

Protocol for Planning and Treatment

The process to be followed when a course of chemotherapy is required to treat:

UPPER GI CANCER

Patient information given at each stage following agreed information pathway

1. DIAGNOSIS

Upper GI Cancer

2. STAGING

Clinical assessment, staging investigations and initial treatment plan

All patients should be staged clinically according to the *TNM* system. (The histological tumour types covered by this protocol are as detailed in AJCC cancer staging handbook, 7th edition.)

Treatment plans can be made at the weekly multidisciplinary meeting (MDM) but patients should be seen by an experienced clinician before making the final decision on the treatment plan. If the plan alters significantly when the patient is seen, the clinician should consider re-discussing the patient at the MDM. In such cases, it is helpful to state whether or not the pathological and radiological findings need review, to prevent unnecessary work for the radiologists and pathologists.

Standard tests: CT scan of thorax, abdomen, and pelvis, full blood count, urea, electrolytes, and liver function tests. *Additional tests* such as CT/Endoscopic ultrasound scans, laparoscopy, endoscopy, and biopsies can be considered at the MDM and by the clinician.

Current MDM Provision:

Single Tayside weekly MDM held on a Wednesday morning at Ninewells Hospital with video link to Perth Royal Infirmary.

As many members of the multidisciplinary team as possible should attend the weekly MDM. In particular the following disciplines should normally attend every meeting: dietetics, oncology, palliative care, pathology, radiology, surgery, and specialist nursing. A record will be kept of which patients are discussed. It helps the pathologist and radiologist to know the reason for discussion and whether review of certain aspects of the case may be omitted.

3. TREATMENT

Oesophageal dysplasia

The management of oesophageal dysplasia is determined by multidisciplinary discussion on a case-by-case basis.

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Oesophageal carcinoma

Surgery for oesophageal carcinoma

T1-3 tumours – the indication for radical surgery is determined by the surgical consultant after appropriate staging investigations (usually upper GI endoscopy, GI protocol CT scan, CT-PET scan and endoscopic ultrasound) have been done.

Chemotherapy for oesophageal carcinoma

Neo-adjuvant chemotherapy

The OEO2 trial showed increased survival and some complete responses with 2 cycles of cisplatin/5-FU chemotherapy. There is little convincing evidence of benefit of adjuvant chemotherapy in oesophageal carcinoma. This would be the normal default regimen for oesophageal carcinomas.

Adjuvant chemotherapy

In fit patients, peri-operative ECF chemotherapy to a maximum of 3 cycles pre-operatively and 3 cycles post-operatively may be considered for those patients with junctional tumours and lower oesophageal, if there is considered potential benefit over the two-cycle regimen.

Radiotherapy for oesophageal cancer

Pre-operative

There is no evidence of benefit of routine pre-operative radiotherapy.

Intra-operative

There is no evidence of benefit of routine intra-operative radiotherapy, but this may be considered as part of a clinical trial.

Post-operative

There is some suggestion that giving radiotherapy after palliative resection may decrease the risk of local recurrence, but may shorten median survival. There is no evidence of benefit after curative resection. Routine post-operative radiotherapy is not recommended, but this may be considered in patients who have a high chance of relapse who have had incomplete resections, and when the residual disease can be localised to allow radiotherapy planning.

Chemo-radiotherapy as primary radical treatment for oesophageal carcinoma

For patients fit for this treatment the treatment regimen should be:

Concurrent chemotherapy with radiotherapy

Cisplatin day 1 and 5-FU days 1-4 weeks one and five Carboplatin AUC 5 may be substituted for the cisplatin pragmatically, in those patients for whom the cisplatin or a fluid load would be contraindicated (e.g. those with ischaemic heart disease). Neoadjuvant cisplatin/5-FU, 2 cycles, may be given to those patients deemed fit for more intensive treatment. (The cycle is every 21 days for neo-adjuvant treatment, but approximately 28 days for concurrent chemoradiotherapy.) Capecitabine may be substituted for 5-FU in dose as per the SCOPE-1 study.

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Radiotherapy

50Gy in 25 fractions over 5 weeks, CT planned volume, by 4-field arrangement

Some patients will be suitable for radical radiotherapy but not for chemotherapy, and they should receive

50-52.5Gy in 20 fractions over 4 weeks using the technique above

Consideration should be given to entry to the SCOPE-1 study.

Stomach carcinoma

(Neo)adjuvant chemotherapy for stomach carcinoma

There is some evidence of survival benefit for peri-operative chemotherapy, although only 2/5 patients are able to complete this¹. For selected fit patients, 3 cycles of neo-adjuvant and 3 cycles of adjuvant chemotherapy (EC bolusF) can be considered. Rarely, neo-adjuvant chemotherapy may be contra-indicated but the patient may be fit for adjuvant chemotherapy after resection; in this case, pragmatically, 4 cycles of ECF/X may be considered.

Intra-operative hyperthermic chemotherapy

Not routinely recommended but may be considered as part of the current clinical trial.

Surgery for stomach carcinoma

T1-3 tumours – the indication for radical surgery is determined by the surgical consultant after appropriate staging investigations have been done.

4. RADIOTHERAPY

For stomach carcinoma

Pre-operative

There is no evidence of benefit of routine pre-operative radiotherapy.

Intra-operative

There is no evidence of benefit of routine intra-operative radiotherapy, but this may be considered as part of a clinical trial.

Post-operative

There is some suggestion that giving chemoradiotherapy after resection of stomach cancer may improve survival. There are concerns, however, over the toxicity of this treatment and about the quality of the surgery in the positive trial (Intergroup). Routine post-operative chemoradiotherapy is not recommended.

Palliative Treatment for oesophagus and stomach carcinoma

Treatment should be directed at symptoms, and surgery and oncological treatment may form part of the management strategy. There is little evidence of significant survival benefit from oncological treatment.

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Clinical Management Guideline – Chemotherapy – Upper GI

Dysphagia

An oesophageal stent should be considered if dysphagia is marked, e.g. patient managing only semi-solid food or liquids only. If the dysphagia is less severe, it may be possible to give palliative radiotherapy or PDT prior to considering other measures. The use of argon beam laser ablation of tumour may also provide relief.

Palliative Radiotherapy for oesophagus would normally be given as:
20Gy in 5 daily fractions over one week

Fit patients with localised but advanced oesophageal carcinoma that is not resectable may be considered for:

30Gy in 10 daily fractions over two weeks, if thought to be advantageous by the clinician

Patients with poor performance status who have bleeding gastric cancers should receive:

8Gy in a single fraction, with ondansetron for anti-emetic effect.

Bleeding from tumour

Consider pre-disposing drugs, and medical management e.g. tranexamic acid. Endoscopically, argon photocoagulation may be used. Palliative radiotherapy should also be considered and should be started as soon as possible.

Photodynamic therapy (PDT)

May be useful in some patients to aid palliation.

Metastatic disease

Patients with metastatic upper GI tumours are treatable but incurable, so all treatment is palliative. The survival of patients with metastatic oesophageal cancer varies from a few weeks to years. Thus, the needs of patients with metastatic disease will vary hugely both between patients and in the same patient over time.

Close liaison is required at all times between primary and secondary care. The palliative care needs of patients should be addressed. In the community this will be through the GP and in hospital through the specialized palliative care services. See SIGN for further guidance.

Local treatments for local problems

e.g. tapping pleural effusion
pinning long bones weakened by bony metastasis
palliative radiotherapy, etc.

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5. CHEMOTHERAPY

For metastatic disease

Secondary spread of the cancer typically involves lymph nodes and liver, and less commonly bone and brain. If the patient is of good performance status, then palliative chemotherapy with ECF/X or EOX (as per REAL-3 trial) should be considered. If liver function is poor (e.g. bilirubin >45) then consideration should be given to giving weekly epirubicin 25mg/m², if treatment is thought to be appropriate. Surgery may be considered in those patients with locally advanced disease without distant metastases, in whom there has been a very good response to palliative chemotherapy. In older patients, it is sometimes appropriate to treat with the 5-FU component only, e.g. De Gramont or Capecitabine.

Second-line chemotherapy

There are less convincing data for the efficacy of chemotherapy for the relief of symptoms following first line treatment. Several drugs have been shown to have activity in the setting of a phase II trial, but none is accepted as standard. Second-line chemotherapy may therefore be considered on an individual basis, e.g. for patients who have had a particularly good response to first line chemotherapy and who have achieved a useful disease-free interval following their first treatment course. Current second line chemotherapy would be mitomycin C and 5-FU or paclitaxel/carboplatin for fitter patients.

Pancreatic cancer and biliary tumours

Curative treatment

Radical surgery, if appropriate, should be performed after staging and assessment by the surgical team.

Adjuvant treatment

Pancreatic cancer

Consider 6 months treatment with gemcitabine.

Ampullary cancer

Chemotherapy not routinely indicated.

Biliary Tumours

Chemotherapy not routinely indicated. Consider entry into clinical trial.

Palliative treatment

Pancreas

Consider gemcitabine or 5-FU-based chemotherapy, monitor disease by imaging and CA19-9 tumour marker. If the disease is inoperable, consider radiotherapy. There is no evidence that routine administration of second-line chemotherapy is effective, but re-challenge in those patients who have responded initially and then relapsed may be worthwhile. Sunitinib can be considered for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours.

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Ampullary and Biliary

Consider 5-FU-based or gem/cisplatin (as per ABC02 trial) palliative chemotherapy.

Hepatocellular carcinoma

Curative treatment

Patients should be surgically assessed with a view to resection.

Palliative treatment

Symptom control using tumour embolisation should be considered. Palliative chemotherapy (anthracycline-based) has poor results, and will not be appropriate for many patients.

Carcinoid tumour/neuroendocrine tumour (NET)

Curative treatment

Serum chromogranin A (CgA) may be a useful marker of response to treatment and urinary 5-hydroxy indole acetic acid (5-HIAA) should be measured. Consider MEN1 syndrome and the need for further tests (such as thyroid, parathyroid, calcium, calcitonin, etc.).

Patients should be surgically assessed with a view to resection. Appropriate imaging (e.g. CT) should be done, in addition to scintigraphy. Scans with both radiolabelled octreotide and with MIBG should be considered.

Palliative treatment

Treatment choices for non-resectable disease include somatostatin analogues, radionuclides, ablation therapies, and chemotherapy. External beam radiotherapy may relieve bone pain from metastases. Chemotherapy may be used for inoperable or metastatic pancreatic and bronchial tumours, or poorly differentiated neuroendocrine tumours. The role of chemotherapy for NETs is uncertain. It is essential to consider the tumour types individually in view of their varying response to chemotherapy, e.g. the highest response rates with chemotherapy are seen in the poorly differentiated and anaplastic NETs with a much lower response rate seen in patients with strongly positive carcinoid tumours. Response rates for pancreatic islet cell tumours vary between 40% and 70% and usually involve combinations of streptozotocin (or lomustine), dacarbazine, 5-fluorouracil, and adriamycin. Good results have been seen from the Mayo clinic where up to 70% response rates with remissions lasting several years have been achieved by combining chemoembolisation of the hepatic artery with chemotherapy.

Standard palliative chemotherapy is the 'Cap-strep' regimen (control arm of the NET 01 trial:

Streptozotocin (1000mg/m²) will be administered intravenously as a 2-hour infusion in normal saline on day 1, repeated every 21 days.

Capecitabine (625mg/m²) will be administered orally, twice daily, commencing day 1, on each day of a 21-day cycle.

Alternatively, ECF chemotherapy may be considered.

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Clinical Management Guideline – Chemotherapy – Upper GI

Patients who have neuroendocrine tumour with small cell cancer features may be considered for platinum/etoposide.

Targeted radiotherapy may be considered, using ^{131}I -MIBG (usually 7.4GBq or less) if the MIBG scan is positive. Referral to Royal Marsden for DOTATOC may be considered for fit patients, able to travel, and who have good renal function but should be passed through the OHMMG.

Sunitinib and Everolimus may be considered for systemic treatment of neuroendocrine carcinoma as per the current SMC guidance.

Gastro-intestinal stromal tumour (GIST)

Curative treatment

Patients with pathological confirmation of GIST should be considered for surgical resection. Adjuvant therapy is not routine, but Imatinib may be considered using for patients who have had higher risk GISTs resected, although there is no proven survival benefit for this strategy as yet, so Imatinib may be reserved for recurrence instead.

Palliative treatment

Imatinib may be useful in the palliative treatment of GIST. Sunitinib may be considered as second-line treatment for progression on Imatinib.

6. FOLLOW UP

All 'operable' cases are assumed to have completed primary therapy, and been seen post-treatment to check wounds, radiation reactions etc. For patients who are managed jointly by the Surgical Clinic and the Department of Radiotherapy & Oncology, follow up will normally be alternated:

Post-oesophagectomy

Clinical follow-up: 3-monthly for the first year, 6-monthly in second year and then annually for a further 7 years. Discharge from hospital clinical follow up to general practitioner at 10 years after treatment.

Locally advanced +/- metastatic

No fixed schedule of follow up, follow-up managed by palliative care/oncologist/surgeon/GP. Depends on symptoms and pace of disease.

Additional Aspects

Patient Information

Locally produced information leaflets provided to all patients. Backup and Cancerlink information booklets are available. Videos, books and tapes also used as required.

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7. CLINICAL TRIALS

All patients are considered for entry into local, national and international trials for which there is local ethical permission.

Current Trials

Investigational: PET-PANC (pancreas)

Radical

- Neo-SCOPE (opening); oesophagus

Adjuvant

- BILCAP, hepatobiliary

Metastatic/locally advanced

- **Immodulon IMM-101, pancreas**

8. TREATMENT DEFINITIONS

CISPLATIN/5FU

Cisplatin 50mg/m² IV Infusion Day 1

5FU 1g/m² IV Infusion Days 1&2

ECBolusF

Epirubicin 50mg/m² IV Bolus Day 1

Cisplatin 60mg/m² IV Infusion Day 1

5-Fluorouracil 600mg/m² IV Infusion Day 2

Repeated every 3 weeks

CAP-STREP

Streptozocin 1000mg/m² IV Infusion Day 1

Capecitabine 625mg/m² PO twice daily Days 1 to 21

Repeated every 21 days for up to 6 cycles

Author: Signature: Date:

Chair: Signature: Date:
(on behalf of OHMMG)

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