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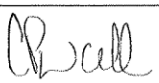
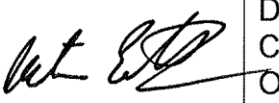
December 2013	1.0	Dr R Goody, Dr C Harrison, Dr C Purcell	Final version issued
June 2016	1.1	Dr C Harrison, Dr C Purcell	Review completed.
March 2017	1.2	Dr C Harrison, Dr C Purcell	Carboplatin included as an option in chemoradiotherapy of the oesophagus. Weekly paclitaxel carboplatin also included.

Authorisation of Systemic Anti-Cancer Treatment (SACT) for Upper GI cancer

	Signature	Print name/Title	Date
Written by Systemic Guidelines author		Dr R Goody Dr C Harrison Dr C Purcell Consultant Clinical Oncologists	18/05/2017
Approved by NICaN Drugs & Therapeutics committee		Dr M Eatock, Consultant Medical Oncologist, Chair of the NICaN Drugs & Therapeutics committee	18/5/17
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These SACT guidelines are being submitted by the authors on behalf of the GI Oncologists group.

Introduction

Affecting approximately 13,500 people per year, oesophago-gastric cancer is the fifth most common malignancy in the United Kingdom and fourth most common cause of cancer death. The incidence of adenocarcinomas of the lower oesophagus and gastro-oesophageal junction is increasing. Prognosis for most patients diagnosed with oesophago-gastric cancer remains poor, with overall 5-year survival rates being approximately 7% for oesophageal and 13% for gastric cancer [1].

In Northern Ireland 185 cases of oesophageal cancer were diagnosed in 2011, with a 1-year overall survival (OS) rate of 43.5% and 5 year OS rate of 19%. In the same year there were 236 cases of gastric cancer diagnosed; 1 and 5-year OS rates are 40.4% and 18.4% respectively [2].

This document provides guidance on treatment of patients with oesophagogastric cancer acknowledging that individual patient factors need to be considered and where possible patients should be offered the opportunity to participate in clinical trials.

Oesophageal Cancer

The two most common types of oesophageal cancer are squamous cell and adenocarcinoma. They tend to develop in different parts of the oesophagus, respond differently to treatment, show different incidence trends, and probably have different causes. The majority of patients (61%) have adenocarcinomas and most of the remainder (26%) have squamous cancers. Potentially curative treatment is with either surgical resection or definitive chemo-radiotherapy.

Pre-/ Peri-operative chemotherapy

Background

The majority of patients present with locally advanced or metastatic disease, with only 25-30% of patients being suitable for potentially curative resection. Even among those who proceed to surgical resection, survival rates are low with approximately 40% alive at 2 years post surgery, and 25% at 5 years [3]. Recurrence may be local in some cases, but distant metastatic recurrence is more frequently seen. Pre-operative or peri-operative chemotherapy is given with the aim

of reducing the rates of distant failure and evidence has confirmed an improvement in survival rates when used in patients with oesophageal cancer.

Evidence supporting the use of pre-operative chemotherapy is from the OEO2 trial. Patients with resectable adenocarcinoma or squamous cell carcinoma of the oesophagus were included. The use of preoperative radiotherapy was not randomized and pre-operative staging used is inadequate by current standards. The use of 2 cycles of cisplatin plus 5-fluorouracil however did show a 9% improvement in 2-year OS compared to surgery alone [4]. On longer term follow up the survival benefit has been maintained [5].

Evidence supporting the use of peri-operative chemotherapy is from the MRC MAGIC study. This compared peri-operative chemotherapy to surgery alone. Chemotherapy consisted of 3 cycles of ECF pre-operatively and 3 cycles post-operatively. Initially only looking at operable gastric adenocarcinomas, inclusion criteria were later extended to include junctional and lower oesophageal adenocarcinomas. The use of peri-operative chemotherapy improved 5-year OS by 13% compared to surgery alone [6]. Capecitabine has been shown to be at least as effective as infusional Fluorouracil in advanced oesophago-gastric cancer [7, 8] and the use of capecitabine instead of infusional Fluorouracil has now become standard practice in many UK centres. In patients with significant dysphagia capecitabine can be dissolved in warm water and swallowed or even administered via a naso-gastric tube [3].

Given the additional survival benefit from peri-operative chemotherapy for adenocarcinomas in the MAGIC study compared to that from preoperative chemotherapy, we routinely offer peri-operative chemotherapy for resectable oesophageal adenocarcinomas. For resectable squamous cancers we offer 2 cycles of Cisplatin Fluorouracil.

The recently completed OEO5 trial compared 2 different neoadjuvant chemotherapy schedules. The final published results are awaited and this may influence practice in the future.

Patient selection

- Patients with stage IA and IB disease do not require neo-adjuvant therapy and should proceed to surgery if deemed appropriate by the MDT.
- Patients with stage IIA (i.e. T2N0G3) – stage IIIB disease should be offered neoadjuvant chemotherapy.

- Patients with stage IIIC disease (i.e. T4N1-2 or any T stage with N3) should only be offered radical treatment after careful discussion.

Consider pre or perioperative chemotherapy for patients with:

- Resectable stage II and III disease
- Good performance status (ECOG 0-1)
- Adequate baseline renal, liver, bone marrow and cardiac function
- Pre-operative staging investigations to include biopsy, EUS, CT scan, PET CT scan and staging laparoscopy with washings for tumours of the lower 1/3
- Adequate fitness for surgical procedure.

Treatment Regimens

For squamous cell carcinomas

Cisplatin 80mg/m^2 iv day 1

and either *5-fluorouracil 4000mg/m^2 iv infusion day 1 over 96 hours*

or *Capecitabine 1000mg/m^2 orally twice daily on days 1-14*

2 x 21 day cycles

Carboplatin (AUC 5) should be substituted in patients with a low GFR or in whom a fluid load would be contraindicated.

Restaging PET CT scan after cycle 2 with rediscussion at Upper GI MDM.

Surgery planned for 8-9 weeks after cycle 2 day 1.

For adenocarcinomas

Epirubicin 50mg/m^2 iv day 1

Cisplatin 60mg/m^2 iv day 1

and either *Fluorouracil 200mg/m^2 per day continuous iv infusion days 1-21*

or *Capecitabine 625mg/m^2 orally twice daily on days 1-21*

3 x 21 day cycles pre-operatively. 3 cycles should be considered postoperatively where recovery from surgery permits this.

Carboplatin (AUC 5) should be substituted in patients with a low GFR or in whom a fluid load would be contraindicated.

In selected cases EOX or EOF is prescribed in the perioperative setting if there is a significant risk of thrombosis.

Epirubicin 50mg/m2 iv day 1

Oxaliplatin 130mg/m^2 iv day 1

and either *Fluorouracil 200mg/m^2 per day continuous iv infusion days 1-21*

or *Capecitabine 625mg/m^2 orally twice daily on days 1-21*

3 x 21 day cycles pre-operatively. 3 cycles should be considered postoperatively where recovery from surgery permits this.

Restaging PET CT scan after cycle 3 with rediscussion at Upper GI MDM.

Surgery planned for 8-9 weeks after cycle 3 day 1.

Postoperatively all cases to be discussed at regional Upper GI MDM with pathology results and referred for assessment as to suitability of receiving 3 cycles of postoperative chemotherapy (ideally within 12 weeks from surgery).

Follow up

There is no clear evidence to support any standard follow up schedule however current practice in oncology is review three monthly year 1, four monthly year 2, six monthly year 3, annually year 4 and 5. Discharge after 5 years.

Investigations as clinically indicated.

Adjuvant Chemotherapy

There is no proven role for postoperative adjuvant chemotherapy for carcinoma of the oesophagus unless this is given as part of a planned course of peri-operative chemotherapy.
It can be problematical given the recovery period that commonly follows oesophagectomy which conflicts with the aims of adjuvant therapy. Evidence regarding postoperative therapy is limited [9,10].

Definitive chemoradiotherapy

Background

There has been no randomised controlled trial comparing definitive chemoradiotherapy (dCRT) to radical surgery. Published data show similar OS rates. Surgery is still considered the gold standard, particularly for adenocarcinomas. There is increasing acceptance of definitive chemoradiotherapy as an alternative radical approach, and it is often considered in patients with inoperable locally advanced disease, patients with medically inoperable disease but with adequate fitness for dCRT, and where patients choose to pursue an organ preserving approach – particularly for cervical and upper oesophageal squamous cell carcinomas where extensive surgery would be required.

Two key trials have demonstrated long term survival from CRT without the use of surgery, and the benefit of the addition of chemotherapy to radiotherapy [11-13]. A later meta-analysis has confirmed a survival benefit for CRT versus radiotherapy alone, but with increased toxicity rates [14]. The recently published UK SCOPE trial, whilst not showing an improved outcome from CRT with the addition of cetuximab, did demonstrate superior disease control and survival rates in the standard dCRT arm compared to any previously published results with a 2-year OS of 56%. This trial has also improved standardisation of oesophageal radiotherapy planning across the UK [15].

Patient selection

Consider definitive chemoradiotherapy for patients with:

- Non metastatic oesophageal cancer with maximum disease length (tumour plus outlying nodes) of 10cm on EUS and PET scan
    - Where disease is surgically inoperable
    - Where patients have medical co-morbidities precluding surgery
    - Where the patient chooses to pursue an organ preserving approach
- Good performance status (ECOG 0-1)
- Adequate baseline renal, liver, bone marrow function
- FEV1 > 1 litre on pulmonary function tests
- Pre-treatment investigations to include biopsy, EUS, CT scan and PET scan

- Bronchoscopy should be performed if direct airways invasion suspected on imaging
- Adequate information to aid radiotherapy planning should be reported on staging EUS (tumour position, length of disease and relationship to fixed anatomy e.g. top of aortic arch).

Treatment Regimens

Cisplatin 60mg/m^2 iv day 1

and either *Fluorouracil 3200mg/m^2 over 96 hours.*

or *Capecitabine 625mg/m2 orally twice daily on days 1-21*

21 day cycle

For middle and lower oesophageal cancers receiving definitive chemoradiation, two cycles of CX or CFU are given neo-adjuvantly and two cycles are given concurrently with radiotherapy. In Upper oesophageal cancers two cycles of CX or CFU are given neo-adjuvantly and, if receiving 60 Gy radiotherapy, weekly cisplatin 40mg/m^2 for 6 weeks.

Carboplatin should be substituted in patients with a low GFR or in whom a fluid load would be contraindicated wither as AUC 5 for 3weekly regime or Carboplatin AUC 1.5 if weekly.

In circumstances when patients have significant ischaemic heart disease standard chemotherapy can be replaced by carboplatin paclitaxel after discussion with treating oncologist.

Carboplatin AUC 5 day 1

Paclitaxel 175mg/m2 day 1

21 day cycle for 2 cycles

Then

Weekly Paclitaxel 50mg/m2

Weekly Carboplatin AUC 2

During 5 weeks of XRT.

Radiotherapy Planning

Patients should ideally have their radiotherapy planning scan performed within 2 weeks of commencing neoadjuvant chemotherapy. Radiotherapy is delivered concurrently with cycles 3 and 4 of chemotherapy and consists of 50 Gy in 25 fractions delivered once daily Monday to Friday over 5 weeks, prescribed to the ICRU reference point. Radiotherapy is CT planned according to the Radiotherapy Department Oesophageal Clinical Protocol.

Follow up

Patients are assessed 6 weeks following completion of dCRT. Following this review, repeat endoscopy and biopsy, and repeat CT scan of chest, abdomen and pelvis is requested to assess response to treatment.

Further investigations as clinically indicated.

If a patient is deemed suitable for salvage oesophagectomy if persisting disease is identified, a PET CT should be requested by 6 months' post treatment.

There is no clear evidence to support any standard follow up schedule however current practice in oncology is review three monthly year 1, four monthly year 2, six monthly year 3, annually year 4 and 5. Discharge after 5 years.

Pre-operative (chemo)radiotherapy

There has been increasing interest in the use of pre-operative radiotherapy or chemoradiotherapy (CRT). A meta-analysis of randomised trials has shown that this approach increases R0 resection rates, reduces loco-regional recurrence and improves survival compared with surgery alone [16]. More recently, a randomised phase III study comparing surgery (S) alone to neo-adjuvant CRT (CRT-S) has shown a near doubling of OS in favour of the CRT-S arm [OS 49 *vs.* 26 months, HR 0.67]. Neo-adjuvant CRT was associated with a pathological complete response rate of 32%, and no increase in surgical mortality [3.8% (S) *vs.* 3.4% (CRT-S)] [17].

Neo-adjuvant CRT is not considered standard treatment in the UK presently however patients should be considered for inclusion into a relevant clinical trial when open to recruitment [18].

Postoperative radiotherapy

Postoperative radiotherapy is not routinely recommended due to a lack of evidence. Trials published in the 1980-1990's demonstrated no survival benefit, although one study showed a reduced local recurrence rate in patients with microscopic or macroscopic residual disease [19-21]. It is difficult to localise the area at risk and fraught with toxicity. It is preferable to identify patients who would be at risk of a R1 resection margin prior to resection and offer them an alternative treatment. This is the subject of ongoing NCRI and MRC trials.

Advanced (metastatic) disease

Background

75% of patients present with metastatic or locally advanced disease. The majority of patients with localised oesophageal cancer eventually relapse with local recurrence or metastatic disease.

Palliative treatment for these patients will depend on their symptoms, performance status, extent of disease and preference for treatment. Options include endoscopic laser ablation, oesophageal stenting, chemotherapy, and radiotherapy.

Palliative chemotherapy

Patient selection

- Adequate performance status (ECOG 0-2)
- Adequate baseline renal, liver, bone marrow and cardiac function
- Up to date baseline CT scan

First line chemotherapy - Treatment Regimens

For Squamous carcinoma

1st line:

Cisplatin 80mg/m^2 iv day 1

and either *Fluorouracil 4000mg/m^2 iv infusion day 1 over 96 hours*

or *Capecitabine 1000mg/m^2 orally twice daily on days 1-14*

Carboplatin (AUC 5) should be substituted in patients with a low GFR or in whom a fluid load would be contraindicated.

3 cycles then repeat CT and continue to a maximum of 6 cycles if responding or stable disease.

In those with 5FU intolerance:

Gemcitabine 1000 mg/m^2 iv day 1 and day 8, and Cisplatin 75 mg/m^2 iv day 1 (Carboplatin AUC5 day 1 may be considered as an alternative to cisplatin)

Cycle repeated every 21 days for 6 cycles

For Adenocarcinoma

1st line:

Epirubicin 50 mg/m^2 iv day 1

Cisplatin 60mg/m^2 iv day 1

and either *Fluorouracil 200mg/m^2 per day continuous iv infusion days 1-21*

or *Capecitabine 625mg/m^2 orally twice daily on days 1-21*

Cycles repeated every 21 days.

Carboplatin (AUC 5) should be substituted in patients with a low GFR or in whom a fluid load would be contraindicated.

Usually a maximum of 6-8 cycles will be administered with response monitored by CT scanning after 3 or 4 cycles and then on completion of treatment.

or

Epirubicin 50mg/m^2 iv day 1

Oxaliplatin 130mg/m^2 iv day 1

and either *Fluorouracil 200mg/m^2 per day continuous iv infusion days 1-21*

or *Capecitabine 625mg/m^2 orally twice daily on days 1-21*

In those with Fluorouracil intolerance:

Gemcitabine 1000 mg/m^2 iv day 1 and day 8, and Cisplatin 75 mg/m^2 iv day 1 (Carboplatin AUC5 day 1 may be considered as an alternative to cisplatin)

Cycle repeated every 21 days for 6 cycles.

For adenocarcinomas only: If the tumour encroaches the oesophago gastric junction, HER-2 status should be requested. If IHC 3+ patient should be treated as per HER-2 positive metastatic gastric adenocarcinoma.

Cisplatin 80mg/m^2 iv day 1

Capecitabine 1000mg/m^2 orally twice daily on days 1-14

Trastuzumab 8mg/kg iv day 1 loading dose cycle 1, otherwise 6mg/kg iv day 1 for cycles 2 onwards.

Cycle repeated every 21 days for 6 cycles.

Trastuzumab is continued until disease progression. Response assessment and cardiac echocardiograph should be performed every 12 weeks.

Second Line Therapy

The proportion of patients well enough to receive second line treatment for advanced oesophageal cancer is likely to be small, however for those who are fit enough to receive treatment a number of agents have been shown to be active with response rates of around 20%.

The agreed second line treatment amongst the GI oncologists is with a combination of irinotecan and 5FU/Folinic acid.

Irinotecan 180mg/m^2 iv day 1
Folinic Acid 200mg/m^2 iv day 1
Fluorouracil bolus 400mg/m^2 iv day 1
Fluorouracil infusion 2400mg/m^2 continuous iv infusion over 48 hours commencing day 1

Cycle repeated every 14 days for up to 12 cycles.

An alternative is taxane based regimens. The Cougar 2 trial[xx] suggests that docetaxel can be recommended as an appropriate second-line treatment for patients with oesophagogastric adenocarcinoma that is refractory to treatment with platinum and fluoropyrimidine. Compared with active symptom control, docetaxel improved survival with no adverse effects on quality of life. Weekly paclitaxel may be an alternative to docetaxel due to a more favourable toxicity profile.

Docetaxel 75mg/m^2 day 1

21 day cycle

or

Paclitaxel 80mg/m^2 weekly

In those receiving second line treatment assessment of response should be after 3 cycles of docetaxel or 6 – 8 weeks of weekly paclitaxel treatment.

Follow up

For patients with advanced oesophageal cancer follow up and imaging should be as clinically directed.

Palliative radiotherapy

This can be considered on a case by case basis for bone pain, tumour overgrowth and for bleeding.

Supportive treatments

These can be discussed and referred through the regional Upper GI MDM and include oesophageal stenting and endoscopic laser ablation**.**

Small cell oesophageal carcinoma

Small-cell carcinoma of the oesophagus is a rare and highly aggressive malignancy. Its incidence constitutes ~0.8%–2.4% of all oesophageal malignancies [23]. Because of the paucity of cases, the optimal therapy has not been defined. Given its

histologic resemblance to pulmonary small cell carcinoma, small cell carcinoma of the oesophagus has commonly been treated with multimodality therapy, including chemotherapy or concurrent chemoradiotherapy. Staging of small cell carcinoma of the oesophagus reflects the staging of pulmonary small cell carcinoma and categorises these tumours as either limited disease (LD) or extensive disease (ED). LD is defined as tumour confined within a localized anatomic region with or without regional lymph node involvement. ED is defined as tumour outside loco-regional boundaries. The approach to treatment requires full staging investigations to be completed.

Optimal therapy for this disease remains unclear. Various combinations of surgery, radiotherapy and chemotherapy have been described in the literature. It is recognised that oesophageal small cell carcinoma is a chemosensitive disease, although responses tend to be short lived, and there is a general consensus in the recent literature that systemic chemotherapy is a mainstay of treatment of oesophageal small cell carcinoma. A review of 199 patients identified chemotherapy (delivered with local therapy) as the factor associated with improved survival in LD patients [24]. There are few reports of surgery being used as a sole treatment modality.

The most common chemotherapy regimen used in the treatment of small cell carcinoma of oesophagus is a platinum compound in combination with etoposide [25].

Patients with oesophageal small cell (both LD and ED) who have suitable performance status (ECOG 0-2) and adequate baseline renal, liver, bone marrow and cardiac function should be considered for chemotherapy. For patients with LD who respond to chemotherapy, radiotherapy to the oesophagus may be considered.

Treatment regimens

Cisplatin 80mg/m^2 iv day 1

Etoposide 100mg/m^2 iv days 1-3

or

Carboplatin AUC 5 iv day 1

Etoposide 100mg/m^2 iv days 1-3 (or *Etoposide* 100mg/m^2 iv day 1, then *Etoposide* 100mg/m^2 po BD days 2&3)

21 day cycle for up to 6 cycles.

Response assessment with CT scan of chest, abdomen and pelvis should be completed after 2-3 cycles.

Treatment with single agent carboplatin (AUC5) IV may be considered in patients felt to be unsuitable for combination chemotherapy.

Gastric cancer

Perioperative chemotherapy

Background

Cancer of the stomach is the 6th most common cancer in the UK, causing over 5000 deaths each year. All treatments aimed at cure involve surgery, but when it is used alone only around 20% of patients are alive after 5 years. The MRC ST02 trial (also known as MAGIC) has shown that progression free and overall survival are significantly improved by the administration of peri-operative chemotherapy with ECF [6]. Capecitabine has been shown to be at least as effective as infusional Fluorouracil in advanced oesophago-gastric cancer [7, 8] and the use of capecitabine instead of infusional Fluorouracil has now become standard practice in many UK centres.

In those patients considered to have resectable disease perioperative chemotherapy with ECX should be considered.

Patient selection

- Patients with Stage IB (T1 N1, T2a/b N0), II, III or stage IV (T4 N1 or N2) with no evidence of distant metastases (M0) where the surgeon believes that an R0 resection can be achieved
- Good performance status (ECOG 0-1)
- Adequate baseline renal, liver, bone marrow and cardiac function
- Pre-operative staging investigations to include OGD, biopsy CT scan and staging laparoscopy and peritoneal washings
- Adequate fitness for surgical procedure

In certain situations, where it would be unsafe to defer surgery to allow the use of neo-adjuvant therapy (i.e. uncontrolled bleeding or gastric outlet obstruction) surgery may be recommended as the primary therapy.

Treatment regimens

Epirubicin 50mg/m^2 iv day 1

Cisplatin 60mg/m^2 iv day 1

and either *capecitabine 625mg/m^2 orally twice daily on days 1-21*

or *Fluorouracil 200mg/m^2 per day continuous iv infusion days 1-21*

3 x 21 day cycles pre-operatively. 3 cycles should be considered postoperatively where recovery from surgery permits this.
Carboplatin (AUC 5) should be substituted in patients with a low GFR or in whom a fluid load would be contraindicated.

In selected cases EOX or EOF is prescribed in the perioperative setting if there is a significant risk of thrombosis.

Epirubicin 50mg/m^2 iv day 1

Oxaliplatin 130mg/m^2 iv day 1

and either *capecitabine 625mg/m^2 orally twice daily on days 1-21*

or *Fluorouracil 200mg/m^2 per day continuous iv infusion days 1-21*

3 x 21 day cycles pre-operatively. 3 cycles should be considered postoperatively where recovery from surgery permits this.

Restaging CT scan after 3 cycles with rediscussion at Upper GI MDM.

Surgery planned for 8-9 weeks after cycle 3 day1.

Postoperatively all cases to be discussed at regional Upper GI MDM with pathology results and referred for assessment as to suitability of receiving 3 cycles of postoperative chemotherapy (ideally within 12 weeks from surgery).

Follow up

There is no clear evidence to support any standard follow up schedule however current practice in oncology is review three monthly year 1, four monthly year 2, six monthly year 3, annually year 4 and 5. Discharge after 5 years.

Investigations as clinically indicated.

Adjuvant chemotherapy

Where patients have been unable to receive pre-operative chemotherapy due to circumstances, there are meta-analysis data to suggest an improvement in overall survival following the use of adjuvant chemotherapy [26].

Patient selection

- Patients considered at high risk of systemic recurrence postoperatively
- Good performance status (ECOG 0-1)
- Adequate baseline renal, liver, bone marrow and cardiac function

Treatment regimens

Epirubicin 50mg/m^2 iv day 1

Cisplatin 60mg/m^2 iv day 1

and either *capecitabine 625mg/m^2 orally twice daily on days 1-21*

or *Fluorouracil 200mg/m^2 per day continuous iv infusion days 1-21*

6 x 21 day cycles

Carboplatin (AUC 5) should be substituted in patients with a low GFR or in whom a fluid load would be contraindicated.

In selected cases EOX or EOF is prescribed if there is a significant risk of thrombosis.

Epirubicin 50mg/m^2 iv day 1

Oxaliplatin 130mg/m^2 iv day 1

and either *capecitabine 625mg/m^2 orally twice daily on days 1-21*

or *Fluorouracil 200mg/m^2 per day continuous iv infusion days 1-21*

Cycle repeated every 21 days for 6 cycles.

Postoperative chemoradiotherapy

An alternative approach for those patients whom have proceeded directly to surgery is adjuvant chemoradiation. This is based on the results from SWOG 0116 study [27]. This advantage is predominantly seen for D0 or D1 resections in those patients who had not received pre-operative chemotherapy, which is standard now in the UK. This regimen is associated with high morbidity.

Patient selection

- Patients considered at high risk of local recurrence postoperatively
- No preoperative chemotherapy
- Good performance status (ECOG 0-1)
- Adequate baseline renal, liver, bone marrow and cardiac function
- DMSA nephrogram demonstrating symmetrical kidney function
- Adequate nutritional status (calorie intake >1500kCal/day)

Treatment regimens

Capecitabine 1250mg/m^2 orally twice daily days 1-14 pre XRT

1 month later:
Radiotherapy to stomach bed: 45 Gy in 25 fractions over 5 weeks
Delivered concurrently with
Capecitabine 900mg/m^2 orally twice daily on radiotherapy days only

1 month later:
2 further cycles
Capecitabine 1250mg/m^2 orally twice daily days 1-14

Advanced (metastatic) Disease

Background

Most patients with gastric cancer present with advanced inoperable or metastatic disease requiring palliative treatment. Co-morbidity and performance status influence treatment selection and patient outcomes. Palliative chemotherapy is offered to fit patients (ECOG performance 0-2) with the intention of improving overall survival,

palliating disease related symptoms and preserving quality of life. Despite treatment the prognosis of metastatic gastric cancer is poor. Median overall survival is typically less than one year, and Cancer Registry statistics for one and 3-year survival rates in Northern Ireland are 21% and 1% respectively [28].

A number of chemotherapy agents, including fluoropyrimidines, platinum compounds, anthracyclines and taxanes have demonstrated activity in metastatic gastric cancer. There have been a number of small trials comparing chemotherapy with best supportive care which show average survival is increased from 3-6 to 9-12 months with chemotherapy [29]. Meta-analysis data suggest that combination chemotherapy improves disease related symptoms in up to 70% of patients, with objective response rates in the order of 40-45%[30].Currently there is no single well established standard of care, but fluoropyrimidine-based and platinum-based combinations are the most widely used regimens. In Northern Ireland the most widely used chemotherapy combination is with epirubicin, cisplatin and capecitabine (ECX).

The REAL-2 trial evaluated oxaliplatin as an alternative to cisplatin and capecitabine as an alternative to 5FU. Overall survival was longer with EOX compared to ECF. Oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, alopecia, renal toxicity and thromboembolism, but with slightly higher incidences of grated 3 or 4 diarrhoea compared to cisplatin. It was concluded that capecitabine and oxaliplatin are at least as effective as fluorouracil and cisplatin respectively [8].

Overexpression of the HER-2 (human epidermal growth factor receptor) proto-oncogene, detectable by immunohistoochemistry (IHC), has been identified in 20% of gastric and in up to 34% of GOJ cancers. An association between HER-2 overexpression and reduced overall survival in stomach cancer has been reported in a number of retrospective studies. Trastuzumab, a monoclonal antibody, inhibits HER-2 oncogenic signalling and has demonstrated a survival advantage when used in combination with chemotherapy in the treatment of HER2 positive breast cancer. Experience in breast cancer has established the role of HER-2 expression as the most important predictive biomarker of response to trastuzumab therapy. IHC scoring of HER-2 is graded as 1+, 2+ or 3+, which correlates with mild, moderate and strong staining intensity. Sensitivity to trastuzumab correlates with staining intensity, and is greatest in IHC 3+ staining tumours.

In the TOGA trial patients who tested positive for HER-2 expression were enrolled into a large phase III trial comparing combination of fluorouracil or capecitabine and cisplatin chemotherapy with or without trastuzumab. A 2.7 month improvement in median survival (13.8 months vs 11.1 months, HR 0.74; 95% CI 0.60-0.91; p=0.0046) was reported for the total trial population receiving trastuzumab and

chemotherapy compared to chemotherapy alone. In patients with IHC 3+ or IHC2+/FISH+ disease, the addition of trastuzumab to chemotherapy extended median survival by 4.2 months (16 months vs 11.8 months; HR 0.65; 95% CI 0.51-0.83), compared to chemotherapy alone. Further analysis of the IHC 3+ group suggests an even greater survival benefit of 5.8 months associated with the addition of trastuzumab to chemotherapy (18 months vs 12.4 months)[31].

In September 2010 NICE approval was granted for the use of trastuzumab in the management of previously untreated HER2 positive metastatic gastric or gastro-oesophageal cancer [32] where the intensity of IHC staining for HER2 is 3+. Trastuzumab is currently funded in N Ireland.

Further studies investigating the use of the monoclonal antibody VEGFR-2 antagonist, Ramucirumab, have demonstrated the combination of ramucirumab with paclitaxel significantly increases overall survival compared with placebo plus paclitaxel.[33]
Ramucirumab is now licensed

- in combination with paclitaxel for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy.
- as monotherapy for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate.

Ramucirumab is not recommended by NICE and therefore is not recurrently funded but is available to self-funding patients.

Patient Selection

- Adequate performance status (ECOG 0-2)
- Adequate baseline renal, liver, bone marrow and cardiac function
- Up to date baseline CT scan

First line chemotherapy – treatment regimens

If HER-2 positive 3+ on IHC

Cisplatin 80mg/m^2 iv day 1

Capecitabine 1000mg/m^2 orally twice daily on days 1-14

Trastuzumab 8mg/kg iv day 1 loading dose cycle 1, otherwise 6mg/kg iv day 1 for cycles 2 onwards.

Chemotherapy Cycles repeated every 21 days X 6

Trastuzumab is continued until disease progression. Response assessment and cardiac echocardiograph should be performed every 12 weeks.

If HER-2 negative

Epirubicin 50 mg/m^2 iv day 1

Cisplatin 60mg/m^2 iv day 1

and either *Fluorouracil 200mg/m^2 per day continuous iv infusion days 1-21*

or *Capecitabine 625mg/m^2 orally twice daily on days 1-21*

Cycles repeated every 21 days.

Carboplatin (AUC 5) should be substituted in patients with a low GFR or in whom a fluid load would be contraindicated.

Usually a maximum of 6-8 cycles will be administered with response monitored by CT scanning after 3 cycles and then on completion of treatment.

or In selected cases EOX or EOF is prescribed if there is a significant risk of thrombosis.

Epirubicin 50mg/m^2 iv day 1

Oxaliplatin 130mg/m^2 iv day 1

and either *Fluorouracil 200mg/m^2 per day continuous iv infusion days 1-21*

or *Capecitabine 625mg/m^2 orally twice daily on days 1-21*

Cycle repeated every 21 days for 6 cycles.

Second line therapy

Irinotecan 180mg/m^2 iv day 1
Folinic Acid 200mg/m^2 iv day 1
Fluorouracil bolus 400mg/m^2 iv day 1
Fluorouracil infusion 2400mg/m^2 continuous iv infusion over 48 hours commencing day 1

Cycle repeated every 14 days

An alternative is taxane based regimens. The Cougar 2 trial[xx] suggests that docetaxel can be recommended as an appropriate second-line treatment for patients with oesophagogastric adenocarcinoma that is refractory to treatment with platinum and fluoropyrimidine. Compared with active symptom control, docetaxel improved survival with no adverse effects on quality of life. Weekly paclitaxel may be an alternative to docetaxel due to a more favourable toxicity profile.

Docetaxel 75mg/m^2 day 1

21 day cycle

or

Paclitaxel 80mg/m^2 weekly

In those receiving second line treatment assessment of response should be after 4 cycles (6 – 8 weeks) of treatment.

Follow up

For patients with advanced gastric cancer follow up and imaging should be as clinically directed.

Palliative radiotherapy

This can be considered on a case by case basis for bone pain, tumour overgrowth and for bleeding.

Supportive treatments

These can be discussed and referred through the regional upper GI MDM.

Small cell carcinoma of the stomach

Small cell carcinoma of the stomach is a rare and highly aggressive malignancy for which optimal therapy has not been defined. Given its histologic resemblance to pulmonary small cell carcinoma, SACT is recognised as an important modality in the treatment of small cell carcinoma of the stomach.

In a review of 107 cases of small cell carcinoma of the stomach in the published literature [34], the majority presented at an advanced stage of disease and a high proportion died within 1 year because of recurrence or metastasis. This confirms the disease generally follows an aggressive course characterized by invasion and metastasis in the early phase. Even when the tumour is limited to the stomach, prognosis appears poor because of early metastasis following surgery. In patients with disease confined to the stomach, surgery alone may not be sufficient treatment and SACT is likely to be required during the course of their treatment. Management of these patients should be discussed within an appropriate multidisciplinary team

The most common chemotherapy approach employed in the treatment of small cell carcinoma of the stomach is use of a platinum compound in combination with etoposide.

Patients with small cell carcinoma of the stomach who have suitable performance status (ECOG 0-2) and adequate baseline renal, liver, bone marrow and cardiac function could be considered for chemotherapy.

Treatment regimens

Cisplatin 80mg/m^2 iv day 1

Etoposide 100mg/m^2 iv days 1-3

or

Carboplatin AUC 5 iv day 1

Etoposide 100mg/m^2 iv days 1-3 (or *Etoposide* 100mg/m^2 iv day 1, then *Etoposide* 100mg/m2 po BD days 2&3)

21 day cycle for up to 6 cycles.

Response assessment with CT scan of chest, abdomen and pelvis should be completed after 2-3 cycles.

Treatment with single agent carboplatin (AUC5) IV may be considered in patients felt to be unsuitable for combination chemotherapy.

Appendices

Staging[35]

Oesophagus and Oesophagogastric junction

Primary tumour (T)

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 inavading other adjacent structures

Regional Lymph nodes (N)

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 seven or more regional lymph nodes

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

Stage Groupings – Squamous cell carcinoma (or mixed)

Stage	**T**	**N**	**M**	**Grade**	**Location**
IA	T1	N0	M0	1,X	Any
IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1,X	Any
IIA	T2-3	N0	M0	1,X	upper/middle lower/unknown
	T2-3	N0	M0	2-3	
IIB	T2-3	N0	M0	2-3	Upper/middle
	T1-2	N1	M0	Any	Any
IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

Stage Groupings -Adenocarcinoma

Stage	T	N	M	Grade
IA	T1	N0	M0	1-2,X
IB	T1 T2	N0 N0	M0 M0	3 1-2,X
IIA	T2	N0	M0	3
IIB	T3 T1-2	N0 N1	M0 M0	Any
IIIA	T1-2 T3 T4a	N2 N1 N0	M0 M0 M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a T4b Any	N1-2 Any N3	M0 M0 M0	Any
IV	Any	Any	M1	Any

Grading

GX Grade cannot be assessed

G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

Stomach

Primary tumour (T)

Tx Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ

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 penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures

T4a Tumour invades serosa (visceral peritoneum)

T4b Tumour invades adjacent structures

Regional Lymph nodes (N)

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 seven or more regional lymph nodes

-N3a Metastasis in 7-15 regional lymph nodes

-N3b Metastasis in 16 or more regional lymph nodes

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis (including positive peritoneal cytology)

Stage Groupings

Stage	**T**	**N**	**M**
IA	T1	N0	M0
IB	T2	N0	M0
	T1	N1	M0
IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
IIIB	T4b	N0-1	M0
	T4a	N2	M0
	T3	N3	M0
IIIC	T4b	N2-3	M0
	T4a	N3	M0
IV	Any	Any	M1

WHO performance status

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

References

[1] The Royal College of Surgeons of England. National Oesophago-gastric Cancer Audit 2012.

[2] Northern Ireland Cancer Registry. Cancer Survival Online Statistics. Oesophagus and Stomach. Accessed September 2013. http://www.qub.ac.uk/research-centres/nicr/CancerData/OnlineStatistics/

[3] NCRI Upper GI Clinical Studies Group. SCOPE 1: Study of Chemoradiotherapy in Oesophageal Cancer Plus or Minus Erbitux. Clinical Protocol, version 5.0. February 2010.

[4] Medical Research Council Oesophageal Working Party. Surgical resection with or without perioperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002;359:1727-1733.

[5] Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomised trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009;27:5062-5067.

[6] Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.

[7]Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696-704.

[8] Cunningham D, Starling N, Rao S, et al. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. N Engl J Med 2008; 358:36-46.

[9] Ando N, Iizuka T, Kakegawa T, et al: A randomized trial of surgery with and without chemotherapy for localized squamous carcinoma of the thoracic esophagus: the Japan Clinical Oncology Group Study. J Thorac Cardiovasc Surg 1997;114:205-9.

[10] Ando N, Iizuka T, Ide H: A randomised trial of surgery alone versus surgery plus postoperative chemotherapy with cisplatin and 5-fluorouracil for localized squamous carcinoma of the thoracic esophagus: The Japan Clinical Oncology Group Study (JCOG 9204). Proc Am Soc Clin Oncol 1999;18:269a.

[11] Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;326:1593-1598.

[12] Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01)—Radiation Therapy Oncology Group. JAMA 1999;281:1623-1627.

[13] Smith TJ, Ryan LM, Douglass HO Jr, et al. Combined chemoradiotherapy vs radiotherapy alone for early stage squamous cell carcinoma of the esophagus: A study of the Eastern Cooperative Oncology Group. Int J Radiat Oncol Biol Phys 1998;42:269-276.

[14] Wong RK, Malthaner RA, Zuraw L, et al. Combined modality radiotherapy and chemotherapy in nonsurgical management of localized carcinoma of the esophagus: a practice guideline. Int J Radiat Oncol Biol Phys 2003;55:930-42.

[15] Crosby T, Hurt CN, Falk S, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol 2013;14:627-37.

[16] Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2003;185(6):538-43.

[17] Van Hagen P, Hulshof MC, van Lanschot JJ, et al; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012 May 31;366(22):2074-84.

[18] NCRI Upper GI Clinical Studies Group. NeoSCOPE: Neo-adjuvant Study of Chemoradiotherapy in Oesophageal Cancer. Clinical Protocol, version 1.0. October 2012.

[19] Fok M, Sham JS, Choy D, et al: Postoperative radiotherapy for carcinoma of the esophagus: a prospective, randomized controlled study. Surgery 1993;113:138-47.

[20] Teniere P, Hay JM, Fingerhut A, et al: Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower esophagus as shown by a multicenter controlled trial. French University Association for Surgical Research. Surg Gynecol Obstet 1991;173:123-30.

[21] Zieren HU, Muller JM, Jacobi CA, et al: Adjuvant postoperative radiation therapy after curative resection of squamous cell carcinoma of the thoracic esophagus: a prospective randomized study. World J Surg 1995;19:444-9.

[22]Hugo E R Ford, Andrea Marshall, John A Bridgewater et al, on behalf of the COUGAR-02 Investigators. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02):
an open-label, phase 3 randomised controlled trial Lancet oncology Vol 15 January 2014

[23]Beyer KL, Marshall JB, Diaz-Arias AA, Loy TS. Primary small-cell carcinoma of the esophagus. Report of 11 cases and review of the literature. J Clin Gastroenterol 1991;13:135-141.

[24]Casas F, Ferrer F, Farrus B, et al. Primary small cell carcinoma of the esophagus: a review of the literature with emphasis on therapy and prognosis. Cancer 1997;80:1366-1372.

[25] Hudson E, Powell J, Mukherjee S, et al. Small cell oesophageal carcinoma: an institutional experience and review of the literature. Brit J Cancer 2007;96:708-11.

[26] GASTRIC(Global Advanced/Adjuvant Stomach Tumor Research International Collaboration)Group, Paoletti X, Oba K, Burzykowski T et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA 2010;303(17):1729-37.

[27] MacDonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345:725-30.

[28] Northern Ireland and Cancer Registry Annual Report. 2007

[29] Wagner AD, Grothe W, Haerting J et al.Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006;24; 2903-2909.

[30] Wagner AD, Unverzagt S, Grothe W, et al: Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 3:CD004064

[31] Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376(9742):687-697.

[32] National Institute for Health and Clinical Excellence. NICE technology appraisal guidance 208. Trastuzumab for the treatment of HER2-positive metastatic gastric cancer. November 2010.

[33]Rainbow study group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric orgastro-oesophageal junction adenocarcinoma (RAINBOW):
a double-blind, randomised phase 3 trial. Lancet Oncol 2014; 15: 1224–35

[34] Namikawa T, Kobayashi M, Okabayashi Tet al. Primary gastric small cell carcinoma: report of a case and review of the literature. Med Mol Morphol 2005;38(4):256-61.

[35] Edge SB, Byrd DR, Compton CC, et al, Eds.(2010) AJCC cancer staging handbook, 7th edition. New York;Springer.