NHS
Kent and Medway
Cancer Collaborative

Oncological Treatment of Upper GI Cancer

Pathway of Care

Kent & Medway Cancer Collaborative

Publication date	March 2026
Expected review date	March 2027
Version number	25
Version status	Final

TABLE OF CONTENTS

1.0 INTRODUCTION

This document has been written to provide guidance on the treatment of Upper GI cancer in the Kent & Medway Cancer Collaborative

Radiotherapy schedules are as defined in the Kent Oncology Centre Quality System Clinical Protocols (Disease Management and Radiotherapy Protocols).

See network chemotherapy prescribing proformas for details of chemotherapy / anti-cancer regimens.

All patients will be considered for entry into a clinical trial (see appendix A).

All patients should be discussed within a multidisciplinary team meeting before commencing initial treatment.

Please note, some of the drugs/doses recommended within this document are outside of the U.K. licensed marketing authorisation.

Consider assessing patients commencing SACT using a validated risk assessment score for thromboprophylaxis. Reference should be made to 'Cancer-associated venous thrombosis in adults (second edition): A British Society for Haematology Guideline.

1.1 Genomic Testing

The National Genomic Test Directory specifies which genomic tests are commissioned by the NHS in England, the technology by which they are available, and the patients who will be eligible to access a test. This is in development; molecular testing for upper GI cancer in Kent will evolve in line with this guidance.

1.1.1 NTRK Fusion Positive

Patients with NTRK gene fusion may be considered for entrectinib or larotrectinib in line with commissioning criteria.

1.1.2 Microsatellite Instability (MSI-H) or Mismatch Repair Deficiency

In selected cases patients with metastatic or locally advanced and unresectable upper gastrointestinal cancers, will be tested for microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR).

Pembrolizumab is recommended as an option for treating tumours with high microsatellite instability (MSI) or mismatch repair (MMR) deficiency in adults with unresectable or metastatic gastric, small intestine or biliary cancer that has progressed during or after 1 therapy, maximum treatment duration 2 years.

1.2 Choice of Platinum / Fluoropyrimidine (or Raltitrexed)

Where indicated in the guidelines, CX or OX (oxaliplatin & capecitabine) or FOLFOX is considered standard treatment. The following drugs may be used as alternatives in the following situations:

- Consider substitution of Cisplatin with Carboplatin (AUC 5) if renal (GFR 30-60mls/min) or auditory dysfunction.
- Consider substitution of Capecitabine with 5FU 200 mg/m^2/day continuous infusion if unable to swallow tablets.
- Consider substitution of Fluoropyrimidine with Raltritrexed in the event of Fluoropyrimidine induced chest pain.

2.0 OESOPHAGEAL CANCER AND TYPE 1/2 GASTRO-OESOPHAGEAL JUNCTION CANCER

Definitions of gastro-oesophageal junction cancers:

- Type I: adenocarcinoma of the distal oesophagus (epicentre of lesion 1-5 cm above GOJ)
- Type II: adenocarcinoma of the cardia (epicentre of lesion up to 1 cm above and 2 cm below GOJ)
- Type III: sub-cardial type adenocarcinoma (epicentre of lesion 2-5 cm below GOJ)

2.1 Squamous cell carcinoma of the oesophagus

2.1.1 Neo-Adjuvant Chemoradiation

Neo-adjuvant chemoradiation may be considered for selected oesophageal cancer patients and should be agreed at MDT

Indications:

- Potentially operable oesophageal cancer
- Performance status 0-1
- T3 N 0-2. Max 5cm tumour length
- T4 if only involving diaphragmatic crus.
- All nodes above diaphragm
- Minimal comorbidity
- Squamous carcinoma
- Agreed at MDT

Chemoradiotherapy regimen:

- Paclitaxel 175mg/m^2 + Carboplatin AUC 5 every 21 days for 2 cycles prior to chemoradiation, then
- Paclitaxel 50mg/m^2 + Carboplatin AUC 2 weekly for 5 weeks.
- Concurrent radiotherapy as defined in the Kent Oncology Centre Quality Systems Clinical Protocols (Disease management and Radiotherapy Protocols).

If there is pathological residual disease at surgery and a complete surgical resection patients can be considered for adjuvant nivolumab.

2.1.2 Radical Chemoradiotherapy

Indications:

- T4N0-1M0
- T1-3N0-1M0 unsuitable/unwilling for surgery (may be considered in preference to surgery for squamous cell carcinoma)

Treatment

- Primary chemotherapy with CX, CarboX, CarboF, CF x 2 cycles
- Chemoradiation with:
  - One 21-day cycle of CX (cisplatin 60mg/m^2 on D1 and capecitabine 625mg/m^2 bd D1-21) concomitantly with radiotherapy (50Gy/25 fractions) followed by CX (cisplatin 60mg/m^2 on D1 and capecitabine 625mg/m^2 bd **D1-14**) concomitantly with radiotherapy (50Gy/25 fractions) NB: Capecitabine stops on last day of RT.

OR

- One 21-day cycle of CF (cisplatin 60mg/m^2 on D1 and 5-Fluorouracil 200mg/m^2/day D1-21) concomitantly with radiotherapy (50Gy/25 fractions) followed by CF (cisplatin 60mg/m^2 on D1 and 5-Fluorouracil 200mg/m^2/day D**1-14**) concomitantly with radiotherapy (50Gy/25 fractions)
  NB: 5-fluorouracil stops on last day of RT.

  Carboplatin may be used in place of cisplatin for patients with renal impairment or ototoxicity.

Carboplatin + paclitaxel to be used in selected patients who are unlikely to tolerate Cisplatin / Fluropyridimine. Alternatively, infused 5-fluorouracil or capecitabine with concurrent radiotherapy may be considered for less fit patients.
Concurrent radiotherapy as defined in the Kent Oncology Centre Quality Systems Clinical Protocols (Disease management and Radiotherapy Protocols).

Tumour assessment

- OGD, CT scan, EUS pre-treatment. Consider PET/CT scan and staging laparoscopy.
- CT scan after 4 cycles of chemotherapy or earlier if no symptom response.
- CT scan and OGD (plus biopsy) 12 weeks post completion of chemoradiation
- Consider surgical resection if residual carcinoma present.

For patients who may be suitable for salvage surgery, 3 monthly OGD and CT scan for 2 years, then 6-monthly for year 3 then annually to 5 years.

2.1.3 Peri-Operative Chemotherapy

Indications:
Oesophageal squamous cell carcinoma considered suitable for curative resection and not suitable for neo-adjuvant chemo-radiation:

- T1, N1-3, M0
- T2a, N0-3, M0
- T2b, N0-3, M0
- T3, N0-3, M0

Treatment

- CX, CF, Carbo X, CarboF x 3 cycles preoperative and 3 cycles post-operative.

Tumour assessment

- OGD, CT scan, PET-CT. Laparoscopy pre-treatment and EUS for tumours involving oesophago-gastric junction as determined by MDT.
- CT scan post completion of neo-adjuvant chemotherapy.

Surgery
Surgery should be performed 6 weeks after completion of neo-adjuvant chemotherapy.

2.2 Adenocarcinoma of the Oesophagus or Type 1 Or 2 Gastro-Oesophageal Junction Cancer

2.2.1 Peri-Operative Chemotherapy

Indications:
Oesophageal and gastro-oesophageal junction adenocarcinoma considered suitable for curative resection:

- T1, N1-3, M0
- T2a, N0-3, M0
- T2b, N0-3, M0
- T3, N0-3, M0

Treatment

- FLOT (only for patients with PS 0-1) x 4 cycles pre-operative and 4 cycles post-operative
- If not suitable for FLOT consider oxaliplatin and modified de Gramont x 4 cycles pre-operative and 4 cycles post-operative
- Or CX, CF, Carbo X, CarboF, OX x 3 cycles preoperative and 3 cycles post-operative.

Tumour assessment

- OGD, CT scan, PET-CT. Laparoscopy pre-treatment and EUS for tumours involving oesophagogastric junction as determined by MDT.
- CT scan post completion of neo-adjuvant chemotherapy.

Surgery
Surgery should be performed 6 weeks after completion of neo-adjuvant chemotherapy.

2.2.2 Neo-Adjuvant Chemoradiation prior to surgery followed by adjuvant immunotherapy (if appropriate)

Neo-adjuvant chemoradiation may be considered for selected oesophageal adenocarcinoma patients and should be agreed at MDT

Indications

- Potentially operable oesophageal cancer
- Performance status 0-1
- T3 N 0-2. Max 5cm tumour length
- T4 if only involving diaphragmatic crus.
- All nodes above diaphragm
- Minimal comorbidity
- Adenocarcinoma
- Agreed at MDT

Chemoradiotherapy regimen

- Paclitaxel 175mg/m^2 + Carboplatin AUC 5 every 21 days for 2 cycles prior to chemoradiation, then
- Paclitaxel 50mg/m^2 + Carboplatin AUC 2 weekly for 5 weeks.

Concurrent radiotherapy as defined in the Kent Oncology Centre Quality Systems Clinical Protocols (Disease management and Radiotherapy Protocols).

If there is pathological residual disease at surgery and a complete surgical resection patients can be considered for adjuvant nivolumab.

2.2.3 Adjuvant Chemoradiation

Adjuvant chemoradiation can be considered for patient with R1 or R2 resection.

Chemoradiation single agent Capecitabine or infused 5-fluorouracil with concurrent radiotherapy.

Concurrent radiotherapy as defined in the Kent Oncology Centre Quality Systems Clinical Protocols (Disease management and Radiotherapy Protocols).

2.3 Adjuvant Chemotherapy for Patients Receiving Upfront Surgery (i.e. Unsuitable for Treatment as per 2.1 and 2.2)

Indications
For patients undergoing surgery for oesophageal carcinoma without pre-operative chemotherapy, there is no proven role for adjuvant chemotherapy. However, in the presence of adverse risk factors (nodal involvement, positive surgical excision margins), adjuvant chemotherapy may be considered on an individual case basis.

Treatment

- Squamous: 6 cycles of CX, CarboX, CF or CarboF
- Adenocarcinoma: 8 cycles of FLOT or FOLFOX, or 6 cycles of CX, CarboX, CF or CarboF or OX

Patients with positive surgical margins may also benefit from postoperative chemoradiation with continuous infusion 5FU 200 mg/m^2/day or Capecitabine 1250 mg/m^2/day with concurrent radiotherapy 50Gy in 25 fractions.

Tumour assessment
End of treatment CT scan

2.4 Palliative Radiotherapy

Palliative external beam radiotherapy to the oesophagus can be offered for symptom control and for consolidating a good response to chemotherapy. The dose and fractionation depend on the stage of disease and performance status of the patient (refer to radiotherapy protocols). Oesophageal brachytherapy can be offered for re-treatment for symptom control.

2.5 Palliative Chemotherapy

Patients with metastatic or locally advanced and unresectable upper gastrointestinal cancers, will be tested for microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR). See section 1.1.2

Patients with adenocarcinoma should also be tested for HER2 expression, and PDL-1 CPS. Patients with squamous cell carcinoma should be tested for PDL-1 CPS and TPS.

2.5.1 First Line Palliative Chemotherapy

Indications

- Metastatic disease
- Localised or locally advanced disease and patient unsuitable for or unwilling to receive 24 weeks combination treatment of Oxaliplatin, Fluoropyrimidine, surgery or radical chemoradiation
- Performance status 0-2

Treatment

- **Pembrolizumab** may be used in combination with chemotherapy listed below for:
  - Previously untreated advanced oesophageal (squamous or adenocarcinoma) expresses PD-L1 with a combined positive score of >/=10

  and
  - Previously untreated advanced HER-2 negative gastric or gastro-oesophageal junction adenocarcinoma either of which expresses PD-L1 with a combined positive score of >/=1.

- 6-8 cycles of:
  - OX

    or
- 6-12 cycles of:
  - Oxaliplatin and de Gramont
- Or alternatively if oxaliplatin is unsuitable or squamous carcinoma 6-8 cycles of:
  - CX
  - CF
  - Carbo X
  - CarboF

- **Nivolumab** in combination with platinum and fluoropyrimidine-based chemotherapy for previously untreated advanced or metastatic **HER-2 negative adenocarcinomas** of the stomach, gastro-oesophageal junction or oesophagus which express PD-L1 with a combined positive score (CPS) of 5 or more.
- **Nivolumab** in combination with fluoropyrimidine- and platinum-based combination chemotherapy (as listed below) is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic **squamous cell or adenosquamous** carcinoma of the oesophagus with a tumour cell PD-L1expression of >/=1% and a PD-L1 combined positive score of <10.

  - Capecitabine & Oxaliplatin

- Or alternatively if oxaliplatin is unsuitable

  - Carbo X (UGI-007)
  - CX (UGI-006)
  - CF (UGI-005)
  - CarboF (UGI-008)

- CX, CF, CarboX, CarboF or OX (standard dose) with trastuzumab for **Her-2 positive adenocarcinoma** of the gastro oesophageal junction.

Tumour assessment

- CT scan pre-treatment
- CT scan post 3-4 cycles (consider suitability for surgery if locally advanced disease down-staged)
- CT scan post 6-8 cycles

2.5.2 Second Line Palliative Chemotherapy

Indications
Patients remaining of good performance status (0-1) following disease progression after first line palliative chemotherapy or radical chemoradiation.

Treatment

(i) Nivolumab for unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma in adults after fluoropyrimidine and platinum-based therapy.

(ii) Disease-free interval from completion of previous chemotherapy > 6 months; consider Platinum/ fluroropyridimine based chemotherapy.

(iii) Disease-free interval < 6 months; There is evidence for-Irinotecan/5FU/Leucovorin (FOLFIRI regimen) or single agent Docetaxel or weekly Paclitaxel. Consider referral for phase I/II clinical trials.

(iv) Irinotecan & Capecitabine can be considered in selected patients. (Algorithm deviation)

(v) Brachytherapy will be considered for patients previously treated with EBR that have local progression and symptoms such as dysphagia and pain.

Tumour assessment
CT scan every 2-3 months

2.5.3 Third or subsequent line Palliative Chemotherapy

Trifluridine & Tipiracil (Ionsurf) for the **third** (or more) line of systemic therapy for locally advanced or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.

3.0 GASTRIC / TYPE 3 GASTRO-OESOPHAGEAL JUNCTION CANCER

3.1 Peri-Operative Chemotherapy

Indications
Gastric or oesophago-gastric junction adenocarcinoma considered suitable for curative resection:

- T1, N1-3, M0
- T2a, N0-3, M0
- T2b, N0-3, M0
- T3, N0-3, M0

Treatment

- FLOT (only for patients with PS 0-1) x 4 cycles pre-operative and 4 cycles post-operative
- CX, CF, Carbo X, CarboF, OX x 3 cycles or FOLFOX x 4 cycles preoperative and 3 cycles (4 cycles of FOLFOX) post-operative

Tumour assessment

- OGD, CT scan, PET-CT and laparoscopy pre-treatment. EUS for tumours involving oesophago-gastric junction
- CT scan post neo-adjuvant chemotherapy

Surgery
Surgery should be performed 6 weeks after completion of neo-adjuvant chemotherapy.

3.2 Adjuvant Chemoradiation

Indications
Adjuvant chemoradiation would only be considered in individual cases after discussion in MDT if a patient has a very high risk of local failure. There is a limited evidence base for this treatment.

Treatment
All cases to be discussed within an MDM.
Capecitabine or infused 5-fluoruracil with radiotherapy for 5 weeks.

Tumour assessment
CT scan 3 months post completion of chemoradiation

3.3 Adjuvant Chemotherapy for Patients Receiving Upfront Surgery

Indications
The role of adjuvant postoperative chemotherapy following resection of gastric cancer remains unclear. A large number of clinical trials have addressed this question, the majority of which have not demonstrated a benefit from treatment. However, many of these trials were of poor methodologic quality, were underpowered to demonstrate a small but clinically relevant survival advantage, and employed chemotherapy regimens with limited activity in the advanced disease setting. Several meta-analyses of these data have been undertaken, which demonstrate a small benefit for adjuvant chemotherapy over no post-operative treatment, with a hazard ratio for survival between 0.72 and 0.88. However, when analysed separately, the positive effect of chemotherapy on survival was confined to Asian trials, with no benefit observed in Western studies.
Therefore, at present, adjuvant chemotherapy should not be recommended routinely. However, in the presence of adverse risk factors (nodal involvement, positive surgical excision margins), adjuvant chemotherapy may be considered on an individual case basis.

Treatment
- Squamous: 6 cycles of CX, CarboX, CF or CarboF
- Adenocarcinoma: 8 cycles of FLOT or FOLFOX, or 6 cycles of CX, CarboX, CF or CarboF or OX

Tumour assessment
CT scan end of treatment

3.4 Palliative Chemotherapy

In selected cases patients with metastatic or locally advanced and unresectable upper gastrointestinal cancers, will be tested for microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR). See section 1.1.2.

Patients with adenocarcinoma should also be tested for HER2 expression and PDL-1 CPS. Patients with squamous cell carcinoma should be tested for PDL-1 CPS.

3.4.1 First Line

Indications

- Metastatic disease
- Locally advanced disease
- Localised disease and patient unsuitable for or unwilling to receive 24 weeks combination treatment of Oxaliplatin, Fluoropyrimidine or surgery
- Performance status 0-2

Treatment

- Pembrolizumab in combination with fluoropyrimidine-based chemotherapy for previously untreated advanced HER-2 negative gastric or gastro-oesophageal junction adenocarcinoma either of which expresses PD-L1 with a combined positive score of >/=1.

- Nivolumab in combination with platinum and fluoropyrimidine-based chemotherapy for previously untreated advanced or metastatic HER-2 negative adenocarcinomas of the stomach, gastro-oesophageal junction or oesophagus which express PD-L1 with a combined positive score (CPS) of 5 or more.

- 6-8 cycles of OX
- 6-12 cycles of Oxaliplatin and deGramont
- Or alternatively if oxaliplatin is unsuitable 6-8 cycles:
    - CX
    - CF
    - Carbo X
    - CarboF

For HER-2 positive patients (IHC3+)

CX or CF, CarboX, CarboF or OX x 6 cycles + trastuzumab until progressive disease in line with NICE TA 208. (N.B. may also be used for patients with HER 2 overexpression as defined by IHC2-positive and a confirmatory SISH or FISH result who have not received prior anti-cancer treatment for their metastatic disease, funding streams for FISH testing are currently under discussion).

Tumour assessment

- CT scan pre-treatment
- CT scan post 3-4 cycles (consider suitability for surgery if locally advanced disease down-staged)
- CT scan post 6-8 cycles

3.4.2 Subsequent (2nd line and Beyond) Palliative Chemotherapy

Indications
Patients remaining of good performance status (0-1) following disease progression after first line palliative chemotherapy or peri-operative chemotherapy.

Treatment

(i) Disease-free interval from completion of previous chemotherapy > 6 months; consider Platinum/ fluroropyridimine based chemotherapy.

(ii) Disease-free interval < 6 months; Consider Irinotecan/5FU/Leucovorin (FOLFIRI regimen), single agent Docetaxel, weekly Paclitaxel or Ramucirumab with paclitaxel (funding approval required).

(iii) Trifluridine & Tipiracil (lonsurf) for the **third** (or more) line of systemic therapy for locally advanced or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.

Consider referral for phase I/II clinical trials.

Tumour assessment
CT scan every 2-3 months

3.5 Palliative Radiotherapy

Palliative radiotherapy to the stomach can be offered for haemostasis if surgery is not indicated, or for pain management.

4.0 PANCREATIC ADENOCARCINOMA

4.1 Neo-Adjuvant

Treatment

- Gemcitabine
- PS 0-1 modified folfirinox* or gemcitabine & capecitabine*

*NB Use palliative regimen.

4.2 Adjuvant Chemotherapy

Indications
Macroscopically completely resected pancreatic adenocarcinoma

Treatment

- Gemcitabine or Gemcitabine & Capecitabine depending on PS
- Adjuvant Modified Folfirinox x 12 cycles

Tumour assessment

- Post treatment CT scan
- Monitor Ca19.9 each cycle

4.3 Adjuvant Chemoradiation (After Completion of Adjuvant Chemotherapy)

Consider adjuvant chemoradiation in selected patients with R1 resection.

4.4 Chemoradiation for Locally Advanced Disease

Indications

- Pancreatic adenocarcinoma confined to pancreas +/- local nodes not amenable to surgical resection
- Performance status 0-1

Treatment

- All patients should initially be offered 6 months of chemotherapy with a first line advanced disease protocol (see section 3.3)
- If disease remains localized and amenable to radical chemoradiation, this may be considered as follows:
    - Capecitabine with concurrent radiotherapy.

Tumour assessment

- Pre-treatment CT scan (plus MRI/ EUS/ laparoscopy as required to determine inoperability)
- CT scan following 12 and 24 weeks Gemcitabine chemotherapy and 12 weeks after completion of chemoradiotherapy.

4.5 Palliative Chemotherapy

In selected cases patients with metastatic or locally advanced and unresectable upper gastrointestinal cancers, will be tested for microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR). See section 1.1.2.

4.5.1 First Line

Indications

- Locally advanced inoperable adenocarcinoma of the pancreas
- Metastatic disease
- Performance status 0-2

Treatment for locally advanced disease:

- Gemcitabine
- PS 0-1 Palliative modified folfirinox or gemcitabine & capecitabine
- Chemoradiation

Treatment for metastatic disease:

- Albumin bound paclitaxel with gemcitabine can be considered only if other irinotecan or oxaliplatin based combination chemotherapies are unsuitable and the patient would otherwise have gemcitabine monotherapy. (Patients should be PS 0-1 and should have had no previous chemotherapy for early disease unless given as a radiation sensitiser in the adjuvant setting and completed at least 6 months previously).
- Folfirinox
- PS 1-2 - Gemcitabine until progression or intolerance

Patients with prolonged disease control (> 6 months) following adjuvant Gemcitabine who remain of good performance status upon disease relapse may be considered for Gemcitabine re-challenge or Fluoropyrimidine-based therapy.

Tumour assessment

- Pre-treatment CT scan
- CT scan after 12 weeks
- CT scan after 24 weeks
- Ca19.9 levels every 4 weeks

4.5.2 Second Line Palliative Chemotherapy

Treatment

Clinicians' choice of fluoropyrimidine/platinum or gemcitabine- based therapy depending on prior therapy**.**

Tumour assessment

CT scan pre-treatment and every 9-12 weeks during therapy

4.6 Palliative Radiotherapy

Palliative radiotherapy to the pancreas can be offered for pain control if other measures have failed such as opiates and nerve blocks. It can also be useful for haemostasis if the tumour is involving duodenum.

5.0 CHOLANGIOCARCINOMA / GALL BLADDER CARCINOMA

5.1 Adjuvant Chemotherapy

Treatment
Consider Capecitabine as per BILCAP trial or entry to clinical trial

Tumour assessment

- Post-operative CT scan
- CT scan post 6 cycles chemotherapy
- Monitor Ca19.9 each cycle

5.2 Palliative Chemotherapy

Request FGFR2 fusion and IDHI mutation testing at baseline for these patients.
In selected cases patients with metastatic or locally advanced and unresectable upper gastrointestinal cancers, will be tested for microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR).

Indications

- Locally advanced inoperable cholangiocarcinoma
- Metastatic disease
- Performance status 0-2

Treatment

- First line Gemcitabine, Cisplatin with Durvalumab up to a maximum of 8 cycles. Durvalumab monotherapy to continue until disease progression, unacceptable toxicity or patient choice.
- Gemcitabine with Cisplatin
- Gemcitabine with Carboplatin (may be used in patients who cannot tolerate cisplatin)
- Gemcitabine for a total of up to 24 weeks
- 6-8 cycles of:
  - OX
  - OF

Pemigatinib may be considered for fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy.

Ivosidenib for the treatment of locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation after 1 or more systemic treatments.

Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement.

Tumour assessment

- Pre-treatment CT scan
- CT scan after 12 weeks
- CT scan after 24 weeks
- Ca19.9 levels every 4 weeks

6.0 HEPATOCELLULAR CARCINOMA

6.1 Localised Disease

All patients should be referred to Kings College Hospital for consideration of resection or chemoembolisation.

6.2 Palliative Chemotherapy

In selected cases patients with metastatic or locally advanced and unresectable upper gastrointestinal cancers, will be tested for microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR). See section 1.1.2

Indications

- Locally advanced disease not amenable to loco-regional therapy
- Metastatic disease
- Performance status 0-2
- Child-Pugh status A (or low burden Child-Pugh B for sorafenib)

Treatment

- Atezolizumab and bevacizumab for 1st line systemic treatment of patients with locally advanced or metastatic and/or unresectable hepatocellular carcinoma.
- Sorafenib for 1st line, or 2nd line if atezolizumab and bevacizumab has been given first line, in patients with Child–Pugh A disease.
- Lenvatinib for 1st line, or 2nd line if atezolizumab and bevacizumab has been given first line, treatment in patients with Child–Pugh A disease.
- Regorafenib for the 2nd line systemic therapy of Child-Pugh A previously treated with sorafenib.
- Cabozantinib for second line of tyrosine kinase inhibitor systemic therapy of Child-Pugh A locally advanced or metastatic hepatocellular carcinoma previously treated with sorafenib.

Tumour assessment

- CT scan pre-chemotherapy
- CT scan post 3 cycles
- CT scan post 6 cycles
- AFP levels before each cycle

7.0 SMALL BOWEL CARCINOMA

7.1 Adjuvant Chemotherapy

Indications

There is no established role for adjuvant chemotherapy, but for selected patients with poor prognostic features, 6-8 cycles of OX, OF or OT may be considered.

7.2 Palliative Chemotherapy Indications

In selected cases patients with metastatic or locally advanced and unresectable upper gastrointestinal cancers, will be tested for microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR). see section 1.1.2

Advanced disease not amenable to surgical resection
Performance status 0-2

Treatment

There is no standard treatment regimen.
Suitable patients may be considered for

- 6-8 cycles of:
  - OX

Or

- 6-12 cycles of:
  - OF
- Or alternatively if oxaliplatin is unsuitable 6-8 cycles of:
  - CX
  - CF
  - Carbo X
  - CarboF

or

- FOLFIRI

Tumour assessment

- CT scan pre-treatment
- CT scan post 3-4 cycles
- CT scan post 6-8 cycles

8.0 GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOURS

8.1 Adjuvant Therapy

Indications
There is no role for adjuvant therapy following surgical resection of gastroenteropancreatic neuroendocrine tumours.

Goblet cell carcinoid tumours of the appendix (adenocarcinoids) with lymph node involvement or T3N0 disease should be considered for adjuvant chemotherapy with 8 cycles of Capecitabine.

8.2 Palliative Systemic Anti-Cancer Therapy

In selected cases patients with metastatic or locally advanced and unresectable upper gastrointestinal cancers, will be tested for microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR). See section 1.1.2

A number of therapeutic options exist as follows:

(i) Surgical resection of hepatic metastatic disease (Refer to Kings College Hospital)

(ii) Embolisation (refer to Kings College Hospital) or radiofrequency ablation of hepatic metastatic disease (Refer to Maidstone Hospital or Kings College Hospital)

(iii) Somatostatin analogue therapy

(iv) Radiolabeled MIBG/ octreotide (Funding approval required.)

- Peptide receptor radionuclide therapy (Lutetium 177 octreotate) should be considered for the treatment of unresectable or metastatic, progressive, well differentiated and somatostatin receptor positive gastroenteropancreatic neuroendocrine carcinoma.

(v) Selective internal radiotherapy (SIRT) (Refer to Kings NET MDT) Funding approval required.

(vi) Systemic anti-cancer therapy

Indications
Active therapy should be considered for:

(i) Symptomatic metastatic disease (e.g. symptoms of the carcinoid syndrome, local symptoms due to tumour mass/ invasion such as pain, haemoptysis, cough, biliary obstruction)

(ii) Rapidly progressive metastatic disease

Treatment
The choice of treatment will be dictated by the clinical situation.

(i) Somatostatin analogue therapy
Highly symptomatic patients should be commenced on a short acting preparation initially (e.g. octreotide 50 mcg s/c bd increased as necessary to 200 mcg tds SC)
Responding patients should then be converted onto a long acting preparation (e.g. Sandostatin LAR 20 mg IM 4-weekly, increased if necessary to 30 mg IM 4-weekly or Somatuline autogel 60 mg s/c 4-weekly, increased if necessary to 120 mg s/c 4-weekly

(ii) Systemic anti-cancer therapy

There is no standard chemotherapy regimen for this disease. Patients with increased likelihood of response to chemotherapy are those with poorly differentiated tumours, particularly those with a high proliferative rate (Ki67>10%), pancreatic neuroendocrine carcinomas.

The following regimens may be considered.

- Streptozocin plus Doxorubicin x 4 cycles
- Carboplatin plus Etoposide x 6 cycles
- Capecitabine plus Temozolomide x 6-8 cycles

There is increasing evidence for the use of targeted therapies in neuroendocrine tumours.
Sunitinib may be considered as 1st, 2nd or 3rd line treatment for well differentiated pancreatic neuroendocrine tumours.
Everolimus may be considered for well differentiated pancreatic, non-functioning gastrointestinal or lung neuroendocrine tumours.

Tumour assessment

Baseline CT scan, octreotide scan, MIBG scan, 24-hour urinary 5-HIAA and VMA, investigation of neuropeptide hormone secretion as clinically indicated, fasting gut hormone profile including chromogranin A and B.

Repeat CT scan and 24-hour urinary 5-HIAA and serum chromogranin A every 3-12 months depending on rate of disease growth.

Repeat CT scan every 12 weeks while receiving cytotoxic chemotherapy

9.0 GASTROINTESTINAL STROMAL TUMOURS

9.1 Adjuvant Therapy

Imatinib 400mg od is recommended as an option as adjuvant treatment for up to 3 years for adults who are at high risk of relapse after surgery for KIT (CD117) -positive gastrointestinal stromal tumours, as defined by the Miettinen 2006 criteria (based on tumour size, location and mitotic rate).

9.2 First Line Metastatic Therapy

Patients presenting with advanced inoperable disease should have tumour specimens sent to the Royal Marsden Hospital for mutational analysis, wild-type c-kit and PDGRFRA should be referred for NTRK fusion analysis.

Imatinib 400mg daily is currently considered standard therapy for all patients.
However, for patients with exon 9 c-kit mutations or wild type, there is emerging evidence for a benefit from higher initial Imatinib doses e.g. 600-800mg daily.

Monitoring for patients receiving imatinib
The occurrence of toxicity following institution of imatinib is unpredictable. The following schedule of assessments should be undertaken, with clinical assessment, FBC, U+E and LFT performed at each of 2 weeks, 4 weeks, 8 weeks, 12 weeks then 3 monthly thereafter.
Tumour assessment should be performed with CT T/A/P every 12 weeks during imatinib therapy (May be extended to every 24 weeks in prolonged stable disease)

9.3 Second Line Metastatic Therapy

Sunitinib 37.5 mg daily continuously.

9.4 Third Line Metastatic Therapy

Regorafenib should be considered for patients' PS 0-1 who have disease progression or intolerance to imatinib and disease progression on sunitinib.

10.0 GUIDELINES ON THE MANAGEMENT OF DRUG-SPECIFIC TOXICITY

10.1 DPD Testing

Fluoropyridimines are rapidly degraded by dihyropyrimidine dehydrogenase (DPD). Therefore, DPD deficiency can lead to severe toxicity or death following treatment with, for example, 5-FU or capecitabine. Homozygotes to DPD are rare (but likely to have severe toxicity or die). However, there are 3-5% of patient who are heterozygotes and are likely to develop toxicity; the clinician may reduce the fluoropyrimidine starting dose in this cohort.

All patients, prior to commencing treatment with a fluoropyrimidine based therapy (5-fluorouracil, capecitabine or tegafur) should be screened for four DPYD gene variants which have been associated with fluoropyrimidine-associated toxicity.

Patients only require this genomic test to be carried out once, at the start of their first fluoropyrimidine treatment, as the results remain applicable to subsequent fluoropyrimidine cycles and future treatment regimens containing a fluoropyrimidine. Within the clinical pathway, the genomic test should be ordered for eligible patients at the point of consent for fluoropyrimidine chemotherapy or earlier if appropriate. Clinicians should follow the UK Chemotherapy Board guidance on dosing adjustments for fluoropyrimidine therapy following detection of a DPYD variant which is available on the KMCC website http://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/network-chemotherapy-prescription-proformas-protocols-nhs-staff-use/

10.2 Uridine Triacetate

Uridine triacetate (Vistoguard) is an antidote for management of early-onset severe or life-threatening toxicity, including diarrhoea, within 96 hours following 5FU or capecitabine administration. It is not licensed in the UK, but is available on an unlicensed basis via a 24/7 emergency ordering service, via tel. 0207 8872235.
The policy statement (link below) from NHSE contains information on inclusion / exclusion criteria and also dosing information.

https://www.england.nhs.uk/wp-content/uploads/2020/03/1929_Policy_Statement_Final_v2.pdf

11.0 APPENDIX A: CLINICAL TRIALS

Refer to the local research team who will provide on request an orientation handbook, list of current trials and associated trial protocols and summaries.

Contact numbers

MTW – Clinical Trials Office	01622 225 033
Darent Valley Hospital – Clinical Trials Office	01322 428 100 ext. 4810
Medway Hospital – Clinical Trials Office	01634 825 094

East Kent Hospitals – Clinical Trials Office:

Solid Tumours (excluding Gynae)	01227 866 393
Gynae Clinical Trials	01843 234 343
Haematology Clinical Trials	01227 864 129

12.0 APPENDIX B: KMCC GUIDELINES ON MANAGING CARDIAC TOXICITY FOR PATIENTS RECEIVING TRASTUZUMAB

- The same monitoring modality should be used throughout the course of treatment and, where possible, this should also include the same operator, machine, and calculation algorithm. Each institution should establish a normal range for the methods used. On the basis that an echocardiogram exposes the patient to less radiation and is usually less expensive than a MUGA scan, the NOG recommend this as the method used to assess cardiac function. ECHOs are reported as a range not an absolute figure, but it is generally accepted that the lower limit of normal (LLN) for cardiac function when measured by an ECHO is 55%.

- Patients developing signs and symptoms of heart failure should have their trastuzumab treatment interrupted, have ACE inhibitor therapy initiated by the oncologist and be referred to a cardiologist. Investigation and treatment is recommended in accordance with present guidelines (NICE, 2003; Bonow et al 2005; Swedberg et al 2005).

- It is the prescriber's responsibility to check that the ECHO/MUGA is satisfactory before continuing treatment.

    - An ECHO/ MUGA should be carried out every 6 months

NB When an ECHO is used to measure cardiac function, LLN can be assumed to be 55%. For MUGA scans, the LLN for the institution should be used.

13.0 PERSONNEL AND CONTACT INFORMATION

A comprehensive, up to date list of MDM contact details can be found on the KMCC website via the following link: http://www.KMCC.nhs.uk

14.0 GLOSSARY

Acronyms in common usage throughout KMCC documentation

BNF	British National Formulary
BOPA	British Oncology Pharmacist Association
CNB	Cancer Network Board
COSHH	Control of substances hazardous to health regulations.
CYP	Children & Young People (in relation to the IOG)
DCCAG	Diagnostic Cross Cutting Advisory Group
DOG	Disease Orientated Group (NSSG/TSSG/TWG)
DVH	Darent Valley Hospital
DGT	Dartford and Gravesham NHS Trust
EK	East Kent
EKHUFT	East Kent Hospitals University Foundation Trust
EPS	Electronic Prescribing System
FP10(HNC)	Prescriptions issued by hospital doctors for dispensing in the community
GP	General Practitioner
HoP	High Level Operational Policy
IOSC	Improving Outcomes: A Strategy for Cancer
IV	Intravenous
K&C	Kent & Canterbury Hospital, Canterbury, (EKHUFT)
KMCC	Kent & Medway Cancer Collaborative
KMCRN	Kent & Medway Cancer Research Network
KOMS	Kent Oncology Management System
LSESN	London & South East Sarcoma Network
MFT	Medway Foundation Trust
MTW	Maidstone & Tunbridge Wells NHS Trust
NHS	National Health Service
NMP	Non-medical prescriber
NPSA	National Patient Safety agency
NOG	Non-Surgical Oncology Group *(Permanent oncologist sub group of the DOGs with a specific responsibility for chemo/rad pathways and advice to the DOG, Network and GEOGRAPHICAL LOCATIONs on new drugs)*
PoC	Pathway of Care *(Network agreed disease site specific clinical guidelines)*
QEQM	Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT)
QoL	Quality of life
QSIS	Quality service information system
QST	Quality Surveillance Team
RAT	Research and Trial Group *(Permanent sub-group of the DOGs with a specific responsibility for taking forward the clinical trials agenda)*
RMH	Royal Marsden Hospital
RNOH	Royal National Orthopaedic Hospital

SACT	Systemic Anti-Cancer therapy
SACT regimen	Systemic Anti-cancer prescription on the electronic prescribing system
SACT protocol	Systemic Anti-cancer protocol on KMCC website
TTO	Treatment to take home
QVH	Queen Victoria Foundation Trust Hospital East Grinstead
UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent

15.0 DOCUMENT ADMINISTRATION

Document Title	Oncological Treatment Guidelines for Upper GI Cancer
Principle author	Caroline Waters
Co-author(s)	Upper GI NOG
Current version number	25
Current status	Final
Agreed as "Fit for Publication" by	UGI NOG
Expected review date by	March 2026

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Revision History			
Date of revision	New Version Number	Nature of Revision	Confirmation of Accuracy by
December 2008 – February 2009	0.1 – 0.4	Guidelines agreed, document transposed into network guidance template, appendix A clinical trials added.	Upper GI NOG
February 2009	1	Agreed	Upper GI NOG
March 2009	1.1-1.3	Changes to sections 9 and 10	Upper GI NOG
August 2009	3.1	Changes from Dr J Waters incorporated	Sarah Wade
August 2009	4	Agreed	Upper GI NOG
February 2010	4.1	Changes agreed at the upper GI NOG	Upper GI NOG
March 2010	5	Changes agreed at the upper GI NOG	Upper GI NOG
November 2010	5.1 – 5.2	Changes agreed at upper GI NOG (sections 7.2, 2.4, appendix B)	Upper GI NOG
December 2010	6	Published	Upper GI NOG
December 2010	6.1	Section 1.1 –neo-adjuvant treatment for oesophageal cancer divided into two sections: chemotherapy and chemoradiotherapy	Upper GI NOG
February 2011	6.2	Changes agreed at the Upper GI NOG	Upper GI NOG
May 2011	7	Published	Upper GI NOG

September 2011	7.1-7.2	Changes following review at Upper GI NOG	Upper GI NOG
October 2011 March 2012	8 8.1	Published	Upper GI NOG
March 2012	9	Published	Upper GI NOG
November 2012 – January 2013	9.1-9.2	Changes following review at the Upper GI NOG	
February 2013	10	Published	Upper GI NOG
May 2013	10.1	Draft – updated in line with NCDF & NHSE lists	
June 2013	11	Final	Upper GI NOG
November 2013-March 2014	11.1	Changes to palliative treatment options for pancreatic adenocarcinoma (section 4.3) Addition of regorafenib (section 9.4) for third line metastatic therapy for GIST	Upper GI NOG
April - May 2014	v12 – 12.2	This version was not published. Changes agreed at the UGI NOG	
June 2014	v13	Published	Upper GI NOG
October 2014	V13.1	Addition of Capecitabine & Temozolomide as a treatment option for PNET (section 8.2)	Upper GI NOG
November 2014	V14	Published	Upper GI NOG
April 2015	V14.1	Changes agreed at the UGI NOG. Revised in line with NCDF list	
September 2015	V15	Published	Tim Sevitt
November 2015	V15.1	Updated in line with published NCDF List	
January 2016	V16	Published	Tim Sevitt
March 2017 onwards	V16.1 -16.2	Addition of Irinotecan / cape to section 2.6 Addition of Gem/ Cape to section 4.1 Addition of Adjuvant chemoradiation after adjuvant chemo – section 4.2 DPD testing – statement added to section 10.1 – re: management of drug specific toxicity. Updated in line with NCDF List for: - albumin paclitaxel and gemcitabine in untreated metastatic pancreatic cancer - section 4.4 - Sorafenib in HCC section 6.2 Update to the criteria for use of Everolimus in NETS – section 8.2	
September 2017	V17	Published.	Upper GI NOG
September 2017	V17.1	Addition of FLOT regimen (section 3.1) Addition of adjuvant capecitabine for biliary tract cancer (section 5.1)	
October 2017	V18	Published	Tim Sevitt
March-Oct 2018	V18.1-V18.5	Section 2.5 Indications updated Section 2.3 Addition of Carboplatin+Paclitaxel Section 3.4 Indications updated Section 3.5 Title updated and treatment Sections 4.4/6.2/8.2/9.4 funding information updated Section 8.2 Addition of Lutetium 177 octreotate Section 14.0 web link updated	Following NOGs 13/03/2018 and 11/09/2018
NOV 2018	V19	Published	Tim Sevitt

March 2019	V19.1-19.2	Section 6.0 Addition of Lenvatinib and Regorafenib Section 4.1 Addition of adjuvant folfirinox for adjuvant pancreas Further amendment 10/09/19 change of name of protocol Section 4.1 Adjuvant modified folfirinox Section 4.4 Palliative modified folfirinox	Upper GI NOG march/sept 2019
September 2020	V20	Published	Mathilda Cominos
June 2021	V20.1-20.6	Overhaul of entire document, changes throughout each section	Changes made at UGI NOG 08.06.21
July 2021	V20.6.1-20.8.1	Updated following virtual review Addition of section 2.2.3 Addition of trastuzumab to section 2.5.1 Reformatted by R.Patel	M. Archer
July	V21	Published	M.Cominos and J.Waters
July-Nov	V21.4-21.10.2	Amended during and following UGI NOG July 2022 and Nov 2022 Sections: 1.2 2.1 2.1.2 2.1.3 2.2 2.2.2 2.5 2.5.1 3.1 3.2 3.4 3.4.1 3.4.2 6.2 9.3 10.1	NOG / C Waters
March	V22	Published	M.Cominos UGI NOG
NOV 2023-Feb 2024	V22.1 to V22.2	MA Updated as per NOG discussion Nov 2023 Remove nivolumab for MSI MMR Add pembrolizumab MSI / MMR for gastric, small intestine, biliary tract: Trifluridine & Tipiracil (lonsurf) added to section 2.5.3 Updated at UGI NOG Feb 2024 Section 2.1.2 updated capecitabine added 27.02.2024 V22.2 circulated for approval via email	
March 2024	V22.3	Updated as per C waters comment for treatment cycles:	

		Section 2.5.1 and 7.2	
June 2024	V23	Final version taken for final approval to UGI NOG 18.06.2024 Cycle length added to section 2.5.1 and section 7.2 and section 3.4.1 Section 2.2.2 updated: word “adenocarcinoma” added	APPROVED at NOG
June 2024	V23	Final	S.Enefer/ NOG
August 2024	V23.1	Draft created: notes added to front page M.Archer	
October 2024	V23.2	Section 2.5.1 updated pembrolizumab indication Section 5 baseline testing included Reference to section 1.1.2 added to all relevant sections Section 7.2 folfiri added as treatment option	NOG 22.10.2024
March-June 2025	V23.3-4	Add futibatinib section 5.2 Add thromboprophylaxis statement section 1 Remove Covid guidance and link	Discussed at NOG and Circulated for vitrtual approval
September 2025	V24	Finalised but not published following further review.	NOG approved.
October 2025	V24.1	Reviewed at UGI NOG Section 3.4.1 updated.	Reviewed at UGI NOG
March 2026	V24.2	Updated as per NOG chair final review. Circulated for virtual approval.	
March 2026	V25	Published	NOG approved Reviewed at NOG and virtual approval received.