in relation to the rationale for selection, risks and benefits with the patient. Patients should be WHO PS 0-2, and placement of a percutaneous gastrostomy tube (RIG), is recommended for patients with high grades of dysphagia or where felt necessary by specialist dietician.

Mandatory staging required prior to definitive radiotherapy;

- PET CT with reference measurements of tumour relative to the top of aortic arch and carina. Reference measurements required for nodes felt to be malignant
- EUS with reference measurements of tumour ab oral relative to the top of aortic arch and carina. Reference measurements required for nodes felt to be malignant
- A bronchoscopy is required for all patients being considered for radiation therapy for oesophageal tumours encroaching, bulging and / or considered at risk of direct invasion in to the airway on any imaging modality

Radiotherapy regimens:

- 55Gy in 20 fractions treating 5 days per week
- 50Gy in 16 fractions treating 5 days per week can be considered as shorter course
- A lower dose of RT (45Gy) may be considered if gastric/small bowel tolerance is of concern.

2.6 Perioperative chemotherapy

Patients with adenocarcinomas of the oesophagus stage T2N0M0 or above (or T1bN0M0 on a case-by-case basis at MDT discussion) that are deemed amenable to surgical resection may be considered for perioperative chemotherapy, as per guidelines for gastric and GOJ cancers. Patients with squamous cell carcinomas (SCC) of the oesophagus stage T2N0M0 deemed amenable to surgical resection may also be considered for neo-adjuvant chemotherapy with cisplatin/capecitabine (based on the OE-02 trial[12,13] data) or perioperative chemotherapy with FLOT/ECX based on extrapolation of data from the FLOT4-AIO[1] and MAGIC/REAL-2 trials[2,3] to oesophageal SCC.

3. PALLIATIVE INTENT PATIENTS - ADENOCARCINOMA OR SQUAMOUS CELL CARCINOMA OESOPHAGUS, GOJ AND STOMACH

The high proportion of patients presenting with advanced disease highlights the fundamental importance of palliative treatment in oesophageal and gastric cancer. Such a principal equally applies to patients with otherwise operable disease who are either unsuitable or unfit for radical intervention. These patients require as careful consideration by the specialist multidisciplinary team as those with potentially curable disease. Furthermore, close liaison between primary and secondary care is essential bearing in mind the short duration of life expectancy after diagnosis. When considering palliative chemotherapy, careful patient selection is vital as those with good performance status (PS) and limited co-morbid disease are far more likely to benefit.

Patients should be offered enrolment into a clinical trial whenever possible.

All patients with gastric or GOJ adenocarcinomas should have the human epidermal receptor 2 (HER2) status of their cancer assessed.

3.1 First-line palliative chemotherapy for oesophageal, GOJ, and gastric cancers

HER2-negative cancers

The recommended first-line chemotherapy regimen for PS 0-2 patients with advanced oesophageal SCC, oesophageal adenocarcinoma, or HER2-negative adenocarcinomas of the GOJ and stomach is OX (oxaliplatin, and capecitabine)[3]. Epirubicin is no longer given due to associated additional toxicities with uncertain additional benefit in the era of available 2nd / 3rd-line therapies. In patients with cardiac co-morbidity cisplatin in combination with S-1 may be considered[14].

HER2-positive cancers

Patients with gastric or GOJ adenocarcinomas who have HER2-positive tumours (3+ on immunohistochemistry (IHC), or 2+ on IHC and fluorescence in-situ hybridisation (FISH) amplified) are recommended to receive chemotherapy with CX-H regimen (cisplatin, capecitabine, and trastuzumab) which provides a survival advantage when compared to chemotherapy without herceptin[15].

3.2 Further palliative chemotherapy for oesophageal, GOJ, and gastric cancers after failure of first-line chemotherapy

Following failure of first line chemotherapy, suitable patients of good performance status may be considered for further treatment. Options may be used sequentially in second or third line, but there is no clear evidence for a benefit beyond second line.

Docetaxel, Paclitaxel and Irinotecan

Taxanes, as 3-weekly docetaxel or weekly paclitaxel, or irinotecan can be considered having demonstrated improved survival and quality of life compared with best supportive care[16-19].

Platinum-combination re-challenge

Re-challenge with first line platinum-based chemotherapy may be considered in patients who have progressed >6 months post completion of treatment and derived initial clinical benefit[20].

Ramucirumab

Two clinical trials have demonstrated a survival benefit with the use of Ramucirumab (a monoclonal antibody targeting VEGFR-2) as monotherapy, or in addition to paclitaxel, over placebo[21, 22]. Currently Ramucirumab is not approved by NICE.

3.3 Palliative radiotherapy

Gastric cancer

Radiotherapy can be used for management of bleeding. It is recommended that patients are haemodynamically stable to have treatment on an out-patient basis. Patients with heavy or acute upper GI bleeding should be considered for gastric artery embolization by interventional radiology or for palliative surgery.

Radiotherapy regimen:

- 30Gy in 10 fraction/20Gy in 5 fractions
- Single 8-10 Gy for bleeding control

Oesophageal cancer

Brachytherapy can be considered for management of dysphagia in patients with localised disease not fit for radical options as evidence suggests advantage in QOL and intervention-free survival[23]

This option will require a referral to a specialist unit with expertise in Intra Luminal Brachytherapy for oesophageal cancer (e.g. Leeds Cancer Centre)

Palliative external beam may also be considered for symptom control e.g. dysphagia/bleeding and as consolidation therapy following response to systemic chemotherapy

Radiotherapy regimens:

- 30Gy in 10 fraction/20Gy in 5 fractions (this regimen may also be used for Type I/II GOJ adenocarcinomas)

4. SMALL CELL CARCINOMA OESOPHAGUS

Small cell carcinoma of the oesophagus is a rare but well recognised histological subtype. Diagnosis requires specialist upper GI pathologist review with neuro-endocrine immuno-histochemistry and Ki67 or MIB-1 proliferative index score. Staging should be the same as for other histological subtypes. For patients with 'limited stage' disease, defined as being encompassible in a tolerable thoracic radiation volume, the recommended treatment is concurrent or sequential CRT as described below[24-26]. Patients who do not meet these criteria are defined as 'extensive stage' and should be referred for palliative platinum/etoposide based chemotherapy under the care of the Neuroendocrine Team at the Christie.

4.1 Concurrent CRT

Eligibility:

- Age ≤ 75 years
- WHO PS 0-1
- No co-morbidity contra-indicating use of cisplatin
- glomerular filtration rate (GFR) > 60ml/min

Recommended Regimen:

- Cycle 1; induction cisplatin/etoposide chemotherapy
- Cycle 2; cisplatin/etoposide chemotherapy with radiotherapy; 45Gy in 30 fractions twice-daily (3 weeks overall treatment time), with minimum 6 hour inter-fraction interval. RT planning scan will be done after cycle 1 has been delivered.

Alternate Regimen:

- Cycles 1 & 2; induction cisplatin/ etoposide chemotherapy
- Cycles 3 & 4; cisplatin/ etoposide chemotherapy with radiotherapy; 50Gy in 25 fractions once-daily (5 weeks overall treatment time). RT planning scan done after first cycle of chemotherapy delivered.

4.2 Sequential CRT

Eligibility:

- patients who does not fit concurrent criteria but are deemed fit enough for chemotherapy
- glomerular filtration rate (GFR) > 40ml/min

Regimen:

- Carboplatin-based chemotherapy, 4 cycles (or more if well tolerated) with an interim restaging CT scan
- Radiotherapy; 50-55Gy in 20 daily fractions once daily (4 weeks overall treatment time)

4.3 Prophylactic cranial irradiation (PCI)

- The evidence for a benefit for PCI in small cell cancer of oesophagus is limited and based mainly on data from small cell lung cancer.
- This can be discussed on a case-by-case basis in patients age ≤ 75 years, PS 0-2, with no prior intra-cranial pathology, and who have achieved a good response seen to chemotherapy.
- PCI cannot be given concurrently with chemotherapy, and the minimum time period between chemotherapy and commencing PCI should be 2 weeks.

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