Contents

Introduction .................................................................................................................................................. 6
Executive Summary ........................................................................................................................................ 8
1 Referrals .................................................................................................................................................. 9
   1.1 Referral for patients with suspected HPB cancer ............................................................................... 9
2 Initial Assessment of Patients with Suspected HPB Cancer .................................................................. 10
   2.1 History and performance status ......................................................................................................... 10
   2.2 Full examination .................................................................................................................................. 11
   2.3 Nutritional assessment ......................................................................................................................... 11
   2.4 Blood tests .......................................................................................................................................... 11
   2.5 Imaging .............................................................................................................................................. 12
   2.6 Pathology ........................................................................................................................................... 13
   2.7 Pre-assessment for potential treatment options ................................................................................... 14
3 Referral for Patients with a Diagnosis of HPB Cancer ............................................................................ 16
   3.1 Referrals to the specialist multidisciplinary team ............................................................................. 16
   3.2 Information to include on referrals ....................................................................................................... 16
   3.3 Standard information to include in referrals to community specialist palliative care teams ...... 17
   3.4 Management of children, teenagers and young adults with diagnosed or suspected HPB cancer ........................................................................................................................................... 17
4 Inter-professional Communication between Secondary and Primary Care .............................................. 19
   4.1 General principles ............................................................................................................................... 19
   4.2 At diagnosis ....................................................................................................................................... 19
   4.3 Multidisciplinary team discussions and decisions ............................................................................... 20
   4.4 Letters from clinics .............................................................................................................................. 20
   4.5 Treatment Record Summary ............................................................................................................... 20
5 Multidisciplinary Team Structure .......................................................................................................... 21
   5.1 Local diagnostic unit ............................................................................................................................ 21
   5.2 Specialist pancreatic centre multidisciplinary team ......................................................................... 22
6 Ensuring Patient-centred Care for All Pathways ...................................................................................... 23
   6.1 Enhancing the patient experience ....................................................................................................... 23
   6.2 Key worker allocation and role ........................................................................................................... 23
   6.3 Psychological support ......................................................................................................................... 24
6.4 Nutritional support........................................................................................................... 24
6.5 Rehabilitation and other therapies ........................................................................... 25

7 Endoscopic Management of Malignant Bile Duct Obstruction........................................ 26
7.1 Introduction .................................................................................................................. 26
7.2 Initial diagnosis .......................................................................................................... 26
7.3 The approach to biliary stenting in malignant pancreato-biliary obstruction ............... 27

8 Pancreatic Cancer ........................................................................................................... 30
8.1 Introduction .................................................................................................................. 30
8.2 Referrals into the multidisciplinary team ................................................................... 30
8.3 Treatment options ...................................................................................................... 31
8.4 Chemotherapy regimens ........................................................................................... 33
8.5 Radiotherapy .............................................................................................................. 35
8.6 Follow-up .................................................................................................................... 38
8.7 Recurrences ................................................................................................................ 38

9 Hepatocellular Carcinoma ............................................................................................. 40
9.1 Introduction .................................................................................................................. 40
9.2 Surveillance .................................................................................................................. 41
9.3 Diagnosis of HCC ...................................................................................................... 41
9.4 Management by specialist multidisciplinary team ...................................................... 42
9.5 Patient management options .................................................................................... 43
9.6 Radiotherapy .............................................................................................................. 45
9.7 Systemic therapies ...................................................................................................... 48
9.8 Specialist palliative care ............................................................................................. 48

10 Gallbladder Carcinoma ................................................................................................ 51
10.1 Introduction ................................................................................................................ 51
10.2 Presentation and diagnosis ....................................................................................... 51
10.3 Management by the specialist multidisciplinary team ............................................. 52
10.4 Management of operable disease .......................................................................... 54
10.5 Management of inoperable disease ....................................................................... 55
10.6 Follow-up .................................................................................................................. 56

11 Cholangiocarcinoma .................................................................................................... 57
11.1 Introduction ................................................................................................................. 57
11.2 Presentation and diagnosis .................................................. 57
11.3 Management by the specialist multidisciplinary team .................. 58
11.4 Treatment options .................................................................. 61
11.5 Chemotherapy ......................................................................... 63
11.6 Radiotherapy ............................................................................ 64
11.7 Specialist palliative care .......................................................... 66
11.8 Follow-up .................................................................................. 66

12 Neuroendocrine Tumours .............................................................. 68
12.1 Introduction ............................................................................. 68
12.2 Investigations and diagnostics .................................................. 68
12.3 Treatment options .................................................................... 69
12.4 Carcinoid heart disease ............................................................ 70

13 Adrenocortical Tumours ................................................................. 71
13.1 Introduction ............................................................................. 71
13.2 Presentation and diagnosis ....................................................... 71
13.3 Management by the multidisciplinary team ................................. 73
13.4 Staging ..................................................................................... 74
13.5 Treatment options .................................................................... 74
13.6 Family history and clinical genetics ............................................ 75

14 Colorectal Liver Metastases ............................................................ 77
14.1 Introduction ............................................................................. 77
14.2 Presentation and diagnosis ....................................................... 77
14.3 Treatment options .................................................................... 79
14.4 Chemotherapy .......................................................................... 82
14.5 Radiotherapy ............................................................................ 83
14.6 Follow-up and recurrence ......................................................... 87

15 Survivorship Guidelines ............................................................... 89
15.1 Discuss a person’s needs .......................................................... 90
15.2 Provide a treatment summary and care plan ................................. 90
15.3 Provide a main contact ............................................................. 90
15.4 Identify post-treatment symptoms ............................................ 91
15.5 Provide support about day-to-day concerns ................................ 91
15.6 Talk about how you feel ................................................................. 91
15.7 Healthy lifestyle ........................................................................ 91
15.8 Self-managed follow-up .............................................................. 93
15.9 Encourage survivors to share their experience ............................ 93

16 Audit ............................................................................................. 94

17 Clinical Research .......................................................................... 95

Appendix 1: Referral Forms ............................................................... 96

Appendix 2: Inter-Trust Referral Forms ............................................. 102

Appendix 3: Quality of Life – Management of the Side Effects of Cancer Therapies ........................................... 114

Appendix 4: LCA Specialist Palliative Care Referral Form .................. 116

Appendix 5: LCA Key Worker Policy .................................................. 119

Appendix 6: Children’s Pathways ...................................................... 121

Appendix 7: Teenagers and Young Adults ......................................... 122

Appendix 8: NCSI Treatment Summary ............................................ 124

Appendix 9: Mitotane Treatment in Adrenocortical Carcinoma – King’s College Hospital Standard Operating Procedure ........................................................................... 126

Appendix 10: LCA Holistic Needs Assessment Tool ............................ 138

Acknowledgements ........................................................................... 139
Introduction

The hepato-pancreato-biliary (HPB) cancer category covers a wide range of gastrointestinal situated malignancies and these guidelines cover the following: pancreatic, liver, biliary, gallbladder, neuroendocrine, adrenocortical as well as colorectal liver metastases – a common subsequent diagnosis following a colorectal cancer primary. It is a grouping of some of the rarer cancers, with 931 new diagnoses within the London Cancer Alliance (LCA) in 2010, accountable for 5% of the total diagnoses of invasive cancers.

For this cohort of patients, when compared with other cancers, survival rates remain poor. Overall 5-year survival rates in the LCA range from just 5–9% for pancreatic cancer and 9–14% for liver cancer – although these compare favourably against national and international data. While HPB cancers are rare, they are the fifth most common cause of cancer death and are likely to become the second most common cause of cancer death within the next few years. This is attributed to late diagnosis which is demonstrated by the 40–50% of patients who will present as an emergency admission prior to diagnosis. In London this is especially pertinent for primary liver cancer which consistently shows a higher incidence than the rest of the country, particularly in the male population.

The LCA Hepato-pancreato-biliary Cancer Clinical Guidelines provide a practical multidisciplinary guide for the diagnosis, treatment, holistic care, quality standards and support of HPB cancer patients across the LCA and the management pathways for benign HPB disorders such as chronic pancreatitis. Currently, there are three treating centres within the LCA: King’s College Hospital NHS Foundation Trust; Imperial College Healthcare NHS Trust; and The Royal Marsden NHS Foundation Trust with Mount Vernon, which is aligned between the LCA and the East of England Strategic Clinical Network, offering medical and clinical oncology only. There are a further 11 Trusts within the LCA which provide an essential role in diagnosing and managing patients’ care locally where applicable.

These guidelines have been adapted from, and supersede, the previous guidelines produced by the former north west, south east and south west London cancer networks and take account of the National Cancer Peer Review Programme Manual for Cancer Services, Upper GI Measures Version 1.0.

The guidelines have been developed by the LCA HPB Pathway Group to ensure that care throughout the LCA conforms to national and international best practice. They draw on the expertise of a range of clinicians from across the LCA’s member organisations, and subsequently reflect the wider HPB cancer pathway. They provide evidence-based clinical information and protocols on all aspects of the HPB cancer pathway, while allowing sufficient flexibility to reflect good local practice, and should be used by clinicians to inform the treatment and care they provide.

The LCA guidelines are designed to be used by all healthcare professionals in Trusts within the LCA who are involved in the care of HPB cancer patients. They have been developed to take into account the wide range of clinical experience of the user and the different clinical settings in which they work. The guidelines are intended to assist in the initial assessment, investigation and management of patients. Adoption of the LCA guidelines will allow widespread implementation of up-to-date and evidence-based management of HPB cancer patients, and will assist in the provision of a consistently high standard of care across the LCA.
All Trusts are expected to be able to provide the standard of care detailed in these guidelines. The guidelines will be reviewed annually to ensure that they are updated with emerging evidence and changes in practice.

Mr Satvinder Mudan
Chair of LCA HPB Pathway Group
Consultant Surgeon and Surgical Oncologist
The Royal Marsden NHS Foundation Trust
Executive Summary

The LCA Hepato-pancreato-biliary Cancer Clinical Guidelines combine the best features of earlier network protocols, and have been developed in agreement with clinicians across the LCA. They combine evidence-based and best practice recommendations with the aim of ensuring that there are equitable, high-quality services across the LCA. The guidelines are multidisciplinary and cover imaging, pathology, surgery, radiotherapy, systemic therapy and survivorship.

- **Chapter 1**, on referrals for suspected malignancies, outlines the setting in which patients typically present and the symptoms which would initiate a referral from primary care.
- **Chapter 2**, on diagnostics, specifies all appropriate tests that should be undertaken by the diagnostic hospital to effectively diagnose HPB cancer. Details of sites specialising in endoscopic ultrasound have also been listed to allow easier referral to this service.
- **Chapter 3** describes the next steps in the management of patients once their diagnosis of HPB cancer has been confirmed. This includes details of the minimum dataset for referral by a specialist multidisciplinary team (MDT) and includes referrals to community specialist palliative care; the majority of patients with an HPB cancer diagnosis are not eligible for curative treatment.
- **Chapter 4** includes communication principles which should be adhered to when information is required to flow between secondary and primary care to ensure it is effective and comprehensive.
- **Chapter 5** sets out the multidisciplinary team (MDT) structure, underlining the minimum requirements for both a local diagnostic MDT and a specialist centre, in line with peer review requirements. This section contains guidelines for vascular resection of pancreas.
- **Chapter 6** covers the most important aspect of the patient’s pathway as it explores the best practice principles specifically targeted at ensuring the best possible experience for this vulnerable disease group.
- **Chapter 7** gives the case for patients who should receive a stent if they present with biliary obstruction. The content of this section is relevant to a number of the HPB tumours and is of particular importance for gastroenterologists working for a diagnostic unit MDT.
- **Chapters 8–14** cover each of the six primary tumours and one common metastatic diagnosis in detail. Each of the chapters gives more detailed diagnostic investigations required for that particular tumour type, both for patients with suspected malignancies and for those who require staging. The selection criteria for patients eligible for radical treatment and list of treatment options are also set out – as well as details of individual chemotherapy regimens and radiotherapy fractions.
- **Chapter 15**, survivorship, details the ongoing care for patients living with their condition beyond treatment and offers clinicians appropriate advice on managing the patients’ needs holistically.

Key priorities will be identified across sub-specialties with a view to auditing compliance, and this is dealt with in **Chapter 16**. And **Chapter 17** stresses that there should be a continued emphasis on national clinical trial leadership, proven to improve the standard of care for all patients.
1 Referrals

1.1 Referral for patients with suspected HPB cancer

1.1.1 Referrals from general practice

Patients can be referred by their GP as an urgent suspected cancer. Those referred urgently are seen according to the 2 week wait rule (2ww). The following should indicate a referral to be made by the GP:

- jaundice (not obviously related to drugs, alcohol or recent foreign travel)
- unexplained upper abdominal pain and weight loss with or without back pain
- oesophagogastroduodenoscopy (OGD) negative upper abdominal pain
- steatorrhoea.

Initial investigations, such as full blood count (FBC), liver function tests (LFTs), urea and electrolytes (U&E) and abdominal ultrasound, may be organised by the GP while waiting for the clinic appointment. The above investigations should not delay referral. Abnormal LFTs found in the course of GP investigations should be further investigated by local or regional gastroenterologists with an interest in pancreatic disease.

A GP upper gastrointestinal (GI) 2ww referral proforma should be completed in full, highlighting the referral criteria in particular. Former network referral proformas still exist (see Appendix 1) and should be completed and sent to LCA Trusts electronically, by fax or by post within 24 hours. The patient will be seen within two calendar weeks from that date. Each diagnostic unit has its own internal arrangements to provide rapid access clinics. In general, the patient is contacted either by phone or letter explaining why they need to be seen urgently.

1.1.2 Outpatients

Patients referred from other consultants can be seen in the rapid access clinic as per a GP urgent referral (see above) or to a joint oncology clinic if a diagnosis has already been made.

1.1.3 Inpatients

Patients with suspected HPB cancer in a local hospital should be referred to the upper GI oncology multidisciplinary team (MDT) within 24 hours of the diagnosis being suspected. Where possible, these patients should all be referred to the upper GI clinical nurse specialist.

1.1.4 Emergency admissions

Patients with possible HPB cancer may present as emergency admissions through the A&E department. Those patients need to be referred to the HPB upper GI MDT meetings and managed accordingly.
2 Initial Assessment of Patients with Suspected HPB Cancer

2.1 History and performance status

The patient’s history and performance status are assessed and recorded in patients presenting with possible HPB cancer. Specific warning signs for each of the separate HPB tumours are documented in their respective chapters.

History includes:

- age
- previous/current occupation
- smoking history
- alcohol consumption
- presenting symptoms:
  - pain
  - weight loss
  - nausea
  - vomiting
  - reduced appetite
  - fatigue
  - anaemia
  - jaundice
  - steatorrhoea
  - new onset of diabetes, type 2
- co-morbidity
- social and family history
- past medical history
- drug history
- nutritional screening completed.

<table>
<thead>
<tr>
<th>ECOG Performance Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 0: able to carry out all normal activity without restriction</td>
</tr>
<tr>
<td>PS 1: restricted in physically strenuous activity but ambulatory and able to do light work</td>
</tr>
<tr>
<td>PS 2: ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>PS 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>PS 4: completely disabled; cannot carry out any self-care; totally confined to bed or chair</td>
</tr>
</tbody>
</table>
2.2 Full examination

The full examination should include:

- weight
- height
- body mass index
- usual/normal weight
- weight loss over what time period?
- neck lymphadenopathy
- abdominal examination for organomegaly.

2.3 Nutritional assessment

Patients presenting with HPB cancer often have significant problems with nutrition. They may present with weight loss, reduced appetite and altered bowel habits, e.g. steatorrhoea. The provision of an adequate diet, even prior to diagnosis, may be a challenge. Hepato-biliary cancers are likely to have a high degree of weight loss when compared with other types of cancer diagnosis. Traditionally these patients have been referred to the dietitian via a locally developed pathway either at the local hospital where the diagnosis was confirmed or at the cancer centre. Nutritional problems may be overlooked and it is recognised nationally that dietetic support is often not suggested to at-risk patients at diagnosis when it would be appropriate to address the support required. For this reason, the clinical nurse specialist can refer patients to the dietitian at any time if dietary issues are identified during treatment or follow-up discussions. It is understood that poor nutritional status can impact on the risks of subsequent treatment options, especially surgery.

At presentation all patients should have a formal nutritional screening and those patients presenting at medium or high risk of malnutrition need an assessment by a registered dietitian. Most will need advice and nutritional supplements while some may need nutritional support with enteral nutrition (either nasoenteric, gastrostomy or jejunostomy).

Pancreatic enzyme replacement should be considered for all patients with a suspected or confirmed diagnosis of pancreatic cancer or those thought to have pancreatic insufficiency. Appropriate counselling on the use of pancreatic enzyme replacement, advice on the use of proton-pump inhibitors and vitamin and mineral supplementation and written information should be provided.

All patients should have appropriate advice and management of gastrointestinal symptoms including early satiety, poor appetite, malabsorption and nausea.

2.4 Blood tests

Please see individual tumour chapters (8–13) for details of the individual tests that should be undertaken based on the suspicion of the different cancers.
2.5 Imaging

There are multiple imaging tests that can be undertaken to diagnose each of the separate tumours and these have been included within the individual chapters. Below is an outline of each of the imaging modalities and specific protocols where necessary.

2.5.1 Ultrasound

Ultrasound remains the first-line investigation for suspected biliary obstruction.

2.5.2 CT imaging

Urgent computed tomography (CT) of chest, abdomen and pelvis should be used if the biliary obstruction is not clearly due to stones if there is any suspicion of malignancy. Use the pancreatic protocol (biphasic CT abdomen with IV contrast + oral waterload). Plan for review at the local multidisciplinary team (MDT) but make a parallel referral to the specialist MDT if appropriate to speed decision making.

2.5.3 Chest X-ray

A chest CT is the ideal for assessing the presence of pulmonary metastases but a chest X-ray is considered satisfactory.

2.5.4 MRI

Magnetic resonance imaging (MRI) is used for problem solving where there is a diagnostic question about a liver lesion not answered by CT scan. MRI can also be used instead of CT in those patients where radiation is to be limited. MRI may also be useful where conspicuity of lesions is limited on CT, such as in liver steatosis, and where staging prior to surgery would be more complete. The high qualitative discrimination of MRI in the pancreas and the liver makes this a useful tool both for diagnosis and surgical planning. Standard sequences should be utilised including diffusion weighted imaging and images post liver specific contrast agents (e.g. Primovist).

2.5.5 PET CT

Positron emission tomography (PET) with [18F]-2-deoxy-D-glucose.

- Pancreatic carcinoma cells have high glucose uptake, like most malignancies.
- Biliary epithelial cell metabolism is assessed in vivo via the glucose analogue [18F]-2-deoxy-D-glucose.
- Glucose and [18F]-2-deoxy-D-glucose are both phosphorylated but the latter is not further metabolised and accumulates in pancreatic carcinoma cells giving rise to ‘hot’ spots.
- PET scan is a useful method of staging and in particular for extent of disease beyond the primary site. The assessment of metabolic response following neoadjuvant chemotherapy can be a useful guide to long term outcome and surgical selection.
2.5.6 Cholangiography

- This is essential for early diagnosis of pancreatic carcinoma and assessing resectability.
- Magnetic resonance cholangiopancreatography (MRCP) is non-invasive and determines the extent of duct involvement by tumour without the risk of endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC).
- ERCP should be available and is favoured above PTC. Facilities for PTC should always be available to deal with cases where attempts at ERCP have failed.
- Bile cytology can be obtained by either ERCP or at PTC.
- The diagnostic yield is increased to 40–70% by a combination of brush cytology and histological biopsy where possible.
- Negative cytology from brushings should not exclude malignancy.
- Both ERCP and PTC allow stent insertion for relief of jaundice.
- Angiography is rarely required as modern high quality CT has a high predictive value for vascular involvement by tumour.

2.5.7 Endoscopic ultrasound

Endoscopic ultrasound (EUS) allows a good view of the distal extrahepatic biliary tree, head of pancreas, gallbladder, regional lymph nodes and local vasculature. EUS is a useful tool for the imaging and staging of pancreatobiliary cancers. Interventional EUS for needle biopsy of a mass lesion aids diagnosis and nodal biopsy can be useful in the staging exercise. Within the LCA, EUS services are available at the following sites:

- Chelsea and Westminster Hospital NHS Foundation Trust
- St George’s Healthcare NHS Trust
- The Royal Marsden NHS Foundation Trust
- Guy’s and St Thomas’ NHS Foundation Trust
- Imperial College Healthcare NHS Trust (St Mary’s Hospital and Hammersmith Hospital)
- King’s College Hospital NHS Foundation Trust.

2.6 Pathology

2.6.1 Request for pathology

The minimum data on cytology/histopathology request forms should be as follows:

- name
- DOB
- hospital number
- sample site (including specific biopsy site)
- sample type
requesting clinician
destination for report (ward, outpatients’ department, etc.)
clinical history
clinical diagnosis.

Desirable/additional information on request forms includes:

- previous histology
- referred cases for second opinion/MDT review. The material received for histology review should include: 1) an accompanying letter stating the reason for referral; 2) the original histopathology report in order to insure full identification of the material received; unstained sections and/or the paraffin blocks in case additional stainings need to be carried out as part of the review.

**2.6.2 Pathology reporting requirements**

The Royal College of Pathologists’ datasets should be used as the reference for standardised histopathology reporting. The two datasets relevant to HPB malignancies are:

1. *Dataset for histopathology reporting of liver resection specimens (including gall bladder) and liver biopsies for primary and metastatic carcinoma (2nd edition)*,
2. *Dataset for the histopathological reporting of carcinomas of the pancreas, ampulla of Vater and common bile duct*,

**2.7 Pre-assessment for potential treatment options**

Both radical surgery and curative chemo-radiation strategies have significant morbidity associated with treatment. Careful co-morbidity assessment is essential in planning treatment strategies. This includes access to cardio-pulmonary exercise testing. All patients should have access to a dietitian for a nutritional assessment and management if required. Patients undergoing surgery should be considered for pre-operative nutritional support, in particular if there has been a weight loss approaching or greater than 10%.

Pre-assessment for surgery must include the following:

- general assessment, including activity levels, by the anaesthetist/intensivist with an option for cardio-pulmonary exercise testing
- routine full blood count (FBC), urea and electrolytes (U&E), and liver function test (LFT) clotting studies
- group and save for all patients
- chest X-ray and electrocardiogram (ECG)
- consent by operating centre surgical team either in pre-clerking or on admission
The administration of deep vein thrombosis (DVT) prophylaxis should be withheld until an anaesthetist has reviewed the patient. The timing of the administration will influence the epidural. It is understood that patients with HPB malignancy are at a higher risk of thromboembolic events.

Patients on anti-coagulation should be given the following instructions:

- low-dose warfarin to be stopped at least 48 hours pre-operatively
- full anti-coagulation should be managed with advice from haematology; warfarin is usually stopped pre-operatively and low molecular weight heparin started at therapeutic dose. This should be omitted on the evening prior to operation.
3 Referral for Patients with a Diagnosis of HPB Cancer

3.1 Referrals to the specialist multidisciplinary team

If investigations suggest or confirm HPB cancer, the patient should be referred to the specialist multidisciplinary team (MDT) at one of the three HPB cancer centres. It is expected that these patients will be discussed in the unit MDT prior to referral. Long delays in referral should be avoided in order to maximise clinical outcomes for patients and to comply with cancer waiting times.

The following patients should be referred to the MDT meeting for discussion on further management:

- any confirmed HPB tumour suitable for treatment with curative intent
- locally advanced or borderline pancreatic tumour deemed irresectable due to the size of tumour and/or local vascular involvement
- chronic pancreatitis where the diagnosis of malignancy cannot be excluded
- gastrointestinal neuroendocrine tumours (both resectable and inoperable)
- patients with colorectal liver metastases at the time those metastases are diagnosed, whether resectable/ablatable at that time or not, so that appropriate clinical trial inclusion and consideration for potential treatment options if disease can be downstaged.

The following patients should be presented in the centre MDT meeting by completing a referral proforma for the purpose of recording information in the database:

- patients with potentially resectable cancer, but with severe co-morbidity rendering the patient inoperable
- clearly inoperable tumours due to extent of disease, such as distant uncontrollable metastases (peritoneal, liver, lung)
- recurrent disease after curative surgery whether considered amenable to further therapeutic intervention or not.

3.2 Information to include on referrals

- Basic patient demographics (including contact telephone number)
- Main symptoms:
  - weight loss
  - dysphagia
  - nausea
  - vomiting
  - reduced appetite
  - fatigue
  - anaemia
  - odynophagia
  - reflux/dyspepsia
  - pain (abdominal and referred)
  - early satiety
• Performance status
• Imaging
• Histology
• Extent of disease
• Body mass index
• Co-morbid disease including past history of malignancy
• Endoscopic ultrasound (where applicable)
• Laparoscopic findings (where applicable)
• Current medications
• Information that was given to the patient.

3.3 **Standard information to include in referrals to community specialist palliative care teams**

• Patient demographics and contact details of family and carers
• Diagnosis and staging information – copies of scans, blood results etc., attached where possible
• Other relevant medical conditions
• Reason for current referral and patient consent to referral
• Urgency of referral
• Service requested
• Patient and carer insight into disease
• Cognitive function/barriers to communication
• Information on family if known
• Referrer’s details including names of other consultants involved in patient’s care
• For patients requiring a hospital inpatient specialist palliative care review, please contact your local hospital specialist palliative care team as per usual hospital policy.

3.4 **Management of children, teenagers and young adults with diagnosed or suspected HPB cancer**

3.4.1 **Children**

Children below the age of 16 years with a diagnosis of cancer or suspected cancer must be referred to the paediatric oncology team at the principal treatment centre (PTC) and must not be managed exclusively by adult site-specific teams.

• The joint PTC for children aged 1 year to 16 years for South Thames is The Royal Marsden (Sutton)/St George’s Hospital.
• The PTC for North Thames (including North West London) is Great Ormond Street Hospital/University College London Hospitals.

• All patients <1 year from both North and South Thames should be referred to Great Ormond Street Hospital.

The paediatric oncology team must liaise with the appropriate site-specific MDT for advice about management and to agree surgical interventions, but overall responsibility for managing the patient remains with the paediatric oncology team.

Please see Appendix 6 for contact information for the children’s PTCs.

3.4.2 Teenagers and young adults

Teenagers aged 16–18 should be managed at a PTC for teenage and young adult (TYA) cancers. Young adults aged 19–24 are given the choice of being managed at a PTC or TYA designated hospital.

• The PTC for TYA for South Thames is The Royal Marsden (Sutton).

• The PTC for North Thames (including North West London) is University College London Hospitals.

All patients within this age range, regardless of place of care, should be referred to the TYA MDT at the relevant PTC.

Please see Appendix 7 for information about how to make a referral and contact information for the PTC and TYA designated centres in the LCA.
4 Inter-professional Communication between Secondary and Primary Care

4.1 General principles

- Communication should be timely and concise.
- Use fax-back route/electronic means for urgent communications (meaning those that need to be with the GP within 24 hours).
- All communications that a patient has been copied into should be written in a format that patients can understand.
- Communications must include:
  - what the patient has been told
  - who told the patient
  - who was there with the patient (e.g. named partner/friend)
  - what written/other information was offered
  - next steps – when the patient is being seen or their treatment started
  - actions for the GP – for information only or suggesting specific GP actions (including information for Macmillan or district nursing colleagues)
  - named care worker in secondary care
  - intent of treatment (curative/palliative)
  - any additional information required from the GP (e.g. co-morbidities status)
  - summary of medication and alterations to medication
  - contact details for further information/discussion.
- Key points of change along the patient journey:
  - referral
  - investigations
  - diagnosis
  - treatment planning at multidisciplinary team (MDT) meetings
  - start of treatment(s)
  - end of treatment(s)
  - completion of active management of cancer (Treatment Record Summary (TRS))
  - follow-up(s).

4.2 At diagnosis

The GP is informed, by telephone or fax, within 24 hours of the patient being told the diagnosis, along with the general management plan (further investigations and treatment). The letter must include:

- what the patient has been told (e.g. prognosis)
- who told the patient
- who was there with the patient (e.g. named partner/friend)
- what written/other information was offered
next steps – when the patient is being seen, further investigations or treatment started
actions for the GP – for information only or suggesting specific GP action	named care worker in secondary care
intent of treatment (curative/palliative)
any additional information required from the GP.

If the patient is told their diagnosis in the joint clinic, information confirming the diagnosis should be sent to the GP within 24 hours.

All inpatients who are given a new diagnosis of HPB cancer will be given a discharge letter to be taken to their GP. In addition, for some patients, the GP surgery will be contacted by phone or fax.

4.3 Multidisciplinary team discussions and decisions

The decisions made at the MDT meetings are conveyed to the patient verbally by their key worker or member of medical team, as appropriate. The patient is also offered a written copy of this information, and a detailed letter summarising the MDT’s management plan is dictated for the GP. This letter will be sent to the GP by post or electronically within 24 hours. It will be made clear when the patient is being seen, and by whom, to discuss MDT decisions. Feedback by the GP will be invited as appropriate.

4.4 Letters from clinics

These will be organised to an agreed format with diagnosis and staging information, intent of treatment and medication highlighted as above. The format can be an agreed template with core fields and areas to add free text.

4.5 Treatment Record Summary

A letter detailing the planned meeting between the clinician (clinical nurse specialist or doctor) and patient at the end of active treatment, to discuss diagnosis, response to treatment and next steps, will be sent to the GP. The TRS should cover psycho-social aspects, signposting to services, anticipated side effects of treatment and signs of disease progression, with management plans clearly highlighted. A holistic needs assessment (HNA) (see Appendix 10) will be undertaken with an approved instrument and summarised. The letter will be sent within 48 hours of the interview, with the patient’s permission.

The LCA Survivorship Group has recommended the adoption of the National Cancer Survivorship Initiative Treatment Summary. A copy of this document can be found at Appendix 8.
5 Multidisciplinary Team Structure

5.1 Local diagnostic unit

Diagnostic tests for suspected HPB cancer should take place under the care of the local diagnostic multidisciplinary team (MDT). There should be a single named lead clinician for the local MDT who should then be a core team member. The core team specific for HPB cancers should include:

- one or more clinicians (physicians or surgeons) specialising in gastroenterology
- an endoscopist of any discipline, who could be one of the other team members
- a histopathologist
- a radiologist
- a clinical oncologist
- a medical oncologist (where the responsibility for chemotherapy is not undertaken by the clinical oncologist core member)
- an upper GI clinical nurse specialist (CNS), with HPB as clearly defined part of job remit
- the MDT coordinator/secretary
- a core member of the specialist palliative care team
- a registered dietitian.

An NHS-employed member of the core or extended team should be nominated as having specific responsibility for users’ issues and for information for patients and carers. Additionally, a member of the MDT should be nominated as the person responsible for ensuring that recruitment into clinical trials and other well designed studies is integrated into the MDT.

All new cancer patients will be reviewed at an MDT meeting for discussion of the initial treatment plan. The team should hold its meetings at least weekly, record core members’ attendance and have a written procedure governing how to deal with referrals which need a treatment planning decision before the next scheduled meeting.

The MDT should agree cover arrangements for each core member. Core members or their arranged cover should attend at least two-thirds of the number of meetings.

The MDT should have agreed a policy whereby all patients diagnosed with HPB cancer are discussed with a member of the relevant specialist team prior to referral to the specialist team or prior to proposed local care. The date at which the discussion took place should be recorded in the case notes.

The MDT should have agreed a policy whereby, after a patient has been given a diagnosis of HPB cancer, the patient’s GP is informed of the diagnosis by the end of the following working day.

The MDT should have completed an audit against the policy of the timeliness of notification to GPs of the diagnosis of cancer.

Diagnosed patients are then referred for discussion at the next specialist MDT meeting or are referred once the necessary investigations have been completed. The specialist MDT meeting will discuss treatment plans and follow-up arrangements to ensure that patients are managed according to LCA Hepato-pancreatico-biliary Cancer Clinical Guidelines.
5.2 Specialist pancreatic centre multidisciplinary team

There should be a single named lead clinician for the specialist pancreatic MDT who should then be a core team member. The lead clinician of the MDT should have agreed the responsibilities of the position with the lead clinician of the host trust.

**Note: The role of the lead clinician of the MDT should not of itself imply chronological seniority, superior experience or superior clinical ability.**

The MDT should provide the names of core team members for named roles in the team.

The core team specific to the specialist MDT should include:

- three or more hepato-pancreato-biliary surgeons
- a physician gastroenterologist
- a clinical oncologist
- a medical oncologist (where the responsibility for chemotherapy is not undertaken by the clinical oncologist core member)
- a histopathologist
- a specialist HPB CNS
- two radiologists – at least one should be an interventional radiologist
- a registered dietitian
- an endoscopist of any discipline who could be one of the other team members
- a core member of the specialist palliative care team
- the MDT coordinator/secretary.

An NHS-employed member of the core or extended team should be nominated as having specific responsibility for users’ issues; a core team member should be trained in endoscopic ultrasonography; and a core member of the MDT should be nominated as the person responsible for ensuring that recruitment into clinical trials and other well designed studies is integrated into the function of the MDT.

The team should hold its meetings at least weekly, record core members’ attendance and have a written procedure governing how to deal with referrals which need a treatment planning decision before the next scheduled meeting.

The MDT should agree cover arrangements for each core member. Core members or their arranged cover should attend at least two-thirds of the number of meetings.

Once a treatment decision has been finalised with the consultant, patients should be seen in an outpatient setting to discuss treatment options. All patients should have access to a CNS who should act as their key worker. All patients should be provided with a written information sheet relevant to their care.

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1 Peer review recommends four. It is recommended that these do not function as OG surgeons. In order to achieve peer review measure 08-2F-314 (a 24-hour surgical on-call rota), at least three specialist consultant surgeons per team would be needed.
6 Ensuring Patient-centred Care for All Pathways

6.1 Enhancing the patient experience

Support during and after treatment is essential for patients and those affected by cancer. Support, in terms of physical, psychological and spiritual needs, should be met throughout the patient journey. Once a diagnosis has been made, patients should be offered a holistic needs assessment (HNA) in line with the survivorship guidelines (see Appendix 10).

Information obtained from the cancer patient experience survey and published literature highlights a number of aspects of care that are important to the patient experience and quality of life (Glaser et al., 2013; Corner et al., 2013). These include the following:

- timely diagnosis
- coordinated care
- support from staff
- good communication
- good healthcare professionals.

For the experience of living with and beyond cancer, support should be given for the following:

- information on side effects and consequences of treatment
- aftercare services
- management of ongoing co-morbidities and physical problems
- ongoing social and financial problems
- ongoing emotional and psychological problems
- coping and self-management strategies.

6.2 Key worker allocation and role

Each patient should have a designated key worker allocated to them. The key worker has five main responsibilities relating directly to the patient’s pathway and care:

- orchestrating assessments to ensure that patients’ needs are elicited
- ensuring that care plans have been agreed with patients
- ensuring that the multidisciplinary team findings from assessments and care plans are communicated to others involved in patient care
- ensuring that patients know who to contact when help or advice is needed, whether that is the key worker or other appropriate personnel
- managing transition of care.

These are in accordance with the LCA key worker policy (see Appendix 5).
6.3 Psychological support

Patients with HPB cancer may require psychological support at any point in the patient journey. These issues, along with any physical problems, can be identified by the HNA undertaken at diagnosis or at any point during or after treatment.

Patients should be cared for by healthcare professionals with the appropriate communication skills, e.g. those who have undertaken the following:

- the Sage and Thyme course
- Advanced Communication Skills
- Level 2 Psychological Support Skills.

Some 25% of patients may require referral to specialist psychological support services. Patients will be offered specific evidence-based treatments according to the problems identified.

Support will be in line with the LCA Mental Health and Psychological Support Pathway Group.

More information relating to survivorship and aftercare services is available in Chapter 15.

6.4 Nutritional support

6.4.1 Nutrition on treatment

- Patients should have access to a specialist dietitian as recommended by their clinician.
- Patients with malabsorption or continued weight loss once treatment commences may benefit from enteral feeding.

6.4.2 Endocrinology referrals

- Patients should be referred for a specialist endocrinology opinion if diagnosed with new onset diabetes or if having difficulty managing glycaemic control in established diabetes. Dietary advice should be available for all patients with respect to managing diabetes.
- Patients who will develop post-surgical diabetes must be reviewed pre-operatively by an endocrinologist.

6.4.3 Nutrition during palliative treatment

- If enteral feeding is likely to be required for a longer period, an endoscopic gastrostomy tube (PEG) should be considered. This can be placed either endoscopically or radiologically. A surgically placed jejunostomy may be considered for some patients.
- There should be close liaison between the centre, local unit and community dietitian for all patients receiving palliative care.

6.4.4 Nutrition during follow-up

- The lead medical team (surgery, oncology, specialist palliative care, or primary care) has responsibility for managing nutritional reviews and actions alongside a dietitian. The nutritional status and plan must be part of any handover between lead medical teams.
• Patients should receive regular post treatment dietetic review and ongoing access to an appropriately trained and supported dietitian.

• A specialist HPB cancer dietitian should be present in all surgical and oncology follow-up clinics. Where this is not currently possible, appropriate referral mechanisms to ensure timely patient-led assessment and intervention is essential.

• Patients should be reassessed at intervals for pancreatic enzyme replacement therapy (PERT), with adequate patient education provided.

• It may be convenient or desirable for those patients on PERT to take an over-the-counter brand of multivitamins with minerals. Malabsorption of vitamins or minerals may occur insidiously even on such replacement. Monitoring should be planned so that there are no surprises.

6.5 Rehabilitation and other therapies

The LCA will provide therapy support for patients as outlined in the National Cancer Action Team rehabilitation pathways for HPB patients.

Supportive care needs, such as pain and fatigue management and physical functioning issues, should be referred to appropriate healthcare professionals. This may include the physiotherapy, occupational therapy and pain management teams.

References


7 Endoscopic Management of Malignant Bile Duct Obstruction

7.1 Introduction

Bile duct obstruction is a common occurrence with pancreato-biliary malignancy. Primary malignancies include pancreatic head cancer, gallbladder carcinoma as well as cholangiocarcinoma and ampullary carcinoma. At the time of presentation, 85% of these primary malignancies have local advanced or metastatic disease which precludes curative resection. The exception to this is ampullary carcinoma which frequently presents at an early phase with bile duct obstruction; curative resection is possible in many cases. Between 80% and 85% of pancreato-biliary malignancies will result in bile duct obstruction at some time during their course. In the large majority of such cases endoscopic biliary drainage is the mainstay of palliative therapy. The relief of obstruction is associated with a number of benefits including management/prevention of sepsis, relief of pruritus as well as an improvement in appetite and general wellbeing. The resolution of jaundice is also a prerequisite to enable provision of most chemotherapeutic regimens.

Metastases from other malignancies such as breast, lung and colon may also cause biliary obstruction. Such metastases may obstruct the biliary tree both by intrahepatic and extrahepatic infiltration/compression. Relief of obstruction has the same potential benefits as are observed with primary malignancies.

7.2 Initial diagnosis

The large majority of cases of pancreato-biliary malignancy presenting with bile duct obstruction and jaundice do so in the absence of significant pain and fever. In such circumstances there is no indication for immediate bile duct drainage. In the majority of cases a transabdominal ultrasound scan is the initial imaging tool. This may provide valuable information as to the presence and site of bile duct obstruction. An ultrasound scan alone is not an adequate investigation to guide endoscopic biliary intervention in suspected malignant obstruction. A multiphase multi-detector contrast-enhanced computed tomography (CT) scan is the imaging procedure most readily available to provide the level of information to direct subsequent management. In most cases this should be sufficient to define the level of obstruction, location and size of any mass lesion as well as evidence of local and distant tumour spread.

Additional information may occasionally be provided by a supplementary magnetic resonance imaging (MRI) scan. Outside the regional centre, the images should be reviewed by a radiologist with an interest in gastrointestinal and pancreato-biliary radiology. At this stage, an initial conclusion should be reached as to the level of obstruction, likely causative lesion and the presence or absence of factors that would preclude an attempt at curative resection. This is then combined with the appropriate clinical data that might also influence operability.

The initial management strategy will be defined as part of the presentation at the MDT meeting, usually in a non-specialised hospital setting. While it is imperative that all cases are forwarded to the specialised centre for further MDT review, there are many cases in which a decision about palliative biliary drainage can be made before referral. This would include cases in which age or performance status precludes surgery. There will also be a high percentage of patients in whom obvious locally advanced or metastatic disease precludes an attempt at resection with a curative intent.

All potentially resectable cases should be referred to the specialist centre. Where there is obstruction of the common bile duct, preferably endoscopic or otherwise percutaneous biliary, stenting might be attempted (see below for guidance as to the type of stent employed).
All cases in which there is evidence of hilar involvement/obstruction should be referred to the specialist centre MDT to define the optimum management strategy.

Obtaining diagnostic cytology or histology should be attempted at the time of endoscopic biliary intervention. The low yield associated with this approach will require many cases to be referred for endoscopic ultrasound and fine needle aspiration (FNA) to gain diagnostic tissue.

**Figure 7.1: The approach to biliary stenting in malignant pancreato-biliary obstruction**

7.3 The approach to biliary stenting in malignant pancreato-biliary obstruction

7.3.1 Prior to curative intent resection

There are data (including meta-analyses) that endoscopic biliary drainage prior to a curative intent resection of a pancreatic head malignancy is associated with an excess risk of adverse events, in particular post-operative infection. There was no observed difference in survival but prior biliary drainage was associated with an increased hospital stay. These data were observed in trials utilising plastic biliary stents. There was also the prerequisite that surgery was carried out promptly. In clinical practice an interval of 3–4 weeks from diagnosis to operation is commonplace. In such circumstances many surgeons prefer endoscopic biliary drainage to reduce the risks of progressive debilitation and cholangitis. This is often prompted when there is an elevation of bilirubin above the 200iu level (an arbitrary figure but indicative of a progressive risk of adverse outcomes with increasing cholestasis).

Recent non-randomised study data have suggested that fully covered self-expanding stents may overcome the adverse events associated with the use of plastic stents in this setting, such as stent migration and early
occlusion. More conclusive evidence is required before metallic stents can be recommended for routine use prior to resection.

7.3.2 Palliation of malignant common bile duct obstruction

If an attempt at curative resection is precluded, then palliative stenting of a common bile duct obstruction is indicated at an early phase. This was initially achieved by placement of a plastic stent across the obstruction. These stents provided good palliation but were prone to occlude, resulting in a recurrence of obstruction and often associated with cholangitis. The median patency time for plastic stents was approximately 120 days.

Episodes of recurrent obstruction required urgent readmission and endoscopic intervention. Chemotherapy was often deferred/delayed by such episodes. The introduction of self-expanding metal stents has provided a means of alleviating the problem of early stent occlusion. Metal stents have been shown to remain patent for a considerably longer time period (median of 240 days) as compared with plastic stents. Despite the much higher cost of metal stents, the comparative trials confirm a cost advantage. If the diagnosis of malignancy is histological/cytological, confirmed palliative stenting can be carried out with an uncovered metal stent. These stents very rapidly become incorporated into the bile duct and cannot be removed.

In the setting of palliation for pancreato-biliary malignancy, the majority of metal stents will remain patent for the period of patient survival. If the diagnosis of malignancy has not been confirmed before the attempt at palliative stenting, a fully covered metal stent should be employed. This type of stent, which is a relatively recent introduction, can be removed from the bile duct (for up to 10–12 months after insertion).

The ability to remove the stent is important for the few instances in which the suspicion of malignancy is not confirmed. Evidence from a number of randomised trials suggests that covered stents have the same or prolonged patency when compared with uncovered metal stents. Migration of covered stents is a recognised problem but appears to be infrequent and has not had an impact on overall efficacy. As such, covered metal stents may replace uncovered stents in the setting of malignant common bile duct obstruction. It is important if a covered stent is placed that this should be deployed distal to the hilum. If a covered stent is deployed across the hilum, this will occlude the bile drainage from the opposite side of the liver.

7.3.3 Palliation of malignant biliary obstruction at the hepatic confluence

Strictures of the biliary tree at the hepatic confluence (liver hilum; proximal strictures) account for approximately 20% of malignant bile duct obstruction. The majority of cases are cholangiocarcinoma, gallbladder cancer and metastatic disease. For the purposes of biliary stenting, all strictures proximal to the level of the common hepatic duct are included. The extent of involvement of the biliary tree is defined in the Bismuth-Corlette classification. The feasibility of palliative stenting is dependent upon the complexity of involvement. Strictures restricted to the common hepatic duct may not present major technical difficulties as the confluence is not involved and the right- and left-sided ducts are in continuity. Involvement of the confluence is associated with loss of communication between the right and left systems. More extensive tumour involvement may dissociate the ductal system proximal to second order level.

Stenting in the presence of proximal obstruction is more challenging than in the case of common bile duct strictures. Successful drainage is less frequently achieved and there are increased risks of adverse outcomes, in particular cholangitis arising from undrained segments. A minimum of 30% of the liver parenchyma needs to be drained to achieve resolution of cholestasis. The optimum management of
proximal strictures should be decided in the context of the specialist centre MDT. Drainage should be avoided before MDT review unless deemed clinically appropriate. The management decisions are dependent upon high-quality imaging and the establishment of a high index of suspicion of malignancy. It is understood that up to 10% of cases referred for management of a suspected hilar malignancy are found to have a benign aetiology. Many of these cases have been found to have an autoimmune origin. A tissue diagnosis of malignancy should be confirmed prior to definitive stenting. A mass lesion can be biopsied percutaneously. Endoscopic cholangioscopy is increasingly available in specialised units and is used to visualise and biopsy hilar lesions. If cholangioscopy is used to confirm the diagnosis, a stent will usually need to be placed to prevent cholangitis. Only plastic stents should be used in this setting. A metal stent should not be placed across the confluence until the diagnosis of malignancy is confirmed. This policy prevents the placement of an irremovable metal stent across a stricture which subsequently proves to be benign. Covered metal stents have no role whatsoever proximal to the common hepatic duct.

In cases in which a curative resection is considered, pre-operative biliary drainage is not of proven value (with respect to pancreatic cancer). If the diagnosis of malignancy has been confirmed, the optimum management is resection without prior drainage. In many cases a period of delay before planned resection leads to increasing cholestasis and the risks associated with this. In these circumstances many hepatobiliary surgeons prefer an internal/external percutaneously placed drainage catheter. This provides some anatomical guidance during the resection. If endoscopic stenting is considered in this setting, then plastic stents should be used to facilitate easy removal at the time of surgery.

Palliative stenting of proximal strictures needs careful planning. Specialist MDT review of cross-sectional imaging is the forum for this decision making. Once the diagnosis of malignancy has been made and definitive palliative stenting planned, the use of uncovered metal stents has replaced the previous use of plastic stents (based upon the increased median timescale for stent patency). There are roles for both endoscopic and percutaneous approaches. In the case of a common hepatic duct stricture, a single stent will provide adequate drainage. If the confluence is involved and the right and left systems dissociated (and may also include dissociation of the right anterior and posterior systems), then the decision to be made is whether a single stent or two stents is indicated. There is little trial data to provide guidance. The decision as to the use of one or two stents is based upon the need to establish drainage of an absolute minimum of 30% of the liver. In many cases (75–80%) this can be satisfactorily achieved by placing one stent. The decision as to the site of stent placement should be made prior to intervention. To prevent cholangitis following intervention, it is important to avoid instilling contrast into segments which are not subsequently drained. Conversely, if a segment is inadvertently contrast filled, then an attempt should be made to establish drainage of this segment.

The placement of two or more stents to establish drainage for confluence obstruction is very technically demanding. The usual process is to place a guidewire into the sectorial ducts that are intended to be drained. Uncovered metal stents are then released. To allow for future intervention in the setting of stent occlusion, it is important that the distal ends of both stents are brought out into the duodenum. This may require stents to be placed in series to cover the whole length of the stricture and common bile duct. Close cooperation between endoscopist and radiologist is essential in planning the intervention. Subtle anatomical issues frequently provide guidance as to whether the percutaneous or endoscopic route is optimum. There are occasions in which the use of a combination of both techniques is indicated; usually in the setting of the right side being endoscopically drained and the left being approached percutaneously.
8 Pancreatic Cancer

8.1 Introduction
About 6,000 new cases of pancreatic cancer are diagnosed annually in the UK; the majority are pancreatic ductal adenocarcinoma. Adenocarcinoma of the pancreas is a highly lethal condition with a case-specific mortality of about 1. There are no early signs such as occult rectal bleeding to allow a screening programme to exist and no diagnostic blood test. The remote, inaccessible location of the pancreas makes it unavailable for clinical examination.

8.2 Referrals into the multidisciplinary team
The local or specialist multidisciplinary team (MDT) may receive referrals of patients admitted as inpatients from other teams within the centre or directly from GPs suspicious of a pancreatic problem on the basis of symptoms, or suggestive on GP-directed imaging such as ultrasound or computed tomography (CT).

8.2.1 Assessment
Symptoms can be variable or even completely absent and in most patients (80%) the presentation is with sudden onset of jaundice.

As well as the generic HPB assessment criteria, careful inquiry should be made for:
- persistent niggling upper abdominal discomfort
- weight loss
- increasing back pain, usually in the upper back
- thrombotic events.

History should also include:
- family history of pancreatic cancer
- heavy exposure to cigarette smoking
- new onset diabetes mellitus
- previous malignancy such as stomach cancer, right-sided colon cancer and uterine cancer chronic pancreatitis.

8.2.2 Diagnosis
Multiple detector computed tomography (MDCT) scan should be carried out with a specific ‘pancreas protocol’ that times the injection of contrast to maximise opacification of the mesenteric vessels and allows the surgeon to determine if resection is possible. Ideally, this should be obtained prior to stenting of the bile duct if at all possible.

CT scan should be sufficient to allow diagnosis and determination of resectability. If there is doubt such as might occur in a very small lesion or where there appears to be inflammatory pancreatic reaction, magnetic resonance imaging (MRI) might be required.
8.3 Treatment options

8.3.1 Surgery

Potentially resectable cases can be considered for operation without a requirement for tissue diagnosis and on the understanding that occasionally the post-resection diagnosis will turn out to be benign.

Inoperable cases, e.g. patients with very poor performance status and those with metastatic disease to liver, lungs or peritoneal disease, can be considered for diagnostic biopsy in the local centre. Such cases should be recorded at the specialist MDT meeting but do not require discussion. Depending on availability, biopsy might be endoscopic ultrasound-guided or guided percutaneous. Cytology obtained at endoscopic retrograde cholangiopancreatography (ERCP) from bile or from brushings is acceptable for diagnosis if classified as C5.

Blood tests should include at least:

- full blood count (FBC)
- liver function test (LFT)
- electrolytes
- cancer antigen (CA) 19-9
- carcinoembryonic antigen (CEA)
- C-reactive protein (CRP)
- coagulation studies.

Potentially resectable or borderline patients should be referred to the specialist centre MDT for formal discussion; referral should be accompanied by history and physical examination data including performance status and imaging with pancreas protocol CT scan and blood test results.

### Table 8.1: Resectability classification*

<table>
<thead>
<tr>
<th>Resectability status</th>
<th>Criteria</th>
<th>Median survival (months)</th>
<th>Approximate % of cases</th>
</tr>
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</table>
| **Resectable**       | • No metastatic disease. No lymph node disease beyond the normal resection field.  
                       • No venous involvement, clear planes around the coeliac, hepatic and superior mesenteric arteries. | 24                       | 5%                     |
| **Borderline**       | • No metastatic disease. No lymph node disease beyond the normal resection field.  
                       • Venous involvement, with narrowing of lumen but without involvement of nearby arteries and with good tumour-free vein either side of involved section to allow safe resection and primary reconstruction or by interposition venous graft.  
                       • Involvement of gastro-duodenal artery up to the origin on hepatic artery, no hepatic artery involvement.  
                       • SMA approximation but not encasement and approximation less than 180°. | 20 (resected) 11 (unresected) | 85%                    |
Resectability status | Criteria | Median survival (months) | Approximate % of cases
--- | --- | --- | ---
Locally advanced | • No metastatic disease. Lymph node disease beyond the normal resection field. Venous involvement beyond that which can be safely reconstructed.  
• Any coeliac axis involvement, splenic artery encasement, hepatic artery encasement. Superior mesenteric artery encasement exceeds 180°. Aortic or inferior vena cava encasement. | 4–9 | 10%
Metastatic | | 3–6 | |

* On 21 January 2010, the American Hepato-Pancreato-Biliary Association (AHPBA) convened a consensus conference on the multidisciplinary treatment of hepatocellular cancer (HCC). The conference was co-sponsored by the Society of Surgical Oncology (SSO), the Society for Surgery of the Alimentary Tract (SSAT) and the University of Texas MD Anderson Cancer Center.

8.3.2 Suitability for neo-adjuvant therapy

Whether initially resectable patients can benefit from neo-adjuvant therapy is not established. Current chemotherapeutic agents in pancreatic cancer have an acceptable response rate of 20–30% which has led to increasing interest in pre-operative therapy both in the neo-adjuvant setting and in the conversion setting (Conroy et al., 2011; Von Hoff et al., 2013). Such patients must be discussed at the MDT meeting and where possible be included in appropriate clinical trials.

Published data demonstrate acceptable response rates but have not demonstrated an effect on survival rate. Such studies that have addressed the issue, both prospective and retrospective, suggest that upfront surgery and neo-adjuvant therapy are associated with similar overall survival rates.

8.3.3 Relief of jaundice before surgery

Please see stenting guidance section in Chapter 7 for details of stenting appropriateness.

8.3.4 Role of vascular resections

Approximation or encasement of the portomesenteric venous system or the coeliac and superior mesenteric arterial system by tumour is not uncommon in pancreatic cancer.

The safety of resection and reconstruction of these visceral vessels has improved greatly. The oncological benefit remains to be established in the case of arterial resections although venous resection is now considered the standard of care where this might be the limiting step to otherwise potentially curative resection. The need for vascular resection is nearly always an inter-operative determination. It follows that the skills set of the surgeon must include the ability to undertake vascular resection (Ravikumar et al., 2014).

8.3.5 Surgical resection

A standard Whipple’s procedure or a pylorus preserving pancreateo-duodenectomy is performed with excision of regional lymph nodes. A tumour that is incompletely excised has a very poor prognosis; the operation must maximise the potential for negative margins. Lymph node dissection should include local and regional lymph nodes.
The pylorus preserving procedure is considered equally effective as the standard Whipple’s procedure except for cancers located in the dorsal part of the head of the pancreas or involving the duodenum.

Transection of the neck of the pancreas at least 1cm from the tumour is over the mid-part of the portal/superior mesenteric vein.

Reconstruction is performed to a single loop or a Roux-en-Y loop of jejunum. In a difficult pancreatic anastomosis a separate Roux loop or a pancreato-gastrostomy or externalisation of the pancreatic duct could be considered for pancreatic anastomosis.

Involvement of the superior mesenteric vein or portal vein is not considered a contraindication for resection provided the prospect of a negative margin can be obtained by venous resection. Reconstruction of the portal/superior mesenteric vein should preferably be performed using a variety of methods (Kaneoka et al., 2009; Smoot et al., 2007; Choudry et al., 2008).

Tumours of the body and tail of the pancreas will be treated with a distal pancreatectomy and splenectomy following appropriate immunisation.

### 8.4 Chemotherapy regimens

#### 8.4.1 Neo-adjuvant

See 8.3.2 for appropriateness (Conroy et al., 2011; Von Hoff et al., 2013). The following chemotherapy regimens may be used depending on performance status:

- FOLFIRINOX
- gemcitabine + capecitabine or gemcitabine + cisplatin (Cunningham et al., 2009)
- gemcitabine alone.

#### 8.4.2 Adjuvant

- Gemcitabine or 5FU/leucovorin (Mayo schedule).

#### 8.4.3 First-line palliative chemotherapy

For patients with locally advanced or metastatic disease at presentation, the following regimens would be considered based upon performance status and family history:

- FOLFIRINOX
- gemcitabine + nab-paclitaxel (Cancer Drugs Fund)
- gemcitabine/cisplatin or gemcitabine + capecitabine
- gemcitabine alone.

#### 8.4.4 Second-line palliative chemotherapy

Patients who received prior gemcitabine would be considered for FOLFIRINOX or capecitabine-oxaliplatin.

Patients who received first-line FOLFIRINOX would be considered for gemcitabine.
Regimen details

**FOLFIRINOX**

- Oxaliplatin 85mg/m²
- Irinotecan 180mg/m²
- Leucovorin 400mg/m²
- 5-fluorouracil 400mg/m² bolus
- 5-fluorouracil 2,400mg/m² IV infusion over 46 hours

Repeated every 2 weeks (Conroy et al., 2011)

Some centres may use a modification of this regimen in which the bolus 5FU is omitted (Mahaseth et al., 2013).

**Gemcitabine + capecitabine (GemCap)**

- Gemcitabine 1,000mg/m² days 1, 8 and 15
- Capecitabine 1,660mg/m² in divided daily doses, days 1–21

Repeated every 28 days

**Gemcitabine + cisplatin (or carboplatin)**

- Gemcitabine 1,000mg/m², days 1 and 8
- Cisplatin 60mg/m², day 1 of carboplatin AUC=4

Repeated every 21 days

**Gemcitabine monotherapy**

1. Adjuvant schedule
   
   Gemcitabine 1,000mg/m², days 1, 8 and 15 every 28 days for 6 cycles
   
   (Oettle et al., 2007; Neoptolemos et al., 2010)

2. Palliative schedule

   Cycle 1: gemcitabine 1,000mg/m², days 1, 8, 15, 22, 29, 36 and 43 followed by a 7-day break
   
   Cycle 2 onwards: gemcitabine 1,000mg/m², days 1, 8 and 15 every 28 days
   
   (Burris et al., 1997)

**Adjuvant 5-fluorouracil + leucovorin**

- 5-fluorouracil 425mg/m², days 1–5
- Leucovorin 20mg/m², days 1–5

Repeated every 28 days for 6 cycles (Neoptolemos et al., 2010)

**Gemcitabine + nab-paclitaxel**

- Nab-paclitaxel 125mg/m², days 1, 8 and 15
- Gemcitabine 1,000mg/m², days 1, 8 and 15

Repeated every 28 days
FOLFOX6
Oxaliplatin  85mg/m²
Leucovorin  400mg/m²
5-fluorouracil  400mg/m² bolus
5-fluorouracil  2,400mg/m² IV infusion over 46 hours
Repeated every 2 weeks

Capecitabine-oxaliplatin (Cap-Ox)
Oxaliplatin  130mg/m², day 1
Capecitabine  1,000mg/m², BD, days 1–14
Repeated every 21 days

8.5 Radiotherapy
The role of radiotherapy in pancreatic cancer remains controversial, largely due to the paucity of well-designed studies, and conflicting data. Techniques have advanced rapidly in the last few years, and radiotherapy now has an increasing role as part of the multimodality therapy of pancreatic cancer. The SCALOP phase 2 trial (Mukherjee et al., 2013) showed capecitabine-based chemo-radiotherapy to be superior to gemcitabine-based chemo-radiation in locally advanced pancreatic cancer. Gemcitabine-based studies have used a multitude of weekly doses from 300–1,000mg/m², with significant haematological toxicity seen in many studies.

ESPAC-5F (borderline resectable disease) and SCALOP2 (LAPC) will both commence recruitment in 2015, and entry of patients to these studies is encouraged.

8.5.1 Locally advanced/borderline resectable disease
If there is no evidence of disease progression following 12 weeks of neo-adjuvant chemotherapy (usually FOLFIRINOX or Gemcitabine – nab Paclitaxel), chemo-radiation should be considered prior to surgery if the tumour is not clearly resectable on post-chemotherapy imaging. Positron emission tomography (PET)/CT is very useful here to exclude the presence of metastatic disease or regional nodes outside a conventional treatment field. All non progressing patients should at the very least be referred to a clinical oncologist to discuss the pros and cons, and benefits/risk profile of chemoradiotherapy.

8.5.2 3D conformal radiation therapy (CRT) or intensity modulated radiation therapy (IMRT) planning

CT planning scan
A 4D scan may be useful, if available, for tumours likely to encounter significant respiratory motion. Palliative treatments may be planned using virtual simulation.

IV contrast e.g. (100ml omnipaque 30 seconds before scan) should be given, and significantly aids delineation of nodal structures within the upper abdomen; 3mm slices should be taken from mid-thorax to below L3 (to allow for dose-volume histogram DVH).
**Position and immobilisation:** The patient lies supine with their arms above their head. Palliative treatments are delivered with the patient supine with their arms by their sides.

### 8.5.3 Delineation of target volumes and organs at risk

**Radical**

**Gross tumour volume (GTV):** Extent of primary tumour and involved nodes.

**Clinical target volume (CTV-T):** The GTV should be encompassed with a 1.5–2.0cm margin (for non 4D planning). The superior margin must encompass the coeliac vessels. The medial wall of duodenal loop with a margin is included for pancreatic head tumours as these tumours may involve the duodenum. The anterior border is 1.5–2.0cm beyond gross disease in order to include the porta hepatis, superior mesenteric and coeliac vessels. The posterior border is approximately 1.5cm beyond the anterior border of the vertebral body to encompass para-aortic nodes.

**Planned target volume (PTV-T) = CTV + 1.5cm (1.0cm for 4D patients):** Occasionally, a ‘boost’ to primary tumour encasing mesenteric vasculature is warranted, and can be delineated as a separate GTV with 1.5cm expansion to PTV (1.0cm for 4D patients). This can alternatively be done as a ‘simultaneous integrated boost’ technique with both fields being treated simultaneously at differing doses per fraction.

#### Organs at risk tolerances

**Table 8.1: Normal tissue dose constraints**

<table>
<thead>
<tr>
<th>Organs at risk</th>
<th>Parameter</th>
<th>Dose (Gy) in 2Gy/#</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver</strong></td>
<td>V30Gy</td>
<td>&lt;50%</td>
</tr>
<tr>
<td></td>
<td>Mean liver dose</td>
<td>&lt;30Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;25Gy (IMRT patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>700cc &lt;25Gy</td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
<td>V18Gy (primary kidney)</td>
<td>&lt;50%</td>
</tr>
<tr>
<td></td>
<td>V18 (secondary kidney)</td>
<td>&lt;10%</td>
</tr>
<tr>
<td></td>
<td>or V20 (L+R kidney)</td>
<td>&lt;20%</td>
</tr>
<tr>
<td><strong>Small bowel</strong></td>
<td>V45Gy</td>
<td>&lt;150 cm$^3$</td>
</tr>
<tr>
<td></td>
<td>V30</td>
<td>&lt;50%</td>
</tr>
<tr>
<td></td>
<td>V35</td>
<td>&lt;35%</td>
</tr>
<tr>
<td></td>
<td>V45</td>
<td>&lt;10%</td>
</tr>
<tr>
<td></td>
<td>V50</td>
<td>&lt;5cc</td>
</tr>
<tr>
<td><strong>Spinal cord</strong></td>
<td>Dmax</td>
<td>46Gy</td>
</tr>
<tr>
<td></td>
<td>0.1cc</td>
<td>44Gy</td>
</tr>
<tr>
<td><strong>Spinal cord PRV</strong></td>
<td>Dmax</td>
<td>50Gy</td>
</tr>
<tr>
<td></td>
<td>0.1cc</td>
<td>48Gy</td>
</tr>
<tr>
<td><strong>Duodenum</strong></td>
<td>V50</td>
<td>&lt;5cc* (IMRT constraint only)</td>
</tr>
<tr>
<td>Organs at risk</td>
<td>Parameter</td>
<td>Dose (Gy) in 2Gy/#</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Stomach</td>
<td>V50</td>
<td>5cc* (IMRT constraint only)</td>
</tr>
</tbody>
</table>

* In cases where the PTV expansion is into the organ at risk, these constraints may have to be loosened after discussion with consultant, or PTV will ultimately have to be compromised in the overlap zone. This will be especially the case where dose ≥54Gy.

### 8.5.4 Dose prescription

Patients having concurrent chemotherapy will be prescribed 45–54Gy to the 100% in 25–30 daily fractions, over 5–6/52 as a single phase treatment (Herskovic et al., 1992). This will normally be delivered with 6MV photons.

IMRT plans should achieve the following parameters for PTV coverage:

- no more than 5% of any PTV will receive <95% or >105% of the prescription dose
- no more than 2% of any PTV will receive <93% of the prescription dose
- no more than 2% of the primary PTV will receive >107% of the prescription with concomitant capecitabine 825mg/m² BD (some centres omit the weekend dosages).

#### Post-operative (adjuvant) chemo-radiotherapy

The main indication is a positive (R1/R2) resection margin. In practice this is usually the posterior margin, with disease extending to the resection margin despite skeletonisation of mesenteric vasculature. It is extremely useful if surgeons site clips at areas of concern, which can be correlated with histopathological reports for radiotherapy planning.

**3D CRT or IMRT planning**

- 45–50.4Gy in 25–28 daily fractions with concomitant capecitabine 825mg/m² BD (some centres omit the weekend dosages).

**Local recurrence following resection (if no previous radiotherapy)**

If there has been no disease progression following 12 weeks of chemotherapy, chemo-radiation should be considered. PET/CT is very useful to exclude the presence of metastatic disease or regional nodes outside a conventional treatment field.

**3D CRT or IMRT planning**

- 4D CT if available
- radiotherapy guidelines – add as per ESPAC-5F protocol
- 50.4–54Gy in 28–30 daily fractions with concomitant capecitabine 825mg/m² BD (some centres omit the weekend dosages).

**Palliation of symptoms**

- Indications: pain secondary to local infiltration, bleeding secondary to duodenal/gastric infiltration
- Virtual simulation
- Doses: 8–10Gy single fraction, 20Gy in 5#, 30Gy in 10#, 27Gy in 6#.
8.6 Follow-up

Post-resection patients should be referred to the oncology clinic for consideration of adjuvant therapies and continued follow-up.

Baseline tests in the oncology clinic should include: CT scan (chest, abdomen and pelvis), blood tests including tumour marker CA 19-9. Clinic review should be every 3 months with repeat CT scan every 6 months.

8.7 Recurrences

When recurrence occurs about 25% have local failure alone, 25% distant failure alone and 50% have local and distant failure together. Careful assessment is required to confirm the pattern of recurrence. High-quality CT is essential and a PET scan may help to distinguish between post-surgical inflammatory changes and recurrence as well as provide response to treatment data.

In rare cases there may be a role for re-resection in local-only recurrence that appears after a long disease-free interval and such a case should warrant MDT meeting discussion.

References


9 Hepatocellular Carcinoma

9.1 Introduction

Hepatocellular carcinoma (HCC) represents the most common primary liver cancer, accounting for approximately 90% of all primary liver malignancies. Today the crude incidence rate in the UK is 6.8 new cases per 100,000. The occurrence of HCC is more in common in males (3.8 new cases/100,000) than females (1.7 new cases/100,000), giving a ratio of 2.23. The incidence of HCC increases with age, reaching a peak at the age of 70 for both sexes.

HCC is strongly related to well-described risk factors, most prominent being chronic viral hepatitis (B and C), alcohol intake and aflatoxin exposure. Liver cirrhosis represents another important risk factor independently of its cause (viral, alcoholic or metabolic). The overall lifelong risk of cirrhotic patients developing HCC amounts to 30%. Nowadays obesity, diabetes mellitus and fatty liver disease have been associated with HCC, although the underlying causative mechanism remains unclear.

Figure 9.1: Patient pathway for suspected HCC
9.2  Surveillance

As the majority of HCCs will develop in patients with established risk factors, surveillance of these patients is of paramount importance for early diagnosis, when all treatment options could be applied. The existing consensus for surveillance includes the following four categories of patients:

- cirrhotic patients Child-Pugh class A and B
- cirrhotic patients Child-Pugh class C who are listed for transplantation
- non-cirrhotic hepatitis B virus (HBV) carriers with active hepatitis or family history of HCC
- non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3.

While the establishment of surveillance protocols needs further discussion, it should be encouraged across the LCA referring centres. A number of patients with detected nodules on imaging on initial assessment, where a diagnosis of HCC was not established, may require surveillance; there should be established pathways for this to happen.

Currently, the surveillance for HCC in the above-mentioned groups consists of liver ultrasound and α-fetoprotein (AFP). The proposed interval for follow-up is every 6 months, with that being revised to 4-monthly intervals when nodules are less than 1cm in size.

9.3  Diagnosis of HCC

The diagnosis of HCC is non-invasive and can be achieved on radiological criteria alone with sufficient fidelity (European Association for the Study of the Liver (EASL), 2012). Lesional biopsy for diagnosis of HCC is limited to small lesions with atypical characteristics on imaging and high clinical suspicion. AFP remains an adjunct to diagnosis and for assessment of treatment.

9.3.1  Radiological diagnosis

The diagnosis of HCC is based on the characteristic vascular pattern of enhancement during contrast-enhanced triple phase computed tomography (CT) scan or contrast-enhanced dynamic magnetic resonance imaging (MRI). HCC is typically enhancing during the arterial phase with washout on portal or late venous phase. One modality usually suffices for diagnosis for lesions more than 1cm (in high volume centres), while two modalities are required for smaller lesions or lower volume centres (EASL, 2012).

The non-invasive radiological criteria for diagnosis of HCC should be applied only to cirrhotic patients.

The following list provides guidance for establishing diagnosis (based on EASL-EORTC consensus).

1. Lesion <1cm:
   - If stable in diameter, to be followed up at 4-monthly intervals with ultrasound.
   - If increasing in size or changing features, needs further investigation.

2. Lesion 1–2cm:
   - Triple phase CT scan and dynamic contrast-enhanced MRI.
   - If there are radiological hallmarks consistent with HCC this can be considered diagnostic.
   - If radiological hallmarks are not consistent with HCC, proceed to biopsy.
   - Biopsy inconclusive: to be followed up at 4-monthly intervals with ultrasound.
3. Lesion >2cm:
- Triple phase CT scan or dynamic contrast-enhanced MRI.
- If there are radiological hallmarks consistent with HCC this can be considered diagnostic.
- If radiological hallmarks are not consistent with HCC, proceed to biopsy.
- Biopsy inconclusive: to be followed up at 4-monthly intervals with ultrasound.

Pathological diagnosis of HCC is recommended for all nodules occurring in non-cirrhotic livers and nodules within cirrhotic livers which have atypical appearance in imaging. For lesions with a diameter of 1–2cm, the pathological diagnosis may be difficult to achieve. Thus a positive tumour biopsy rules in the diagnosis of HCC but a negative biopsy does not rule out malignancy. Review of the biopsies should be done by experienced liver pathologists and should follow the existing guidelines from the International Consensus Group for Hepatocellular Neoplasia.

9.4 Management by specialist multidisciplinary team

9.4.1 Referral into the specialist multidisciplinary team
Patients should be referred to a specialist centre:
- if a nodule has been detected on a patient under a surveillance programme
- if unexplained decompensation occurs on an otherwise stable cirrhotic
- if a liver lesion is found incidentally.

Figure 9.2: HCC patient treatment pathway
9.4.2 Minimum dataset for referral (see Appendix 2)

Patient referral should include liver function markers to enable accurate staging of liver disease, and, where available, the imaging that depicted the suspicious lesion, and an assessment of overall performance status.

9.4.3 Initial assessment of a patient presenting with HCC

Every patient diagnosed with HCC should undergo full assessment to address six main issues:

- cause (if any) of underlying liver disease
- liver function and degree of portal hypertension
- tumour stage
- scope for improvement in liver function
- co-morbidities
- performance status.

9.4.4 Specialist multidisciplinary team assessment

When the diagnosis of HCC has been established, a chest CT +/- bone scintigraphy (for symptomatic patients) should be used to complete the staging process. The specialist multidisciplinary team (MDT) meeting will assess the stage of HCC, the severity of the underlying liver disease and the performance status of the patient prior to formulating a management plan.

Staging of HCC

MDT meetings should undertake anatomical staging and functional assessment. Anatomical staging of HCC patients is undertaken using the Tumour Node Metastasis (TNM) staging system which is currently mandatory for all solid cancers in the UK.

The most widely accepted and implemented system for functional assessment is the Barcelona Clinic Liver Cancer (BCLC) classification system for HCC as it incorporates tumour-related prognostic variables, liver function, performance status and treatment-dependent variables. It is expected that this will be followed across all LCA sites.

9.5 Patient management options

MDT meeting decisions regarding management should be based on the BCLC staging system, and should be tailored to the individual patient.

9.5.1 Resection

Resection should be the first-line treatment for small solitary tumours with well-preserved liver function. For patients with multifocal tumours within the Milan criteria, (see section 9.5.2) but not suitable for transplantation, the MDT should develop protocols for enrolment for surgery or loco-regional treatments.

Resection in non-cirrhotic HCCs in patients with limited pre-existing liver disease should follow standard pre-operative assessment as with any other liver tumours. Resection of HCC mandates careful pre-operative evaluation of liver reserve and portal hypertension. Existing guidance for evaluation of portal hypertension (hepatic vein gradient pressure <10mmHg, platelet count more than 100, evidence of variceal
circulation, splenomegaly etc., normal bilirubin) should be obtained in every patient scheduled to undergo liver resection. Liver resection for HCC in cirrhotics should follow the principles of modern liver surgery and should be carefully executed with a balance between tumour clearance and parenchyma preservation.

It is expected that, with careful patient selection, pre-operative evaluation and appropriate peri-operative management, the mortality rate will not exceed 3%.

### 9.5.2 Liver transplantation

Patients identified following initial MDT assessment found to have HCC within current UK transplant criteria, should be referred to the liver transplant centre for further evaluation and management.

Patients are selected for liver transplantation according to the Milan criteria:

- a single lesion no greater than 5 cm
- or 3 lesions with none greater than 3 cm
- without evidence of gross vascular invasion
- without regional lymph node or distant extrahepatic metastasis
- with good performance status.

Current transplant criteria include:

- single HCC less than 5cm, not suitable for resection
- multifocal HCC up to 5 nodules with maximum diameter of 3cm
- solitary HCC 5–7cm in diameter with favourable tumour biology (no progression after 6 months of follow-up).

### 9.5.3 Loco-regional treatments

**Trans-arterial chemo embolisation (TACE)**

TACE using either conventional inert embolic material (e.g. coils) or drug eluting beads is the most widely used treatment modality for intermediate stage (BCLC-B) HCC and/or as an interim treatment while the patient is waiting for liver transplantation. The use of drug eluting beads appears to have less systemic effect as compared with conventional TACE. TACE is not indicated when there is evidence of extrahepatic disease or where the risk of hepatic decompensation is increased as in patients with advanced stage of cirrhosis. Similarly, the risk–benefit ratio is not favourable in patients with gross macro-vascular tumour invasion.

**Ablative therapies**

Currently, the most widely local ablative treatment used is radio frequency ablation (RFA), while in the past ablation with ethanol injection has been used. Other ablative techniques reported include cryo-ablation and microwave ablation. Ablative techniques should be considered as the treatment of choice for patients not suitable for surgery, in tumours less than 5cm in diameter. Ablative techniques can be used in isolation or in conjunction with TACE as consolidation treatments in solitary tumours not suitable for resection, although robust evidence is lacking.
9.6 Radiotherapy

Historically, the role of radiotherapy for liver tumours has been limited by the risk of radiation-induced liver disease (RILD). RILD is characterised by anicteric hepatomegaly, ascites and elevated alkaline phosphatase occurring within 3 months of liver irradiation. Recently, advances in radiotherapy technique (including radiotherapy planning, motion management strategies and image guidance) have made it possible for radiation to be delivered conformally to partial liver volumes.

Awareness of important dose-volume effects, in conjunction with advances in radiotherapy technique, has allowed the development of stereotactic body radiation therapy (SBRT) techniques or hypofractionated IMRT for hepatic malignancy.

Radiation therapy has an important role for HCC unsuitable for, or resistant to, other loco-regional liver-directed therapies. Radiotherapy does not feature in many consensus guidelines or documents, largely due to a relative lack of Level 1 randomised trial data.

Radiotherapy may have an increasing role to play in the management of HCC in the near future. Many phase II studies have reported excellent local control rates and equivalence with other forms of local ablative therapy. The advantages of radiation are mainly that larger lesions can be treated effectively (up to 8cm), and lesions in close proximity to major vasculature, biliary tree or diaphragm are treatable.

Radiotherapy has also been successfully used to bridge patients through to liver transplant, although currently published studies have small numbers and further data are required. Ideally this should be accomplished within the context of a clinical trial if one is available.

Radiotherapy can now be considered an alternative local ablative therapy for patients with HCC, and a detailed discussion of the benefits and risks of each individual local ablative therapy should be considered by the specialist MDT for each patient’s case.

Radiotherapy can be delivered as hypofractionated intensity modulated radiation therapy (IMRT) or stereotactically (stereotactic ablative radiation therapy (SABR)). Please note, at the time of writing there is no national tariff for SBRT, and an individual funding request will need to be made for this route.

9.6.1 Patient selection criteria for radiotherapy

Inclusion criteria

- For HCC, enhancement typically in the arterial phase on two imaging modalities and AFP increased on a background of liver disease
- Biopsy-confirmed immunohistochemical (IHC)
- Inoperable tumour or tumour inappropriate for other treatment modalities, or as a bridge to transplant for HCC
- Karnofsky Performance Status ≥60
- Life expectancy >3 months
- Child-Pugh class A, or B7/8
- >700cc of uninvolved liver
- No chemotherapy within 2 weeks prior to, and 4 weeks after, SABR
• No, or limited and potentially treatable, extrahepatic disease
• Patient must have recovered from any previous therapy (such as surgery, chemotherapy or radiotherapy to other areas) with a minimum of 2 weeks’ break (for HCC, anthracycline-based chemotherapy should be completed 4 weeks before SBRT)
• Up to 3 metastases, with no limitation on actual size of a given tumour provided functional residual volume, and organs at risk (OAR) dose constraints can be met
• Adequate organ function, defined as: haemoglobin 9.0g/dL, absolute neutrophil count 1.5bil/L, platelets 80bil/L, bilirubin <3 times upper limit of normal, INR <1.3 or correctable with vitamin K and unless the patient is taking warfarin/coumarin, AST or ALT <5 times upper limit of normal. Creatinine less than 200umol/L (if creatinine is above the normal range, consideration should be given to dynamic renal scintigraphy (renography) if there is anticipated to be any appreciable renal dose from the delivery of the treatment).

Exclusion criteria
• Active hepatitis or clinically significant liver failure (encephalopathy, portal hypertension, varices)
• Clinically apparent ascites
• Prior radiotherapy to the right upper abdomen (unless 700cc normal unirradiated liver <17Gy)
• If patient is for fiducial placement: gold allergy, coagulopathy preventing safe fiducial placement
• Any previous radiotherapy where the mean dose to the liver was 15Gy (conventional fractionation), or where beams would be likely to overlap with those used to deliver SBRT, or where previous doses to other critical normal structures would make re-irradiation unsafe
• Any other severe co-morbidity such as unstable angina, congestive cardiac failure or transmural MI requiring hospitalisation in the preceding 6 months, or acute bacterial/fungal infection requiring intravenous antibiotics
• Central nervous system metastases.

9.6.2 Local ablation of hepatocellular carcinoma

IMRT planning
• 4D CT preferable if available
• Fiducial marker insertion 7 days prior to radiotherapy planning scan is preferred – fiducial-guided image-guided radiotherapy (IGRT) is the preferred option; those using CyberKnife will have Synchrony’s active respiratory tracking
• Gross tumour volume (GTV)–planned target volume (PTV) margin will depend on the delivery vehicle (CyberKnife vs gantry linac) and the IGRT method.

Suggested fractionation schemes
• 18–30Gy in a single fraction (SABR)
• 45–60Gy in 3# over 3–10 days (SABR)
• 50–60Gy in 5# over 5–12 days (SABR)
• 60Gy in 8# over 10 days (IMRT or SABR)
• 50–60Gy in 10# over 12 days (IMRT)
• Palliation of liver pain – 8Gy single fraction, 20Gy in 5#, 30Gy in 15#

**Acute toxicity**

• Overall, rates of Grade 1–2 toxicity are reported to range from 0–27% and Grade 3–4 toxicities are observed in around 5%. The rate of morbidity for liver radiation is reported to be independent of dose-fractionation schedule, and the toxicity rates are consistently low despite the heterogeneity of dose-fractionation schedules and delivery systems. The likely explanation is the limited dose delivered to uninvolved liver and the parallel functioning of liver parenchyma. The most commonly reported toxicities are fatigue, right upper quadrant pain, low-grade pyrexia, transaminase rise (normally settles by 3 months post-treatment), nausea and loss of appetite.

• A syndrome of minor pain, fever and chills is observed in some patients: Grade 1 (requiring no treatment) in 14%, and Grade 2 (requiring treatment with analgesics/steroids) in 13%, usually occurring within 1–3 weeks of treatment. Rates of gastric ulceration and oesophagitis are low (G2 7%, G3 in 3%) and most centres advise the use of prophylactic proton-pump inhibitors. The rates of RILD are notably very low in all published series. Child-Pugh class B and hepatitis B carriage are associated with greater risk of RILD.

• Rates of transaminase derangement are also low. For example, Grade 1–2 elevation of liver function tests were observed in 28% of patients treated with 30–55Gy (median 48Gy) by Ibarra et al. (2012), Katz et al. (2007; 2012) and Milano et al. (2012), and transient elevation of liver enzymes described as mild-moderate is noted in 31–36% of patients receiving 25–60Gy in 3 fractions.

• Several studies have reported the use of liver SBRT in patients who have previously undergone surgical resection and/or RFA, and reported low levels of toxicity, suggesting that SBRT is safe to use in this context.

**Table 9.1: SBRT liver: suggested constraints**

<table>
<thead>
<tr>
<th>Organs at risk</th>
<th>Single fraction constraints</th>
<th>Three-fraction constraints</th>
<th>Five-fraction constraints</th>
<th>10-fraction constraints</th>
<th>Dose limiting toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver</strong></td>
<td>700cc &lt;9Gy</td>
<td>700cc &lt;17Gy V15 &lt;50% V21 &lt;30%</td>
<td>700cc &lt;21Gy</td>
<td>700cc &lt; 25Gy</td>
<td>RILD (Radiation induced liver disease)</td>
</tr>
<tr>
<td><strong>Spinal cord</strong></td>
<td>V10 &lt;0.35cc V7 &lt;1.2cc 14Gy point dose</td>
<td>V18 &lt;0.35cc V12 &lt;1.2cc 22Gy point dose</td>
<td>V23 &lt;0.35cc V14.5 &lt;1.2cc 30Gy point dose</td>
<td>V30 &lt;0.35cc 35Gy point dose</td>
<td>Myelopathy</td>
</tr>
<tr>
<td><strong>Oesophagus</strong></td>
<td>V12 &lt;5cc 15Gy point dose</td>
<td>V18 &lt;5cc 25Gy point dose</td>
<td>V20 &lt;5cc 35Gy point dose</td>
<td>V30 &lt;5cc 40Gy point dose</td>
<td>Stenosis/fistula/perforation</td>
</tr>
<tr>
<td><strong>Heart/ pericardium</strong></td>
<td>V16 &lt;15cc 22Gy point dose</td>
<td>V24 &lt;15cc 30Gy point dose</td>
<td>V32 &lt;15cc 38Gy point dose</td>
<td>V32 &lt;15cc 40Gy point dose</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Organs at risk</td>
<td>Single fraction constraints</td>
<td>Three-fraction constraints</td>
<td>Five-fraction constraints</td>
<td>10-fraction constraints</td>
<td>Dose limiting toxicity</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------------</td>
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<td>--------------------------</td>
<td>------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Rib</td>
<td>V22 &lt;1cc 30Gy point dose</td>
<td>V29 &lt;1cc 37Gy point dose</td>
<td>V35 &lt;1cc 43Gy point dose</td>
<td>V35 &lt;1cc 45Gy point dose</td>
<td>Chronic pain or fracture</td>
</tr>
<tr>
<td>Skin</td>
<td>V23 &lt;10cc 26Gy point dose</td>
<td>V30 &lt;10cc 33Gy point dose</td>
<td>V37 &lt;10cc 39.5Gy point dose</td>
<td>V37 &lt;10cc 45Gy point dose</td>
<td>Chronic ulceration</td>
</tr>
<tr>
<td>Stomach</td>
<td>V11 &lt;10cc 12Gy point dose</td>
<td>V16.5 &lt;10cc 22Gy point dose</td>
<td>V18 &lt;10cc 32Gy point dose</td>
<td>V30 &lt;10cc 40 Gy point dose</td>
<td>Chronic ulcer/ fistula/perforation</td>
</tr>
<tr>
<td>Duodenum</td>
<td>V11 &lt;5cc V9 &lt;10cc 12Gy point dose</td>
<td>V16.5 &lt;5cc V11.5 &lt;10cc 22Gy point dose</td>
<td>V18 &lt;5cc V12.5 &lt;10cc 32Gy point dose</td>
<td>40Gy point dose</td>
<td>Chronic ulcer/ fistula/perforation</td>
</tr>
<tr>
<td>Jejunum/ileum</td>
<td>V12 &lt;5cc 15Gy point dose</td>
<td>V18 &lt;5cc 25Gy point dose</td>
<td>V19.5 &lt;5cc 35Gy point dose</td>
<td>40Gy point dose</td>
<td>Enteritis/obstruction/ perforation</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>V14 &lt;20cc 18Gy point dose</td>
<td>V24 &lt;20cc 28Gy point dose</td>
<td>V25 &lt;20cc 38Gy point dose</td>
<td>40Gy point dose</td>
<td>Colitis/fistula/perforation</td>
</tr>
<tr>
<td>Renal hilum/ vascular trunk</td>
<td>10.6Gy to 67% 18.6Gy to 67%</td>
<td>23Gy to 67% 25Gy to 67%</td>
<td>Malignant hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>200cc &lt;8.5Gy 200cc &lt;16Gy</td>
<td>200cc &lt;17.5Gy 200cc &lt;18Gy</td>
<td>Renal dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung (R &amp; L)</td>
<td>1,500cc &lt;7Gy 1,500cc &lt;11.5Gy</td>
<td>1,500cc &lt;12.5Gy</td>
<td>V5 &lt; 50% V20 &lt; 25%</td>
<td>Pneumonitis</td>
<td></td>
</tr>
</tbody>
</table>

Note: Point dose <0.035cc.

### 9.7 Systemic therapies

**Sorafenib** is the most widely used systemic therapy. It should be considered in patients with advanced disease and/or extrahepatic disease and those who progress through loco-regional treatment (TACE or ablation). Careful assessment of liver reserve should precede its application.

**Other systemic therapies:** systemic chemotherapy with single or combination of existing agents is not recommended outside clinical trials, while newer systemic therapies await careful evaluation and should be considered only within trials.

### 9.8 Specialist palliative care

#### 9.8.1 Introduction

For patients with advanced tumours not suitable for the treatments outlined above and/or prohibitive performance status, a robust palliative care package to address any physical, psychological, social, emotional or spiritual symptoms arising from both the tumour and the underlying liver disease should be implemented.
Key stages for consideration of specialist palliative care needs

There are key points in a patient’s illness, when their palliative care needs should be specifically considered. These include:

- pre-diagnosis if advanced disease is suspected
- diagnosis
- at commencement of definitive treatment of the disease
- on completion of the primary treatment plan
- on disease recurrence or relapse
- at the point of recognition of incurability
- end of life care
- other times requested by a patient.

Depending on the severity or complexity of symptoms, this may prompt referral to the relevant multiprofessional specialist palliative care (SPC) services.

Within the LCA, SPC teams offer a consultative service for all patients, based on physical, psychological, social, emotional or spiritual symptoms or needs, irrespective of diagnosis.

Services are available within Trusts, hospices and community settings.

9.8.2 Referral

Guidance from the LCA Palliative Care Group regarding referral to SPC services suggests the following:

1. The patient has active, progressive advanced disease, a limited prognosis and the focus of care is on quality of life, for example:
   - potentially fatal conditions where treatment has changed from curative to palliative intent (e.g. cancer, multiple co-morbidities where curative treatment is no longer possible)
   - complex symptom control issues during treatment
   - treatment available to prolong life but prognosis is uncertain (e.g. advanced chronic obstructive pulmonary disease, advanced heart failure)
   - palliative treatment from the outset with no cure available (e.g. motor neurone disease, multiple systems atrophy, advanced dementia).

2. The patient has unresolved complex needs that cannot be met by the team responsible for the patient’s care. These needs may be physical, psychological, social and/or spiritual. Examples may include complicated symptoms, difficult family situations, or ethical issues regarding treatment decisions.

If in any doubt, please contact the SPC team available in all LCA Trusts.

Referral can be made by an appropriate healthcare professional, with the consent of the patient, where the patient has capacity for this consent (see Appendix 4).
All patients should have contact with a specialist nurse (usually their key worker) from referral into secondary care. SPC input should be available, when required, both at the MDT meetings and at the initial consultation.

Patients who may benefit from SPC services should be identified, the referral discussed with the patient and carers and then referral made as soon as possible.

The SPC team within each Trust is available for advice about symptom management.

It is also important to consider whether, if it has not been done already, referral should be made to the relevant community SPC service for ongoing support of the patient at home, following diagnosis in the outpatient department or hospital discharge. Again, the hospital SPC team can advise.

9.8.3 Management

LCA SPC teams have adopted the Palliative Care Adult Network Guidelines available at: http://book.pallcare.info/.

References


10 Gallbladder Carcinoma

10.1 Introduction

Gallbladder carcinoma (GBC) is the most common malignant lesion of the biliary tract, accounting for 46% of all primary biliary tract malignancies, and is the fifth most common digestive tract malignant neoplasm. It is a disease associated with increased mortality, with reported 5-year survival between 0 and 10% in most studies. The estimated incidence of GBC in the USA is 2.5 per 100,000, which gradually increases with age, with most cases being diagnosed in the seventh decade of life. There is a female preponderance with GBC, as women are affected 2 to 6 times more often than men. Also there is geographical and ethnic variation in the occurrence of GBC, with highest incidences to be reported among Native Americans, South American populations, in Poland and the north of India.

The most common mode of diagnosis for GBC is during laparotomy or laparoscopy for gallstone disease. Among the risk factors associated with GBC, more prominent are gallstone disease and chronic inflammation, gallbladder polyps, chemical/environmental carcinogens, ulcerative colitis and primary sclerosing cholangitis. Since the signs and symptoms of GBC are vague and can easily be attributed to gallstones, and given the number of laparoscopic cholecystectomies performed within the metropolitan area of London daily, it is easy to see the magnitude of the problem. Early GBC treated with aggressive surgery in conjunction with adjuvant chemotherapy and/or radiotherapy may offer improved survival.

10.2 Presentation and diagnosis

The presentation of a patient with GBC is usually one of the following:

- GBC incidentally diagnosed on pathological examination of the specimen after cholecystectomy
- GBC found at the time of cholecystectomy for presumed benign disease
- suspected GBC from a pre-operative examination.

This order of cases corresponds to the frequency of presentation, i.e. the most common presentation of a patient with GBC is an incidental finding during cholecystectomy. Some 75% of patients with GBC who are referred pre-operatively with the suspicion of malignancy are beyond the limits of resection. The most common symptoms on presentation are abdominal pain or biliary colic, which can be easily attributed to gallstone disease. Patients with more advanced disease may also present with jaundice, malaise and weight loss.

The most common investigation for suspected gallstones is ultrasound scan. Gallbladder cancer can be masked by gallstones. There should be a high index of suspicion during ultrasound scan for patients who present with atypical symptoms of gallstone disease.

Where there is sufficient radiological or clinical suspicion of gallbladder cancer, cross-sectional imaging in the form of a computed tomography (CT) or magnetic resonance (MR) scans should be undertaken. CT can diagnose GBC as well as detect local invasion of the liver, lymph node involvement and the presence of hepatic or peritoneal metastases. Where gallbladder cancer is diagnosed pre-operatively, the majority of patients are beyond resectability for cure.
10.3 Management by the specialist multidisciplinary team

10.3.1 Triggers for referral

Patients who should be referred to an HPB multidisciplinary team (MDT) meeting include:

- patients with suspicious findings on imaging
- all patients where the post-operative pathology report demonstrates cancer.

In cases where there is intra-operative suspicion for GBC, suspicious lesions from the entire abdominal cavity should be biopsied. If there is evidence of peritoneal or omental disease, this should be biopsied and cholecystectomy not attempted. Where suspicion arises during the gallbladder dissection and it is safe and feasible to discontinue the operation, this course of action should be adopted. If it is not deemed safe, the operation should be completed.

10.3.2 Minimum dataset for referral

The patient referral should include a detailed clinical history, cross-sectional imaging in the form of a CT scan (ideally a triple phase CT scan), tumour markers (carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9). In cases of patients where the diagnosis is made post-operatively, the referral should also include the suspicious slices from the specimen. In these cases it is important that further management is guided by the depth of invasion and the cystic duct margin.

10.3.3 Initial assessment of a patient with GBC or suspicion of GBC

The purpose of the MDT meeting differs depending on whether there is suspicion of GBC pre-operatively or whether it is an incidental diagnosis.

For patients suspected to have GBC:

- diagnosis
- staging
- assess operability
- develop a management plan.

For patients diagnosed with GBC:

- completion of staging
- assess the need for completion of treatment with radical surgery or other modality.
Figure 10.1: Pathway for patient with suspected GBC

Suspicion of GBC

MDM (CT, tumour markers, PS)

No GBC

Not diagnostic

GBC confirmed

Further diagnostic tests (MRI, PET, ERCP)

Exit pathway

Staging

Resectable

Radical surgery

Downstaging chemo-radio

Disease progression

Palliation

Unresectable

Followed up

Complication extended cholecystectomy

Resectability

Disease response

Resectable disease

Resectable disease

Radical surgery

Staging of disease

GBC confirmed

Staging

Early GBC Tis, T1a

Locally advanced T1b, T2

Advanced GBC T3, T4

Diagnosed GBC

MDM (specimen margins, CT, tumour markers, PS)
10.3.4 Staging

The staging of GBC according to the 7th AJCC classification is as follows:

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1–3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4</td>
<td>N0–1</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Note: N2, which corresponds to lymph node disease involving the coeliac axis and/or the aortocaval recess lymph nodes

Achieving staging may require further cross-sectional imaging, positron emission tomography (PET) CT or laparoscopy.

10.4 Management of operable disease

The goal of surgical management is to achieve R0 resection, which offers the best chance for disease-free and overall survival. This can be achieved in approximately half of the patients. The spectrum of surgical approaches varies from simple cholecystectomy to hepato-pancreato-duodenectomy. The best surgical approach is determined by the T-staging of GBC; hence a proper pathology report in patients who are found incidentally to have GBC is of paramount importance. The two key points in this case are the depth of invasion of the gallbladder wall and the margin of the cystic duct.

Criteria for inoperable disease are:

- T4 tumour, when R0 resection cannot be achieved through en bloc resection
- left hepatic artery invasion is a marker of inoperable disease; on the contrary, when the right hepatic artery is involved, this could be amenable to en bloc resection by means of right heptectomy, providing that remaining vascular structures are not involved
- portal vein invasion, if R0 resection cannot be achieved
- port site metastasis, even in the absence of evident peritoneal disease elsewhere
- the patient is assessed as unfit to undergo a major procedure in order to achieve R0 resection.

The surgical options for GBC depend on the T-staging and include:

- simple cholecystectomy
- extended cholecystectomy, referring to a liver wedge resection of 2cm depth around the gallbladder bed and lymph node dissection +/- excision of extrahepatic biliary tree if cystic duct margin is positive
- extended cholecystectomy with en bloc resection of segments IVB and V and lymph node dissection
- right heptectomy with biliary tree excision and lymph node dissection
- hepato-pancreato-duodenectomy and lymph node dissection.
10.4.1 Surgical treatment according to T-staging

Cases of gallbladder cancer discovered incidentally during a cholecystectomy should be referred to an HPB centre.

For early GBC Tis and T1a (invasion of lamina propria)

Curative resection can be achieved with simple cholecystectomy. For T1b lesion (invasion of the muscle layer) the management is controversial as up to 30% may have N (+). To this end, extended cholecystectomy (with regional lymph node clearance – N1 level) may be beneficial.

T1 tumours

A laparoscopic cholecystectomy may be sufficient for a T1a tumour but has suboptimal oncological results for a T1b as the dissection of the gallbladder is subserosal. Where pre-operative staging is greater than T1a, open operation should be performed.

T2 GBC (locally advanced)

Extended cholecystectomy is the standard of care along with N1 lymph node dissection and should be offered to all patients with an incidental finding of GBC as a completion procedure. There is still debate as to whether the extended cholecystectomy should refer to a wedge resection of gallbladder bed or resection of segments IVB/V as well as the extent of lymph node clearance (N1 or N2 level). There is no study available comparing survival between the two approaches. Up to 25% of patients may have N2(+) disease. In these cases, N2 lymph node clearance would be advocated. Account should be taken of other tumour-related adverse prognostic factors, such as lymphatic, perineural and vascular invasion.

T2+ tumours

In cases of gallbladder cancer where the cystic duct margin is positive, excision of the extrahepatic biliary tree should be undertaken in order to acquire oncologically negative margins to the resection.

Advanced GBC (T3 or T4)

We advocate complete en bloc resection if it is technically feasible and the physiological status of the patient allows it, along with N2 lymph node dissection.

10.5 Management of inoperable disease

10.5.1 Chemotherapy

Chemotherapy has an established role in the management of inoperable and metastatic biliary tract cancers. Evidence has demonstrated an improvement in survival and quality of life with palliative chemotherapy. Cisplatin (25mg/m² IV) and gemcitabine (1,000mg/m² IV) chemotherapy, both administered on days 1 and 8 of a 3-weekly cycle, was established as the standard of care following the reporting of the ABC-02 trial (Valle et al., 2010). This demonstrated a median overall survival of 11.7 months compared with 8.1 months with gemcitabine alone (p<0.001). A subsequent meta-analysis with the Japanese BT22 study has confirmed the significant improvement in survival (HR = 0.65, 95% CI 0.54–0.78, P <0.001) with the combination compared with gemcitabine monotherapy (Valle et al., 2014). Activity with the use of 5-fluorouracil and oxaliplatin has been observed as a second-line therapy (Bridgewater et al., 2013). The ABC-06 trial is evaluating the survival benefits of the same and patients considered for second-line treatment should be recruited to this study.
There is no evidence to support the use of adjuvant chemotherapy and patients should be considered for participation in appropriate clinical trials, such as the BILCAP trial. There is no evidence for the routine use of neo-adjuvant chemotherapy. MDTs may consider the option of neo-adjuvant cisplatin and gemcitabine to assess disease biology and attempt down-staging in cases of borderline resectability.

There is a role for chemo-radiation in the management of biliary tract cancers. There is growing interest in this, particularly in respect of locally inoperable hilar cholangiocarcinomas (Polistina et al., 2011). Such patients should be considered for entry into a clinical trial.

10.5.2 Radiotherapy and chemo-radiotherapy

Adjuvant chemo-radiotherapy has shown an overall survival benefit post-surgical resection, but again the data have been extracted from rather underpowered studies and the chemotherapy given was 5-FU rather than gemcitabine.

Post operative radiotherapy to the surgical bed should be strongly considered in addition to adjuvant chemotherapy treatment for patients who have a positive resection margin at surgery (R1/R2 resection). Discussion with a clinical oncologist is advised.

For patients with locally advanced biliary tract carcinoma which is not amenable to surgery, radiotherapy can have a role as a consolidation treatment in chemotherapy responders. This can be administered using standard fractionation (45 – 54Gy in 25 – 30# with capecitabine – see Chapter 8) or hypofractionated IMRT/SBRT (see Chapter 9). Again the pros and cons, benefits and risks should be discussed by a clinical oncologist with the patient.

10.5.3 Other loco-regional treatments

To date, there are no available studies examining the benefit of radio frequency ablation (RFA) or trans-arterial chemo embolisation (TACE) in the setting of inoperable GBC.

10.6 Follow-up

Patients post-R0 resection for GBC should be followed by 6-monthly CT scan and tumour markers. For patients with incidental T1a GBC, we would recommend follow-up for 2 years post-laparoscopic cholecystectomy.

References


11 Cholangiocarcinoma

11.1 Introduction

Cholangiocarcinoma (CC) is the second most common primary liver tumour after hepatocellular carcinoma. It affects both sexes equally and is associated with grave prognosis. There are no available epidemiologic data for the incidence of CC in the UK.

Cholangiocarcinoma has been associated with several risk factors, including age >65 years, chronic intraductal stones, biliary duct adenomas and biliary papillomatosis, smoking and Thorotrast, a previously used radiological agent. More prominent risk factors are primary sclerosing cholangitis (PSC), with or without ulcerative colitis, and congenital abnormalities of the bile duct including Caroli’s disease and choledochal cysts. They are associated with a lifetime risk of developing CC which is estimated at 5–15% for PSC, 7% for Caroli’s disease and 5% for choledochal cysts.

Cholangiocarcinoma is typically classified according to its anatomic location as intrahepatic (20–25%), perihilar (Klatskin tumours) (50–60%), distal or extrahepatic (20–25%) and multifocal (approximately 5%). The above classification strongly correlates with the clinical presentation of the patient. In general, only extrahepatic (perihilar or distal) CCs present with obstructive jaundice, while intrahepatic CCs are usually incidental findings on imaging performed for deranged liver function tests (LFTs) or for symptoms of malaise and weight loss.

Of particular usefulness is the Bismuth-Corlette classification of perihilar tumours which aids surgical planning:

- **Type I**: below confluence of left and right hepatic ducts
- **Type II**: reaching confluence but not involving left or right hepatic ducts
- **Type III**: occluding common hepatic duct and either right (IIIa) or left (IIIb) hepatic duct
- **Type IV**: multicentric or bilateral intrahepatic segmental involvement; or involving the confluence and both right and left hepatic ducts.

11.2 Presentation and diagnosis

The usual clinical presentation of intrahepatic CC is malaise and deranged LFTs. The standard diagnostic test is a computed tomography (CT) scan.

Patients with extrahepatic CC usually present with obstructive jaundice. A CT scan and endoscopic retrograde cholangiopancreatography (ERCP) are used to confirm diagnosis of a tumour and identify whether a dominant stricture is present.

The single most effective modality for the diagnosis of CC is a triple phase CT scan which can also serve as staging modality. Other diagnostic tests such as magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) are helpful for delineating vascular involvement and ductal anatomy; this is of particular importance if surgery is anticipated. Positron emission tomography (PET) CT scan is now increasingly used for completion of staging. It is characterised by low sensitivity and high specificity and is particularly helpful in characterising enlarged lymph nodes and excluding or confirming distant metastases.
The association of PSC and CC remains high. In clinical practice the vast majority of patients younger than 40 years of age with CC will have a background of PSC. The diagnosis of CC can be extremely difficult in patients with PSC, as the biliary tree is diseased so the soft tissue around the bile ducts could be inflammatory and not malignant. Patients who have been diagnosed with PSC are usually followed up with a specific protocol in order to exclude CC, especially if they have been listed for transplantation. It is worth noting that the majority of patients with PSC who develop CC will do so in the first 3 years following diagnosis of PSC. It is important that the presence of CC is excluded at the time of diagnosis of PSC.

Patients with known PSC should have regular surveillance in order to identify early dominant stricture which could represent a developing CC. The existing guidelines for surveillance of patients with PSC will be standardised and implemented across the LCA. These protocols should include regular axial imaging with MRI/MRCP and carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9.

Any abnormal radiological or clinical biochemistry findings should prompt additional investigations such as CT scan, ERCP and/or spyglass endoscopy for brush cytology or biopsy. If the findings of cytology are atypical or dysplastic, the patient should undergo repeat ERCP and consideration should be given to liver transplant assessment. If the cytology is normal, the patient should undergo an interval ERCP with repeat of tissue sampling. A confirmed diagnosis of CC will prompt referral for oncological assessment.

11.3 Management by the specialist multidisciplinary team

11.3.1 Triggers for referral

- All patients who present with primary liver tumour and have concomitant suspicious symptoms such as weight loss.
- Patients with obstructive jaundice who are found to have a dominant stricture of their biliary tree.
- All patients with PSC who either present with or develop dominant stricture on their imaging or demonstrate a clinical or biochemical deterioration of their baseline status.

11.3.2 Minimum dataset for referral

The patient referral should include a detailed clinical history, tumour markers including CEA, CA 125 and CA 19-9 and, most importantly, a triple phase CT scan of their abdomen. Initial assessment of the patient’s general health should be incorporated within the referring data as performance status is the most significant determinant of early survival following surgery for CC.

11.3.3 Initial specialist multidisciplinary team assessment

Every new patient with suspected biliary malignancy should be referred to the specialist HPB multidisciplinary team (MDT) meeting.

The purpose of the MDT meeting is to:

- complete diagnosis and staging
- assess operability
- develop a management plan.
11.3.4 Staging

The staging of CC according to TNM classification is as follows:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumour invasion limited to the mucosa or muscle layer</td>
</tr>
<tr>
<td>II</td>
<td>Local invasion</td>
</tr>
<tr>
<td>III</td>
<td>As stages I and II but involving regional and hepatoduodenal lymph nodes or invasion of adjacent tissues</td>
</tr>
<tr>
<td>IV</td>
<td>Extensive invasion of the liver, adjacent structures, or lymph nodes, and/or distant metastases</td>
</tr>
</tbody>
</table>

Once CC is suspected, comprehensive staging must be carried out to screen for metastatic disease. Up to 50% of patients are lymph node positive, and 10–20% have peritoneal involvement at presentation. A chest CT should be performed for completion of staging and before definitive surgery; a staging laparoscopy should always precede this in order to exclude peritoneal disease.
Figure 11.1: Pathway for patient with suspected cholangiocarcinoma

Suspected cholangiocarcinoma (CT, MRI/MRCP, CEA, CA 125, CA 19-9, LFTs, performance status)

HPB MDT

Diagnosis confirmed

Oncological and physiological assessment of operability (completion staging, PET, PS)

Inoperable or unfit for surgery
  - Biopsy confirmation, biliary drainage and consideration for palliative systemic and loco-regional therapies

Unfit or unwilling for active treatment
  - Palliation/palliative care

Operable and fit for surgery
  - Biliary drainage
  - Staging laparoscopy
  - Liver volumes/portal vein embolisation

Borderline resectable?
  - Consideration for down-staging chemotherapy

Progression or no response
  - Palliation/palliative care

Further diagnostics required (MRI, ERCP, PET, biopsy/brushings, tumour markers)

No tumour

Exit pathway

Surveillance or interval investigations if PSC
11.3.5 Pathological reporting

Pathology reports should stage patients according to the latest UICC TNM Classification of Malignant Tumours, 7th edition, 2009. Sobin, Gospodarowitcz and Wittekind editors) TNM pathological staging with specific reference to histological type and grade, lymph node status, resection margins, and vascular and perineural invasion.

11.4 Treatment options

11.4.1 Operable disease

Figure 11.2: Surgical options for patients with cholangiocarcinoma

Surgery offers the best option for long-term survival to patients with CC. The median survival for inoperable CC either intrahepatic or extrahepatic is less than 12 months. Surgery should be attempted only when R0 resection is expected to be achieved. Failure to achieve R0 resection is associated with a mean survival of less than 3 months. For perihilar and intrahepatic CCs, specific consideration should be given to the remnant liver volume. Liver volumetry should be an integral part of the overall assessment of operability. It is expected that the majority of patients scheduled to undergo extended hepatectomies will have had portal vein embolisation.

The pre-operative criteria for inoperable disease in cases of intrahepatic CC are:

- locally advanced tumour involving bilaterally inflow and outflow
- multiple intrahepatic tumours
- extrahepatic metastatic disease
- poor performance status.
The pre-operative criteria for inoperable disease in cases of distal CC are:

- locally advanced tumour with vascular involvement that does not permit a safe oncological and/or anatomical reconstruction
- extrahepatic disease
- poor performance status.

The pre-operative criteria for inoperable disease in perihilar tumours are:

- tumour extension to second order biliary radicles bilaterally
- encasement or occlusion of the main portal vein proximal to its bifurcation without a safe option for resection and reconstruction
- atrophy of one hepatic lobe with contra-lateral portal vein branch encasement or occlusion
- atrophy of one hepatic lobe with contra-lateral tumour extension to secondary biliary radicles
- unilateral tumour extension to secondary biliary radicles with contra-lateral portal vein branch encasement or occlusion
- poor performance status
- inadequate predicted liver remnant, even after liver volumes manipulation
- extrahepatic disease.

The surgical options for CC depend on the anatomic location of the tumour and include:

- hepatectomy
- excision of the extrahepatic biliary tree only
- Whipple’s
- hepato-pancreato-duodenectomy.

**Principles of resection**

- Aim to achieve R0 resection.
- Vascular resection and reconstruction should be undertaken if it aids the aim of R0 resection.
- Regional lymphadenectomy should include all perihilar, retroportal, coeliac axis and peripancreatic lymph nodes.
- Resection of the caudate lobe should always be performed in Klatskin III and IV tumours.
- When only extrahepatic biliary tree excision is thought to be sufficient for tumour clearance, this should be carried from the intrapancreatic portion of the common bile duct (CBD) to the liver hilum incorporating the bifurcation and assessing the caudate branch that drains at the confluence of right and left ducts.
- Where possible, particularly in distal CCs, resection margins should be assessed with frozen section intraoperatively.
With regards to extrahepatic biliary tree excision only for mid-CBD tumours: although there is still support in the literature for this approach, MDTs should be aware of the limited lymph node dissection achieved. It should be exercised cautiously in very localised tumours and most likely in poor surgical risk candidates.

Of paramount importance is the optimisation of the liver prior to definitive surgery in case of intrahepatic and hilar tumours. There are two major key points: pre-operative biliary drainage and portal vein embolisation. Drainage of the prospective remnant liver segments is of paramount importance for both alleviating the incidence of post-operative ‘small for size’ and also aiding hypertrophy following portal vein embolisation. The route and choice of biliary drainage should be decided based on anatomical feasibility during the MDT assessment of the patient. Bare metal stents should be avoided if surgery is anticipated.

Right portal vein embolisation (and, where appropriate, segment IV portal branches) should be performed when an extended right hepatectomy is planned and liver volumetry suggests the left lateral segment is of inadequate volume. Assessment of its efficacy should be undertaken 4 to 6 weeks later by CT volume studies.

### 11.4.2 Pre-operative biliary stenting in distal cholangiocarcinoma

Pre-operative biliary stenting in cases of distal CC (and pancreatic head cancers) to alleviate jaundice has been debated extensively. There is growing evidence that the risk of complications (sepsis, pancreatitis, etc.) may outweigh potential benefits and delay definitive surgery. Please refer to Chapter 7 for more guidance.

### 11.4.3 Inoperable disease

For patients with inoperable disease, the obstructive jaundice should be relieved by means of either ERCP or percutaneous transhepatic cholangiography (PTC) and metal stent insertion.

Patients can be considered for palliative chemotherapy and clinical trials. The MDT meeting should address the issue of fitness of the patient to receive palliative chemotherapy and take account of the patient’s wishes.

### 11.4.4 Liver transplantation

Currently, liver transplantation for hilar and intrahepatic CCs is prohibited in the UK. There is now significant experience reported with this approach worldwide. It is envisaged that a similar approach may become available in the UK in the future.

### 11.5 Chemotherapy

Chemotherapy has an established role in the management of inoperable and metastatic biliary tract cancers. Evidence has demonstrated an improvement in survival and quality of life with palliative chemotherapy. Cisplatin (25mg/m² IV) and gemcitabine (1,000mg/m² IV) chemotherapy, both administered on days 1 and 8 of a 3-weekly cycle, was established as the standard of care following the reporting of the ABC-02 trial (Valle et al., 2010). This demonstrated a median overall survival of 11.7 months compared with 8.1 months with gemcitabine alone (p<0.001). A subsequent meta-analysis with the Japanese BT22 study has confirmed the significant improvement in survival (HR = 0.65, 95% CI 0.54–0.78, P <0.001) with the combination compared with gemcitabine monotherapy (Valle et al., 2014). Activity with the use of 5-flourouracil and oxaliplatin has been observed as a second-line therapy (Bridgewater et al., 2013).
The ABC-06 trial is evaluating the survival benefits of the same and patients considered for second-line treatment should be recruited to this study.

There is no evidence to support the use of adjuvant chemotherapy and patients should be considered for participation in appropriate clinical trials. There is no evidence for the routine use of neo-adjuvant chemotherapy. MDTs may consider the option of neo-adjuvant strategies to assess disease biology and attempt down-staging in cases of borderline resectability.

There is no established role for chemo-radiation in the management of biliary tract cancers. There is growing interest in this, particularly in respect of locally inoperable hilar CCs (Polistina et al., 2011). Such patients should be considered for entry into a clinical trial.

11.6 Radiotherapy

The role of radiotherapy in CC remains controversial, largely due to the paucity of data. Techniques have advanced rapidly in the last few years, and radiotherapy has a role to play in highly selected patient groups.

Post operative radiotherapy to the surgical bed should be strongly considered in addition to adjuvant chemotherapy treatment for patients who have a positive resection margin at surgery (R1/R2 resection). Discussion with a clinical oncologist is advised.

For patients with locally advanced biliary tract carcinoma which is not amenable to surgery, radiotherapy can have a role as a consolidation treatment in chemotherapy responders. This can be administered using standard fractionation (45 – 54Gy in 25 – 30# with capecitabine – see Chapter 8) or hypofractionated IMRT/SBRT (see Chapter 9). Again the pros and cons, benefits & risks should be discussed by a clinical oncologist with the patient.

11.6.1 Inoperable local cholangiocarcinoma – hilar/intrahepatic cholangiocarcinoma (IHC)/extrahepatic cholangiocarcinoma (EHC)

If there is no disease progression following 12 weeks of neo-adjuvant gemcitabine + cisplatin chemotherapy, chemo-radiation should be considered as consolidation therapy for local control. PET/CT is very useful here to exclude the presence of metastatic disease or regional nodes outside a conventional treatment field.

11.6.2 3D conformal radiation therapy (CRD) or intensity modulated radiation therapy (IMRT) planning

CT planning scan

A 4D scan may be useful, if available, for tumours likely to encounter significant respiratory motion. Palliative treatments may be planned using virtual simulation.

IV contrast (100ml omnipaque 30 seconds before scan) should be given, and significantly aids delineation of nodal structures within the upper abdomen; 3mm slices should be taken from mid-thorax to below L3 (to allow for dose volume histogram (DVH)).

Position and immobilisation: The patient lies supine with their arms above their head. Palliative treatments are delivered with the patient supine with their arms by their sides.
11.6.3 Delineation of target volumes and organs at risk

Radical

- Gross tumour volume (GTV): Extent of primary tumour.
- Clinical target volume (CTV-T): The GTV should be encompassed with a 1.5–2cm margin.
- Planned target volume (PTV-T) = CTV + 1.5cm (1.0cm for 4D patients).

Organs at risk tolerances

Table 11.1: Normal tissue dose constraints

<table>
<thead>
<tr>
<th>Organs at risk</th>
<th>Parameter</th>
<th>Dose (Gy) in 2Gy/#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>V30Gy</td>
<td>&lt;50%</td>
</tr>
<tr>
<td></td>
<td>Mean liver dose</td>
<td>&lt;30Gy &lt;25Gy (IMRT patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>700cc &lt;25Gy</td>
</tr>
<tr>
<td>Kidney</td>
<td>V18Gy (primary kidney)</td>
<td>&lt;50%</td>
</tr>
<tr>
<td></td>
<td>V18 (secondary kidney)</td>
<td>&lt;10%</td>
</tr>
<tr>
<td></td>
<td>or V20 (L+R kidney)</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>V45Gy</td>
<td>&lt;150 cm³</td>
</tr>
<tr>
<td></td>
<td>V30</td>
<td>&lt; 50%</td>
</tr>
<tr>
<td></td>
<td>V35</td>
<td>&lt;35%</td>
</tr>
<tr>
<td></td>
<td>V45</td>
<td>&lt;10%</td>
</tr>
<tr>
<td></td>
<td>V50</td>
<td>&lt;5cc</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Dmax</td>
<td>46Gy</td>
</tr>
<tr>
<td></td>
<td>0.1cc</td>
<td>44Gy</td>
</tr>
<tr>
<td>Spinal cord PRV</td>
<td>Dmax</td>
<td>50Gy</td>
</tr>
<tr>
<td></td>
<td>0.1cc</td>
<td>48Gy</td>
</tr>
<tr>
<td>Duodenum</td>
<td>V50</td>
<td>&lt;5cc* (IMRT constraint only)</td>
</tr>
<tr>
<td>Stomach</td>
<td>V50</td>
<td>&lt;5cc* (IMRT constraint only)</td>
</tr>
</tbody>
</table>

* In cases where the PTV expansion is into the organ at risk, these constraints may have to be loosened after discussion with consultant, or PTV will ultimately have to be compromised in the overlap zone. This will be especially the case where dose ≥54Gy.

11.6.4 Dose prescription

Patients having concurrent chemotherapy will be prescribed 45–54Gy to the 100% in 25–30 daily fractions, over 5–6/52 as a single phase treatment (Herskovic et al., 1992). This will normally be delivered with 6MV photons.

IMRT plans should achieve the following parameters for PTV coverage:

- no more than 5% of any PTV will receive <95% or >105% of the prescription dose
• no more than 2% of any PTV will receive <93% of the prescription dose
• no more than 2% of the primary PTV will receive >107% of the prescription with concomitant capecitabine 825mg/m² BD (some centres omit the weekend dosages).

**Post-operative (adjuvant) chemo-radiotherapy**

The main indication is a positive (R1/R2) resection margin.

**3D CRT or IMRT planning**

- 45–50.4Gy in 25–28 daily fractions with concomitant capecitabine 825mg/m² BD (some centres omit the weekend dosages).

**Local recurrence following resection (if no previous radiotherapy)**

If there has been no disease progression following 12 weeks of chemotherapy, chemo-radiation should be considered. PET/CT is very useful to exclude the presence of metastatic disease or regional nodes outside a conventional treatment field.

**3D CRT or IMRT planning**

- 4D CT if available
- 50.4–54Gy in 28–30 daily fractions with concomitant capecitabine 825mg/m² BD (some centres omit the weekend dosages).

**Borderline resectable disease**

If there has been no disease progression following 12 weeks of chemotherapy, chemo-radiation should be considered. PET/CT is very useful to exclude the presence of metastatic disease or regional nodes outside a conventional treatment field.

**3D CRT or IMRT planning**

- 4D CT if available
- 50.4–54Gy in 28–30 daily fractions with concomitant capecitabine 825mg/m² BD (some centres omit the weekend dosages).

**11.6.5 Photodynamic therapy**

This refers to localised tissue necrosis through visible or near-infrared light after administering photosensitising agent. The effect of phototoxicity lasts for 4–6 weeks post-treatment. It can provide for effective palliative treatment in selected patients with perihilar tumours that are not surgical candidates.

**11.7 Specialist palliative care**

For patients with poor performance status, not suitable for either surgery or palliative chemotherapy, early involvement of specialist palliative care services should be sought. Wherever possible biliary drainage should be achieved.

**11.8 Follow-up**

Successfully resected patients should be followed-up with CT scan (chest, abdomen and pelvis) and tumour markers on a 6-monthly basis.
References


12 Neuroendocrine Tumours

12.1 Introduction

Neuroendocrine tumours (NETs) are a diverse group of rare tumours. Recent years have seen developments in the management of NETs, including in diagnostic tools and treatments. As this is a rare disease and there is a lack of randomised studies, the evidence for treatment is weak compared with that for common cancers. The need for evidence-based standards has been recognised. Guidelines were published in 2012 by the UK and Ireland Neuroendocrine Tumour Society (UKI NETS) (Ramage et al., 2012). The European Neuroendocrine Tumour Society (ENETS) has published a number of guidelines on the diagnosis and treatment of NETs (Plöckinger et al., 2009). A further publication has set out recommendations for the implementation of these guidelines and, in 2010, a paper focusing on the management of patients with metastases from the peritoneum, lung, bone, brain and other rarer sites (O’Toole et al., 2010). These guidelines will be used to inform the management of patients with NETs.

In addition to these guidelines on gastro-enteric-pancreatic NETs, ENETS is producing guidelines on the management of pulmonary NETs. These are expected by end of 2014. It is anticipated that these guidelines will be appropriate to the care of such patients within the LCA.

The recommendations in the UKI NETS guidelines are summarised below:

• multidisciplinary teams (MDTs) should provide guidance on the definitive management of patients with all varieties of NETs
• the core members of an MDT will include physicians (gastroenterologists, oncologists +/- endocrinologists), surgeons, radiologists, nuclear medicine specialists, histopathologists and clinical nurse specialists.

12.2 Investigations and diagnostics

12.2.1 Genetics

• A family history should be taken and an examination performed to exclude familial cancer syndromes (e.g. multiple endocrine neoplasia 1 and 2, Von Hippel-Lindau syndrome, neurofibromatosis type 1 and Carney complex.
• In all cases where there is a family history of NETs, or a second endocrine tumour, a familial syndrome should be suspected.
• In all patients, secondary tumours and other gastrointestinal malignancies should be considered.

12.2.2 Diagnostic investigations

Biochemical investigations

• Tumour markers
• Functional tests to include a 24-hour urine 5HIAA and fasting gut peptide.
Radiology

- For detecting the primary tumour, a multimodality approach is best. Computed tomography (CT), magnetic resonance imaging (MRI) and somatostatin receptor scintigraphy (SSRS) are required. For NETs of unknown primary, DOTATATE positron emission tomography (PET)/CT is recommended.
- For assessing secondaries, DOTATATE PET/CT is the most sensitive modality. Where this is not available, SSRS in combination with CT is the preferred option.
- Grade 3 poorly differentiated neuroendocrine tumours may be fluorodeoxyglucose (FDG) avid but may not have sufficient octreotide receptors for registration on octreo-scans or Gallium octreotate PET.
- When a primary has been resected, cross-sectional imaging (CT and MRI) and SSRS may be indicated for follow-up.

Endoscopic

- Endoscopy including video capsule endoscopy and endoscopic ultrasound has a role in the diagnosis and staging of gastric, small bowel and hindgut NETs.
- Endoscopy therapy can be used with curative intent for some patients with Grade 1/2 gastric and duodenal NETs.
- In patients with completely endoscopically resected gastric and duodenal NETs, endoscopic surveillance is recommended. If any abnormality is found, further evaluation with endoscopic ultrasound may be warranted.
- Rectal ultrasound and colonoscopy have a role in surveillance of hindgut NETs >2cm in diameter or those of 1–2cm with adverse features (vascular invasion, invasion into muscularis, atypical histology).

Pathology

- Pathology is the diagnostic gold standard.
- Pathology reporting and reviews should be made by the multidisciplinary team (MDT) pathologist.
- Pathological characterisation and classification of NETs should be based on the WHO 2010 classification, the Union for International Cancer Control (UICC) TNM (7th edition) and the European Neuroendocrine Tumour Society (ENETS) site-specific T-staging system.

12.3 Treatment options

The aim of treatment should be curative where possible. The main aim is to keep the patient disease- and symptom-free for as long as possible and to maintain quality of life. The staging of tumour, histological grade and secretory profile should be determined before planning treatment. Choice of treatment depends on the symptoms, stage, histological features and degree of radionuclide uptake.

12.3.1 Surgery

Surgery should be offered when NETs are resectable and there is curative intent (or when debulking offers palliation). Surgery should be considered in those with liver metastases and potentially resectable disease.
12.3.2 Not suitable for surgery

For those not fit for surgery, the aim of treatment is to improve symptoms, maintain an optimal quality of life and, where possible, improve survival. Treatment choices for non-resectable disease include:

- somatostatin analogues
- radionuclide therapy
- loco-regional treatments including radio-frequency ablation (RFA), (chemo) embolisation and selective internal radiation
- systemic anti-cancer therapy
- palliative external beam radiotherapy – bone metastases
- consider for inclusion in clinical trials.

12.3.3 Ablation

In metastatic NETs, RFA or microwave ablation most commonly has a role in small volume tumours, paucilesional disease or in combination with resection.

12.4 Carcinoid heart disease

- All patients with midgut NET and all patients with carcinoid syndrome should be screened for carcinoid heart disease (CHD): this may include N-terminal pro-brain natriuretic peptide (NT-proBNP) and echocardiography.
- Patients with elevated NT-proBNP (>260pg/mL (>30pmol/L) based on single institution data) should be screened with echocardiography.
- Referral of patients with confirmed CHD to a cardiology department with expertise in dealing with CHD should be considered.
- Cardiac surgery should be considered in appropriate cases and should be performed in selected centres with experience of dealing with patients with NET.

References


Further reading

13 Adrenocortical Tumours

13.1 Introduction

Adrenal masses are common, with radiological studies demonstrating a 4% prevalence in adults (Mantero et al., 2000; Bovio et al., 2006; Kloos et al., 1995).

The prevalence of adrenocortical cancer (ACC) in a newly identified adrenal mass varies from 1% to 12% (Mantero et al., 2000; Kloos et al., 1995; Barzon et al., 2003), depending on which series is considered. A further 5% (approximately) of adrenal masses represent metastatic disease from primary cancer at another site. Some 20–25% of adrenal masses are clinically and biochemically functional, manifesting as cortisol excess, aldosterone excess and pheochromocytoma (Lam and Lo, 2002; Young, 2007).

These guidelines give recommendations and standards for the assessment of an adrenal mass detected incidentally or identified because of symptoms or from screening due to a known predisposition. They also give recommendations and standards of care for the investigation and management of suspected or confirmed adrenocortical carcinoma and pheochromocytoma.

13.2 Presentation and diagnosis

Adrenal masses are often identified though imaging undertaken without the prior expectation of adrenal pathology. Adrenal masses identified in this way are sometimes called incidentalomas; this term is potentially unhelpful and misleading since it pre-supposes that the patient has no symptoms relating to the mass and it also introduces a value judgement implying the clinical irrelevance of the mass.

There are several pre-existing publications giving recommendations for the investigation of adrenal masses. Clinical teams should be aware of current published guidelines.

The evaluation of an adrenal mass will include a clinical, radiological and biochemical assessment. Pre-operative cytological or histological assessment by biopsy is rarely needed.

13.2.1 Clinical assessment

All patients found to have an adrenal mass should have a clinical assessment, looking for evidence of endocrine hormone excess or deficiency. This assessment should be performed by a clinician with endocrinology training and should occur prior to a discussion of surgery.

13.2.2 Radiological assessment

Patients with an adrenal mass should have appropriate dedicated radiological assessment of the mass. Pre-contrast computed tomography (CT) scan is the first-line modality of choice. If the pre-contrast CT does not demonstrate a lipid-rich lesion (identified by HU<10 units), a contrast-enhanced CT scan should be performed with delayed imaging at 15 minutes to assess the contrast washout (CT with washout). An in and out of phase magnetic resonance imaging (MRI) scan is an alternative to CT. Post-contrast abdominal CT scan alone is inadequate.

In cases of suspected or confirmed ACC, CT chest and fluorodeoxyglucose positron emission tomography (FDG PET) should be obtained to complete the staging.
In cases of suspected pheochromocytoma, mIBG radionucleotide imaging should be obtained to assess the functionality of the mass and to complete the staging. FDG PET should also be considered for staging. Ultrasound assessment of the neck should be performed to assess for and exclude cervical paraganglioma.

### 13.2.3 Biochemical assessment

All patients with an adrenal mass which is clinically suspected to be non-functioning should have, at least, a basic biochemical assessment including:

- overnight dexamethasone (1mg) suppression test; morning serum cortisol after dexamethasone the previous evening
- adrenocorticotropic hormone (ACTH) (required unless the overnight dexamethasone suppression test shows full suppression of cortisol)
- plasma metanephrines or 24-hour urine collection for catecholamines or metanephrines
- if hypertensive, serum renin and aldosterone should also be measured.

### 13.2.4 Suspected adrenocortical carcinoma (pre-operative assessment)

Where there is a significant suspicion of adrenocortical carcinoma, additional pre-operative biochemical assessment is needed. The set of recommended tests are specified by the European Network for the Study of Adrenal Tumours (ENSAT, 2005).

The recommended tests include:

- a 24-hour urine sample to be assessed for both steroid profile and free cortisol
- serum progesterone, 17-hydroxyprogesterone, dehydroepiandrosterone, androstenedione, testosterone, 17 beta oestradiol.

These additional urine and serum markers are clinically useful both to confirm the diagnosis of adrenocortical malignancy and to identify a tumour marker for future follow-up.

### 13.2.5 Suspected pheochromocytoma (pre-operative assessment)

Patients who are suspected to have a pheochromocytoma should have a pre-operative biochemical assessment which includes urine and plasma catecholamines and metanephrines.

Patients who have a confirmed or suspected functioning pheochromocytoma should have pre-operative alpha blockade established prior to surgery.
Table 13.1: Assessment of an adrenal mass

<table>
<thead>
<tr>
<th></th>
<th>Basic tests (minimum assessment)</th>
<th>Additional tests</th>
<th>Suspected or confirmed pheochromocytoma</th>
<th>Suspected or confirmed adrenocortical cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical assessment</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td>Pre-contrast CT</td>
<td>CT with washout</td>
<td>mIBG ultrasound neck (FDG-PET)</td>
<td>CT chest</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FDG PET</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td>Serum potassium</td>
<td>ACTH DHEAS</td>
<td>Plasma metanephrines 24 hour urine catecholamines</td>
<td>Serum progesterone 17-hydroxyprogesterone dehydroepiandrosterone (DHEAS) androstenedione testosterone 17-beta oestradiol</td>
</tr>
<tr>
<td></td>
<td>Overnight dexamethasone (1mg) suppression test</td>
<td></td>
<td></td>
<td>24-hour urine sample to assess for both steroid profile and free cortisol</td>
</tr>
<tr>
<td></td>
<td>Plasma metanephrines OR 24-hour urine catecholamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If hypertensive: serum renin and aldosterone</td>
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</tr>
</tbody>
</table>

13.3 Management by the multidisciplinary team

13.3.1 Timeline for assessment of urgent cases

Patients who are referred with hazardous adrenal masses should be assessed urgently. Hazardous adrenal masses include suspected adrenocortical carcinomas, any lesions >4cm, and any mass suspected to be a pheochromocytoma.

For hazardous adrenal masses, the assessment and treatment decision should be completed within 31 days of referral. Surgery, if indicated, should be performed within 62 days from the date of referral. These recommendations are consistent with current NHS cancer waiting time targets.

13.3.2 The multidisciplinary team

The principle of multidisciplinary team (MDT) management of tumours, either under investigation or known cancer, is well established and is the recommendation of the Manual of Cancer Services Standards (NHS, 2001).

Not all cases need an MDT discussion but patients identified to have an adrenal mass for which surgery is being considered should have their investigations reviewed in an adrenal or neuroendocrine tumour MDT meeting. This review will occur within the designated timeframe for assessment. The core membership of such a meeting would include a minimum of: an endocrinologist, a radiologist, a histopathologist and an endocrine surgeon. A written MDT meeting report should be generated, including a synthesis of findings and a management plan. This report should be circulated to the patient, the GP and other relevant stakeholders.
13.3.3 Clinical nurse specialist support

Patients being assessed for surgical and/or adjuvant therapy for an adrenal tumour should have access to a clinical nurse specialist/key worker who is experienced in supporting patients with adrenal tumours. This is to facilitate the provision of information and psychological support to patients and their families at all stages of the pathway from investigation and diagnosis to surgery and follow-up.

Patients with a confirmed diagnosis of adrenal cancer should have the telephone and email contact details of their key worker, who will be the main point of contact between the patient and the MDT, and act as advocate for the patient.

13.3.4 Regional adrenal cancer treatment centres

Currently, adrenal tumour assessment and management may occur at a number of Trusts across the LCA as there is no process for the designation of regional adrenal cancer treatment centres. The LCA may in the future recognise a network of regional adrenal cancer treatment centres.

13.4 Staging

The TNM staging system proposed by the ENSAT network is the preferred method of staging.

<table>
<thead>
<tr>
<th>ENSAT stage</th>
<th>TNM</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1, N0, M0</td>
<td>Tumour ≤5 cm</td>
</tr>
<tr>
<td>II</td>
<td>T2, N0, M0</td>
<td>Tumour &gt;5 cm</td>
</tr>
<tr>
<td>III</td>
<td>T1–T2, N1, M0</td>
<td>Lymph node involvement and/or tumour infiltration into surrounding tissue</td>
</tr>
<tr>
<td></td>
<td>T3–T4, N0–N1, M0</td>
<td>and/or a tumour thrombus in the vena cava and/or renal vein</td>
</tr>
<tr>
<td>IV</td>
<td>T1–T4, N0–N1, M1</td>
<td>Metastatic disease</td>
</tr>
</tbody>
</table>

Guidelines from the Royal College of Pathologists (RCP, 2012) describe in more detail the recommended histopathology dataset and staging for ACC. These guidelines reference the ENSAT guidelines.

13.5 Treatment options

13.5.1 Surgical management

Surgery for adrenal masses should be performed by a surgeon who is experienced in adrenal surgery and who performs more than 20 procedures each year. The American Association of Endocrine Surgeons (AAES) suggests that a specialist adrenal surgeon should be defined as one who performs 20 procedures per year (AACE/AAES, 2009).

If ACC is suspected, surgery should be performed consistent with oncological principles.

13.5.2 Adjuvant therapy and follow-up

Patients who have a malignant adrenal tumour or a tumour of uncertain malignant potential should remain under the management of an adrenal tumour MDT meeting.

A personalised schedule for follow-up clinical assessment, imaging and biochemical assessment should be determined. Imaging adjuvant therapy (including the use of mitotane, chemotherapy and radiotherapy) will be coordinated by the adrenal tumour MDT meeting.
For further details see European Society of Medical Oncology (ESMO) guidelines (Berruti et al., 2012).

**Mitotane**

Mitotane is an oral adrenolytic chemotherapy which has an established adjuvant role in treating Stage IV ACC but can also be used in Stage II or III disease. It is a very lipophilic drug and accumulates in adipose tissue from where it is slowly released back into the bloodstream. This means that plasma mitotane levels may substantially increase during ongoing treatment. Treatment should be monitored by measurement of plasma mitotane levels, aiming for the therapeutic range of 14–20mg/L. Therapeutic drug monitoring (Lysosafe Service) is provided by HRA Pharma. Treatment must be commenced in staged doses according a specific regimen. The high dose accelerated regimen has been reported to achieve a therapeutic level more quickly, with no increase in side effects.

A predictable side effect of mitotane is adrenal insufficiency. Glucocorticoid replacement is prescribed from initiation. High doses are needed (hydrocortisone 40–60mg) to overcome mitotane effects on the glucocorticoid axis. Other side effects include gastrointestinal and neurological toxicity together with secondary hypothyroidism and hypogonadism (see Appendix 9).

### 13.6 Family history and clinical genetics

Genetic screening should be offered to all patients with a confirmed pheochromocytoma or paraganglioma, with the exception of patients >50 years of age with a solitary intra-adrenal lesion, who do not require screening.

All patients diagnosed with adrenal cancer should be asked whether there is a family history of adrenal, colorectal or endometrial cancer. Where appropriate, they should be referred for consideration of genetic testing.

**References**


**Further reading**


14 Colorectal Liver Metastases

14.1 Introduction
The benefits of liver resection for colorectal metastases is recognised. There are no randomised studies assessing outcome following resection compared with no treatment or other therapeutic modalities in patients with known resectable liver metastases as it is generally considered unethical not to offer surgery for resectable disease.

There has been increased interest in more aggressive chemotherapy regimens that have been reported to not only control metastatic disease but also to render some advanced liver metastases resectable. Other new modalities have become available that allow safe ablation of liver metastases without the need for surgical intervention.

This chapter was written in collaboration with the LCA Colorectal Cancer Pathway Group. The guidance in this chapter should not necessarily be regarded as the standard of care for all patients.

However, it is understood this field is rapidly evolving. Patients must be managed on the basis of all clinical data available for that case and in light of guidance and future advances in clinical knowledge.

The guidance was adapted from the British Society of Gastroenterology website, www.bsg.org.uk.

14.2 Presentation and diagnosis

14.2.1 Clinical features
These symptoms may be caused by swelling of the liver. These and other symptoms may be caused by adult primary liver cancer or by other conditions. A doctor should be consulted if any of the following problems occur:

- a hard lump on the right side just below the ribcage
- discomfort in the upper abdomen on the right side
- pain around the right shoulder blade
- unexplained weight loss
- jaundice (yellowing of the skin and whites of the eyes)
- unusual tiredness
- nausea
- loss of appetite.

The vast majority of colorectal liver metastases (CLM) will be picked up via the patient’s follow-up for their colorectal primary tumour. Robust protocols should be in place to ensure that patients identified in this way are referred to the appropriate specialist multidisciplinary team (MDT) for appropriate discussion of treatment options.

The LCA has clear inward referral pathways.
14.2.2 Imaging

Patients with suspected CLM should have a computed tomography (CT) scan of the chest, abdomen, and pelvis performed with intravenous contrast and a multi-detector CT prior to referral for management by the specialist MDT.

When the patient is initially referred to the centre MDT for collaborative management of their hepatic metastatic disease, it is essential that imaging is included in the referral. Contrast-enhanced CT of chest, abdomen and pelvis remains the gold standard in imaging patients with CLM and patients should not be referred until this has been undertaken.

Subsequent imaging may not be required, but if it is then the following will be considered:

- ultrasound
- magnetic resonance imaging (MRI)
- positron emission tomography (PET) scan
- portal vein embolisation (PVE) (for liver volume modulation prior to resection).

At the time of treatment for CLM, the latest axial staging imaging must not be more than 6 weeks old. Further axial imaging in the form of MRI will normally be used after review of the initial CT at the centre HPB MDT meeting in cases where diagnosis is uncertain or additional information is required prior to planning surgery (i.e. vascular and/or biliary anatomy considerations).

The role of PET scanning is under evaluation worldwide and definitive results are awaited. The decision on whether a PET scan is an appropriate investigation will be made at the centre HPB MDT meeting on a case-by-case basis.

14.2.3 Interventional radiology

Therapeutic interventional radiology procedures relevant to colorectal liver metastatic disease are provided as follows:

- radiofrequency ablation (RFA) is available at all three centres in the LCA
- Selective Internal Radiation Therapy (SIRT) is available only through the “Commissioning through evaluation” programme at 10 designated centres in England. Within the LCA it is only available at King’s College Hospital NHS Foundation Trust.

14.2.4 Histopathology

The histopathology report of the resected liver specimen must include specific details which can be used to determine prognosis. These should include number, size and location of metastases, resection margin clearance from tumour, capsular invasion, degree of differentiation, presence of necrosis, vascular and lymphatic invasion, and lymph node status if sampled.
14.3 Treatment options

**Figure 14.1: Pathway for management of synchronous liver metastasis from colorectal cancer**

- Colorectal cancer with synchronous liver metastases
  - Referral to joint colorectal cancer and liver MDT
  - Systemic chemotherapy +/- radiotherapy for rectal cancer
  - Complete or partial response, resectable liver metastases
  - Stable disease, resectable liver metastases
  - Progressive disease or unresectable liver metastases
  - Joint colorectal cancer and liver MDT
    - Colorectal resection first
    - Liver resection first
    - Palliative treatment or other treatment modalities
      +/- Post-resection systemic chemotherapy
Figure 14.2: Pathway for management of liver metastasis from resected colorectal cancer

14.3.1 Surgery
Liver metastatectomies are performed at LCA liver centres (Hammersmith Hospital, The Royal Marsden and King’s College Hospital) where all core members of the liver MDT are in place. All liver metastatectomies are performed at these three sites within the LCA.

Surgery is the only curative treatment for patients with liver carcinoma. Surgery cures only a minority of patients with liver carcinoma.

14.3.2 Liver resection for colorectal metastases
- The aim of liver resection (resectability) is to remove all macroscopic disease with clear (negative) margins and leave sufficient functioning liver.
- Patients with solitary, multiple and bi-lobar disease who have had radical treatment of the primary colorectal cancer are candidates for liver resection.
- The ability to achieve clear margins (R0 resection) should be determined by the radiologist and surgeon in the regional hepatobiliary unit.
- The surgeon should define the acceptable residual functioning volume, approximately one-third of the standard liver volume, or the equivalent of a minimum of two segments.
- The liver surgeon and anaesthetist should take the clinical decision regarding fitness for surgery. If deemed medically unfit for surgery, patients should be considered for ablative therapy.
• Patients with extrahepatic disease who should be considered for liver resection include those with:
  – resectable/ablatable pulmonary metastases
  – resectable/ablatable isolated extrahepatic sites (e.g. spleen, adrenal or resectable local recurrence)
  – local direct extension of liver metastases (e.g. to diaphragm/adrenal) that can be resected.

• Normal contraindications to liver resection would include uncontrollable extrahepatic disease such as:
  – non-treatable primary tumour
  – widespread pulmonary disease
  – loco-regional recurrence
  – peritoneal disease
  – extensive nodal disease, such as retroperitoneal, mediastinal or portal nodes
  – bone or central nervous system metastases.

14.3.3 Tumours borderline for resection

Those patients with tumours thought to be borderline for resection may have resectable or ablable disease and should be referred for discussion with the regional hepatobiliary unit before chemotherapy. Resectability may be increased via the following:

• **Portal vein embolisation** – When, on CT volumetric studies, the expected remnant functional liver mass after the proposed hepatectomy would be marginal or inadequate, percutaneous right PVE should be explored as a mode to induce compensatory hypertrophy of the unaffected part of the liver, thus facilitating an extended right hepatectomy. If a satisfactory response is achieved, then resection is scheduled no later than 6–8 weeks after the PVE.

• **Two-stage hepatectomy** – For patients with bi-lobar multi-nodular disease when complete removal of all tumours is thought not possible with a single procedure, a two-stage approach can be adopted by first resecting the most tumour-laden lobe. Allowing for a period of 6 weeks for regeneration of the remnant liver, resection is then completed with removal of part of the remaining liver lobe. This approach can be combined with PVE prior to the first stage and/or RFA of the remnant tumours at either stage.

• **Laparoscopic liver resection** – In recent years there has been a very dynamic expansion in the application of laparoscopic techniques in HPB surgery. There are now enough data to support its role in the treatment of patients with CLM. Although almost any type of liver resection can be performed laparoscopically, there is not wider consensus for a blanket application of the method, owing predominantly to the lack of long-term survival data.

Every patient with CLM who requires resection of up to two liver segments in anatomically favourable sites should be considered for laparoscopic liver resection. It is envisaged that as experience and data accumulate, the spectrum of this mode will increase.

14.3.4 Ablative therapy

• The decision to offer ablative therapy to patients with hepatic metastases should be made by the regional hepatobiliary unit.

• Patients who are not candidates for resection should be considered for inclusion in clinical trials.
14.3.5 **Patients not suitable for resection or ablative therapy**

Patients with advanced disease unsuitable for liver resection or ablative therapy should be referred to the clinical or medical oncologist with a special interest in colorectal cancer for further management and supportive care.

**Synchronous metastases**

- Management of accessible small metastases detected pre-operatively should be discussed with the specialist liver centre for consideration of combined resection.
- Lesions discovered at operation should not be biopsied.
- Excision of small atypical lesions should not be considered without discussion with the regional hepatobiliary unit.
- Patients should be referred for consideration of liver resection after recovery from primary surgery.
- Patients with potentially resectable liver disease who have undergone radical resection of the primary tumour should be considered for liver resection before consideration of chemotherapy.
- Patients with unfavourable primary pathology such as perforated primary tumour or extensive nodal involvement should be considered for adjuvant chemotherapy prior to liver resection and be restaged at 3 months.

14.3.6 **Biliary decompression and stents**

Biliary obstruction rarely happens in patients with CLM except in cases of very advanced disease with a large volume of liver disease. These patients will usually be considered for specialist palliative care.

14.4 **Chemotherapy**

Enrolment of patients in clinical trials is encouraged where possible, including non-chemotherapeutic approaches.

In all cases of metastatic colorectal cancer, molecular analysis to determine the presence of mutations in KRAS, NRAS and where possible BRaf should be performed as soon as the diagnosis is made and treatment is being considered.

14.4.1 **Operable or potentially operable metastatic disease**

- All patients with liver metastases should be discussed at the liver MDT at the outset and a treatment sequence and plan agreed.
- The optimal sequencing of surgery and chemotherapy is unknown. No trials have been performed directly comparing peri-operative chemotherapy to adjuvant treatment. The optimal approach should be decided by the MDT on a case-by-case basis.
- In the case of synchronous metastatic disease with an in situ non-obstructing primary, there is no evidence to dictate the optimal sequencing of resection of the primary, metastectomy and delivery of chemotherapy. This should be decided by the MDT on a case-by-case basis.
• Neo-adjuvant chemotherapy increases the risk of chemotherapy-induced hepatotoxicity (which can impact on surgical morbidity). This must be considered when determining the sequencing of hepatic surgery and peri-operative chemotherapy. The duration and regimens will be discussed and agreed with the liver MDT. It is unlikely that beyond 5 months of neo-adjuvant chemotherapy there will be incremental benefit at the expense of further hepatotoxicity.

• There is no conclusive evidence to support the addition of biological therapy to chemotherapy in the peri-operative/adjuvant post-metastectomy setting. Triplet chemotherapy regimens may result in higher response rates but this may not be correlated with improved survival.

14.4.2 Stage IV – inoperable metastatic disease

Patients with inoperable metastatic disease can be divided into two groups:
• borderline resectable – this is defined on a patient-by-patient basis by the relevant MDT meeting
• palliative.

The options for chemotherapy are the same in these two groups and this will be one of the factors influencing choice of regimen. In the former, the goal is a high response rate to maximise the prospect of sufficient down-sizing to permit resection. Such patients will routinely be offered doublet (or triplet) chemotherapy with or without biological agents.

There are no phase III data on the benefits of bevacizumab in addition to chemotherapy for patients with borderline resectable disease. Some phase II studies (BOXER, OLIVIA) have indicated high response rates with encouraging long-term outcomes for patients managed peri-operatively with bevacizumab-containing chemotherapy regimens (Gruenberger et al., 2013; Wong et al., 2011). Conversely, the GONO trials of triplets did not demonstrate an increase in rates of R0 resection (Falcone et al., 2013). The optimal duration of chemotherapy prior to resection is not known. It is recommended that re-evaluation imaging is performed at least every 3 months. Those who have become resectable could either proceed to surgery or complete chemotherapy (usually for a total of 6 months) before resection.

Details of the regimens used can be found in the chemotherapy section of the LCA Colorectal Cancer Clinical Guidelines.

14.5 Radiotherapy

There is a mounting evidence base for the use of stereotactic body radiation therapy (SBRT) for liver metastases. Papers are mainly retrospective case series with some prospective phase I and II trials. In addition, there is significant heterogeneity in patient selection, size and number of lesions treated, dose-fractionation, prescription points and dosimetric criteria within these published studies.

Until recently SBRT was mainly used as a last resort when the liver metastases were no longer amenable to other treatment. Patients were often heavily pre-treated with chemotherapy, surgery or other local ablative therapies.

Several factors predicting local control may be identified, which may help in patient selection for treatment. The most consistently observed correlation with local control is baseline tumour volume (Rusthoven et al., 2009). The number of tumours up to 3 and the size of the tumour <6cm predict better outcomes.
14.5.1 External beam radiotherapy (and chemo-radiation)

- There is currently no evidence to support adjuvant post-operative radiation therapy.
- There is no phase III evidence for radiotherapy improving survival or the quality of life in advanced disease but mounting phase 2 data. Phase III trials are underway.
- The role of chemo-radiation (chemotherapy combined with local radiation) remains to be established in randomised clinical trials as local and systemic toxicity is also concomitantly increased.
- Hypofractionated IMRT or SABR should be considered for patients with oligometastatic disease who are unwilling or unsuitable for other local ablative therapies.
- Radiation alone still has potential important palliative value for painful tumours, uncontrolled bleeding, etc.

14.5.2 Patient selection criteria for radiotherapy

Inclusion criteria

- Irresectable tumour or tumour inappropriate for other treatment modalities
- Karnofsky Performance Status ≥ 60
- Life expectancy >3 months
- >700cc of uninvolved liver
- No chemotherapy within 4 weeks prior to, and 4 weeks after, stereotactic ablative radiation therapy (SABR)
- No, or limited and potentially treatable, extrahepatic disease
- Patient must have recovered from any previous therapy (such as surgery, chemotherapy or radiotherapy to other areas) with a minimum of 2 weeks’ break
- No limitation on actual size of a given tumour or number of tumours, provided functional residual volume, and organs at risk dose constraints can be met
- Adequate organ function, defined as: haemoglobin 9.0g/dL, absolute neutrophil count 1.5bil/L, platelets 80bil/L, bilirubin <3 times upper limit of normal, INR <1.3 or correctable with vitamin K and unless the patient is taking warfarin/coumarin, AST or ALT <5 times upper limit of normal. Creatinine less than 200umol/L (if creatinine is above the normal range, consideration should be given to dynamic renal scintigraphy (renography) if there is anticipated to be any appreciable renal dose from the delivery of the treatment).

Exclusion criteria

- Active hepatitis or clinically significant liver failure (encephalopathy, portal hypertension, varices)
- Clinically apparent ascites
- Prior radiotherapy to the right upper abdomen (unless 700cc normal unirradiated liver <17Gy)
- If patient is for fiducial placement: gold allergy, coagulopathy preventing safe fiducial placement
• Any previous radiotherapy where the mean dose to the liver was 15Gy (conventional fractionation), or where beams would be likely to overlap with those used to deliver SBRT, or where previous doses to other critical normal structures would make re-irradiation unsafe

• Any other severe co-morbidity such as unstable angina, congestive cardiac failure, pulmonary hypertension or transmural MI requiring hospitalisation in the preceding 6 months, or acute bacterial/fungal infection requiring intravenous antibiotics

• Central nervous system metastases.

**Suggested fractionation schemes**

• 18–30Gy in a single fraction (SABR)
• 45–60Gy in 3# over 3–10 days (SABR)
• 50–60Gy in 5# over 5–12 days (SABR)
• 60Gy in 8# over 10 days (IMRT)
• 50–60Gy in 10# over 12 days (IMRT)

• Palliation of liver pain – 8Gy single fraction, 20Gy in 5#, 30Gy in 15#

**Acute toxicity**

Overall, rates of Grade 1–2 toxicity are reported to range from 0–27% and Grade 3–4 toxicities are observed in around 5%. The rate of morbidity for liver radiation is reported to be independent of dose-fractionation schedule, and the toxicity rates are consistently low despite the heterogeneity of dose-fractionation schedules and delivery systems. The likely explanation is the limited dose delivered to uninvolved liver and the parallel functioning of liver parenchyma. The most commonly reported toxicities are fatigue, right upper quadrant pain, low-grade pyrexia, transaminase rise (normally settles by 3 months post-treatment), nausea and loss of appetite.

A syndrome of minor pain, fever and chills is observed in some patients: Grade 1 (requiring no treatment) in 14%, and Grade 2 (requiring treatment with analgesics/steroids) in 13%, usually occurring within 1–3 weeks of treatment. Rates of gastric ulceration and oesophagitis are low (G2 in 7%, G3 in 3%) and most centres advise the use of prophylactic proton-pump inhibitors. The rates of radiation-induced liver disease (RILD) are notably very low in all published series. Child-Pugh class B and hepatitis B carriage are associated with greater risk of RILD.

Rates of transaminase derangement are also low. For example, Grade 1–2 elevation of liver function tests were observed in 28% of patients treated with 30–55Gy (median 48Gy) by Ibarra et al. (2012), Katz et al. (2007; 2012) and Milano et al. (2012), and transient elevation of liver enzymes described as mild-moderate is noted in 31–36% of patients receiving 25–60Gy in 3 fractions.

Several studies have reported the use of liver SBRT in patients who have previously undergone surgical resection and/or RFA, and reported low levels of toxicity, suggesting that SBRT is safe to use in this context.
Table 14.1: SBRT liver: suggested constraints

<table>
<thead>
<tr>
<th>Organs at risk</th>
<th>Single fraction constraints</th>
<th>Three-fraction constraints</th>
<th>Five-fraction constraints</th>
<th>10-fraction constraints</th>
<th>Dose limiting toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>700cc &lt;9Gy</td>
<td>700cc &lt;17Gy V15 &lt;50% V21 &lt;30%</td>
<td>700cc &lt;21Gy</td>
<td>700cc &lt;25Gy</td>
<td>RILD (Radiation induced liver disease)</td>
</tr>
<tr>
<td>Spinal cord</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>V10 &lt;0.35cc</td>
<td>V18 &lt;0.35cc V12 &lt;1.2cc</td>
<td>V23 &lt;0.35cc V14.5 &lt;1.2cc</td>
<td>V30 &lt;0.35cc 35Gy point dose</td>
<td>Myelopathy</td>
</tr>
<tr>
<td></td>
<td>V7 &lt;1.2cc 14Gy point dose</td>
<td>22Gy point dose</td>
<td>30Gy point dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagus</td>
<td>V12 &lt;5cc 15Gy point dose</td>
<td>V18 &lt;5cc 25Gy point dose</td>
<td>V20 &lt;5cc 35Gy point dose</td>
<td>V30 &lt;5cc 40Gy point dose</td>
<td>Stenosis/fistula/perforation</td>
</tr>
<tr>
<td>Heart/ pericardium</td>
<td>V16 &lt;15cc 22Gy point dose</td>
<td>V24 &lt;15cc 30Gy point dose</td>
<td>V32 &lt;15cc 38Gy point dose</td>
<td>V32 &lt;15cc 40Gy point dose</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Rib</td>
<td>V22 &lt;1cc 30Gy point dose</td>
<td>V29 &lt;1cc 37Gy point dose</td>
<td>V35 &lt;1cc 43Gy point dose</td>
<td>V35 &lt;1cc 45Gy point dose</td>
<td>Chronic pain or fracture</td>
</tr>
<tr>
<td>Skin</td>
<td>V23 &lt;10cc 26Gy point dose</td>
<td>V30 &lt;10cc 33Gy point dose</td>
<td>V37 &lt;10cc 39.5Gy point dose</td>
<td>V37 &lt;10cc 45Gy point dose</td>
<td>Chronic ulceration</td>
</tr>
<tr>
<td>Stomach</td>
<td>V11 &lt;10cc 12Gy point dose</td>
<td>V16.5 &lt;10cc 22Gy point dose</td>
<td>V18 &lt;10cc 32Gy point dose</td>
<td>V30 &lt;10cc 40 Gy point dose</td>
<td>Chronic ulcer/ fistula/perforation</td>
</tr>
<tr>
<td>Duodenum</td>
<td>V11 &lt;5cc V9 &lt;10cc 12Gy point dose</td>
<td>V16.5 &lt;5cc V11.5 &lt;10cc 22Gy point dose</td>
<td>V18 &lt;5cc V12.5 &lt;10cc 32Gy point dose</td>
<td>40Gy point dose</td>
<td>Chronic ulcer/ fistula/perforation</td>
</tr>
<tr>
<td>Jejunum/ ileum</td>
<td>V12 &lt;5cc 15Gy point dose</td>
<td>V18 &lt;5cc 25Gy point dose</td>
<td>V19.5 &lt;5cc 35Gy point dose</td>
<td>40Gy point dose</td>
<td>Enteritis/obstruction/ perforation</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>V14 &lt;20cc 18Gy point dose</td>
<td>V24 &lt;20cc 28Gy point dose</td>
<td>V25 &lt;20cc 38Gy point dose</td>
<td>40Gy point dose</td>
<td>Colitis/fistula/perforation</td>
</tr>
<tr>
<td>Renal hilum/ vascular trunk</td>
<td>10.6Gy to 67%</td>
<td>18.6Gy to 67%</td>
<td>23Gy to 67%</td>
<td>25Gy to 67%</td>
<td>Malignant hypertension</td>
</tr>
<tr>
<td>Kidney</td>
<td>200cc &lt;8.5Gy</td>
<td>200cc &lt;16Gy</td>
<td>200cc &lt;17.5Gy</td>
<td>200cc &lt;18Gy</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Lung (R &amp; L)</td>
<td>1,500cc &lt;7Gy</td>
<td>1,500cc &lt;11.5Gy</td>
<td>1,500cc &lt;12.5Gy</td>
<td>V5 &lt; 50% V20 &lt; 25%</td>
<td>Pneumonitis</td>
</tr>
</tbody>
</table>

Note: Point dose <0.035cc.
14.6 Follow-up and recurrence

14.6.1 Follow-up

Following a liver resection for CLM at the centre MDT, patients will be seen in the centre HPB outpatient clinic 2–3 weeks post-discharge. By then plans for further treatment should be in place with the local oncologist. If there are no active surgical/hepatological issues, patients can be discharged from further HPB follow-up. Referral back to the specialist liver MDT would be triggered by evidence of disease of recurrence within the remaining liver on surveillance CT scans.

In cases where further surgery (i.e. a staged hepatectomy) or other interventional procedures (i.e. RFA) are planned, or in cases where there is known residual disease within the liver, patients will continue to attend HPB outpatient clinics until all active issues are resolved.

Although the issue of post-liver resection baseline CT scan is still a matter for debate, it is appropriate for these patients to have a CT scan locally 4–6 weeks after their resection when post-operative changes have diminished and regeneration would be expected to have mostly completed. It would also roughly match the initiation of their adjuvant chemotherapy (when appropriate).

The CT surveillance will follow an agreed monthly pattern for the first 3 years following liver resection, as the bulk of recurrences are observed during that timeframe, and a 12-monthly pattern thereafter until 5 years post-resection. These surveillance CTs should be promptly sent for review at the centre MDT meeting. If recurrence is detected, the patient should be sent for review at the centre MDT meeting.

Clinical examination, liver function tests and tumour markers should be part of the surveillance protocol. These should be undertaken locally.

14.6.2 Recurrent metastatic liver disease

Patients who have undergone a liver resection for their CLM and present with recurrent disease in their liver remnant should be assessed for repeat hepatectomy in the same way as for their first resection. Repeat hepatectomies for CLM in high volume centres follow the same pattern of morbidity and mortality as the primary liver resections. The prognosis for these patients seems to be unaffected by the number of liver resections, but rather by the ability to remove all measurable disease with enough remnant functional liver.

References

Falcone A, Cremolini C, Masi G et al. (2013) FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in inoperable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group. Journal of Clinical Oncology 31(suppl; abstr 3505), http://meetinglibrary.asco.org/content/115186-132.

Gruenberger T, Bridgewater JA, Chau I et al. (2013) Randomized, phase II study of bevacizumab with mFOLFOX6 or FOLFOXIRI in patients with initially inoperable liver metastases from colorectal cancer: Resectability and safety in OLIVIA. Journal of Clinical Oncology 31(suppl; abstr 3619^), http://meetinglibrary.asco.org/content/115679-132.


**Further reading**


Primrose JN, Falk S, Finch-Jones M et al. (2013) A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild-type patients with operable metastases from colorectal cancer: the new EPOC study. *Journal of Clinical Oncology* 31(suppl; abstr 3504).

15 Survivorship Guidelines

As cancer treatments become more effective, more people are living with and beyond cancer with specific needs as a direct result of the cancer and its treatment. The consequences of cancer treatment are dependent on multiple factors and affect each person differently. Consequences may be physical (e.g. cardiovascular conditions, impact on fertility, bone health and gastrointestinal); emotional and psychological (e.g. anxiety, self-confidence and depression); social; spiritual; or cognitive. They can impact on every aspect of a person and on their family’s lives, from the ability to work, through to the ability to have a family or to participate in social activities. It is widely acknowledged that cancer survivors have a multitude of unmet needs following treatment, with a majority still having some needs 6 months later. Good survivorship care enables the person to live as full and active a life as possible.

Survivorship can be defined as:

“cover[ing] the physical, psychological and economic issues of cancer, from diagnosis until end of life. It focuses on the health and life of a person with cancer beyond the diagnosis and treatment phases. Survivorship includes issues related to the ability to get health care and follow-up treatment, late effects of treatment, second cancer and quality of life. Family members, friends and caregivers are also part of the survivorship experiences.”

National Cancer Institute, Dictionary of Cancer Terms, definition of ‘survivorship’

The National Cancer Survivorship Initiative (NCSI) vision document (Department of Health, 2010) mandated five shifts in care for individuals completing cancer treatment. NCSI advocates cancer being treated as a chronic illness, with patients empowered and supported to take an active role in their care. Improving Outcomes: a Strategy for Cancer (Department of Health, 2012) states that people living with and beyond a cancer diagnosis should have their full needs addressed to prevent long-term disability, enabling them to live a full, active, good quality life for as long as possible. Work within the NCSI has to date focused on survivorship from the end of treatment, but its report, Living With and Beyond Cancer: Taking Action to Improve Outcomes (NCSI, 2013) acknowledges that survivorship care from the point of diagnosis is also vital. It challenges services to develop further and focuses on five different areas:

• information and support from diagnosis
• promoting recovery
• sustaining recovery
• managing consequences
• supporting people with active and advanced disease.

The importance of good survivorship care is well known: those who have unmet needs are 20% more likely to visit their GP and twice as likely to attend A&E than age-matched healthy people. They are more likely to be unemployed and many report economic hardship. Much has been achieved both nationally and locally to address this agenda. It is essential that in the LCA our patients have access to high-quality, equitable survivorship services on a par with the best in the country. We will continue to build on the successes to date.
The Consequences of Cancer and its Treatment (CCaT) collaborative group (a Macmillan Community of Interest) produced a guidance document that includes ‘10 Top Tips’ for patients. These cover the key components of good survivorship care, and the LCA expects services to address these areas. The following nine points for professionals, are based on the CCaT’s work.

15.1 Discuss a person’s needs

The holistic needs assessment (HNA) (see Appendix 10) has been shown to be effective in identifying a person’s areas of concern. It can take many forms and the LCA has developed its own tool, based on the concerns checklist and distress thermometer. The tool allows patients to specify what is of most concern to them, and so directs subsequent discussion and intervention to addressing these needs. It has scope to cover physical, emotional, spiritual, finance and welfare, and practical concerns. It is anticipated that as the HNA becomes embedded within the pathway, patients will start to ask for an HNA and professionals need to be able to respond to this.

**Recommendation:** Every patient should be offered an HNA at key pathway points, including at diagnosis and end of treatment, and whenever a person requests one.

15.2 Provide a treatment summary and care plan

A treatment summary provides a summary of the cancer treatments received by the end of the first treatment, planned follow-up (including mechanisms for these) and signs and symptoms of which to be aware. The aim is to provide information not only to the patient, but also to the GP about possible consequences of cancer and its treatment, signs of recurrence and other important information. Please see the National Cancer Survivorship Initiative (NCSI) treatment summary at Appendix 8.

A care plan is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention, or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

**Recommendation:** An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA and associated written care plan, and should also include the discussion and provision of a comprehensive treatment summary.

15.3 Provide a main contact

Several pieces of UK-wide work have shown the necessity of a key contact, or key worker (see Appendix 5), not least the national Cancer Patient Experience Survey. It is now agreed that both patients and GPs (and other healthcare professionals) benefit from having a named person to contact if they need help or advice about issues related to consequences of cancer and its treatment.

**Recommendation:** The treatment summary should include the details of a key worker in addition to details of who to contact out of hours. This should be sent to the GP, the patient and any others the patient identifies as necessary.
15.4 Identify post-treatment symptoms

As discussed above, cancer and its treatments can have far-reaching consequences and people with associated unmet needs are more likely to access healthcare services than their healthy counterparts. Providing information on likely post-treatment symptoms (e.g. early lymphoedema) and how these can be managed or avoided, allows people to seek the right help from the right people at the right time.

**Recommendation:** Information on anticipated or possible consequences of cancer treatment and what to do if they occur should be routinely provided to all patients. This should be done from the time of discussion of treatment onwards, with the information clearly reiterated during the end of treatment consultation.

15.5 Provide support about day-to-day concerns

Life changes following a cancer diagnosis. It is recognised that people need help and support to find a ‘new normal’. This may cover any one of a multitude of aspects, from work and education, through to financial worries and needing help with caring responsibilities. Help should be offered at all key points in the pathway, but may be of particular relevance at the end of treatment point and may well be highlighted in the HNA. There are various options for written information provision (e.g. Macmillan Cancer Support information leaflets and information prescriptions) as well as some specialist services (e.g. Citizens Advice). Reports published by the NCSI, available on the NCSI website, may be of use to professionals. Support is also available to patients from Pancreatic Cancer UK, who can be contacted via their website, www.pancreateiccancer.org.uk.

**Recommendation:** Patients should be routinely asked about whether they need support with day-to-day issues and referrals made to specialist services when necessary.

15.6 Talk about how you feel

Having a cancer diagnosis has an emotional impact, and at the end of treatment, people experience a wide range of emotions. Sometimes, these can be dealt with by the person alone or with support from the key worker and others, but some people will need referral to psychological support services. This may be true for not only patients but their family and carers too.

**Recommendation:** Use an HNA to identify emotional concerns. Further screening tools (e.g. the Hospital Anxiety and Depression Scale) should be considered, with subsequent referrals made as necessary.

15.7 Healthy lifestyle

There is a growing body of evidence which supports the adoption of a healthy lifestyle for those who have had a cancer diagnosis.

**15.7.1 Smoking cessation**

Tobacco smoking is the main cause of preventable morbidity and premature death in England. End of treatment provides an opportunity to deliver stop smoking interventions at a point at which an individual may be more susceptible to health advice and hence more motivated to quit.
**Recommendation:** All current smokers should be asked about their smoking habit, and offered smoking cessation advice with onward referral to local services as necessary.

### 15.7.2 Diet

The role that diet can play in cancer incidence has been widely documented. Research has now moved to look at its influence beyond treatment. The nutritional issues during or following treatment include weight loss or gain; changes in body composition (e.g. loss of muscle mass); and particular eating difficulties (e.g. swallowing problems and limited capacity for food). There are also long-term symptoms (e.g. changes in bowel habits for those who have had pelvic radiotherapy).

Receiving advice from an appropriately trained professional has been shown to improve quality of life, reduce risk of recurrence and risk of developing a new primary or other chronic disease, such as heart disease or diabetes. The aim of dietary advice is also to counter the adverse effects of cancer treatment. To date, most of the work has been done in breast, colorectal and prostate cancer. The World Cancer Research Fund (WCRF) (2007) recommends the following for all cancer survivors:

- Be as lean as possible within the normal body weight range.
- Be physically active as part of everyday life.
- Avoid sugary drinks and limit the consumption of energy-dense foods.
- Eat mostly foods of plant origin.
- Limit intake of red meat and avoid processed meat.
- Limit alcoholic drinks.
- Limit consumption of salt. Avoid mouldy cereals or pulses.
- Aim to meet nutritional needs by diet alone.

**Recommendation:** Patients are provided with dietary advice, based on the WCRF recommendations at the end of treatment, with referral to specialist dietitians as required.

### 15.7.3 Physical activity

There has been a dramatic rise in the amount of high-quality published research on the role of exercise in cancer in recent years. Physical activity results in improvement in quality of life, fitness and function and symptoms related to cancer and its treatments. It reduces cancer recurrence, incidence of second cancers and reduces both all-cause and cancer-specific mortality.

There is wide consensus that cancer survivors should exercise to the same level as the general population for health benefits. Research suggests that a combination of cardiovascular and muscular strength training has additional benefits over undertaking only one type of exercise.

**Recommendation:** Patients should be encouraged to maintain or increase their level of physical activity both during and after treatment in line with national guidance. They should be referred for specialist assessment by a physiotherapist as necessary.

Patients should also be offered access to a health promotion event, such as a health and well-being clinic at the end of treatment.
15.8 Self-managed follow-up

There is a move towards increased self-management and follow-up closer to home. This has clear benefits to patients, including reduced anxiety in the lead-up to routine appointments and less interference in their day-to-day life caused by travelling to hospitals. In addition, research has shown that recurrence is more likely to be detected by the patient themselves between appointments, rather than at the outpatient appointment. By reducing unnecessary appointments, Trusts are able to see new patients more quickly and spend more time with more complex patients.

For self-management to be effective, patients need to be given the right information about signs and symptoms of recurrence and clear pathways to follow if they have concerns. They should also be guaranteed a fast, explicit route to re-access services if necessary. A telephone helpline is suggested, which should be staffed by senior, experienced staff.

**Recommendation:** In addition to the use of treatment summaries (as described above), services should investigate the feasibility of rolling out self-managed/patient-led follow-up.

15.9 Encourage survivors to share their experience

Sharing the experience of living with and beyond cancer can be beneficial to patients themselves, their carers and others who have a cancer experience. Providing feedback on experience, and volunteering and participation in research can all have a positive impact on the patient.

**Recommendation:** Patients should be offered information on local support groups and where they can access further information on sharing their experiences.

To summarise, these guidelines set out how to best address survivorship care, based on best available evidence, current national policy and guidance and in response to work such as the Cancer Patient Experience Survey.

**References**


16 Audit

The assessment and evaluation of outcomes is a fundamental component of the management of HPB cancer and was highlighted in the Improving Outcomes guidance. This process is continuous and should be based in the multidisciplinary team (MDT). In addition to core clinical information, the MDT should record clinical and pathological stages and details of co-morbidity and performance status and patient-reported outcomes.

All patients should be entered into the Cancer Outcomes Services Dataset (COSD), including both core and site-specific data items where appropriate. Output from the National Cancer Registration Service (NCRS) should be reviewed regularly at unit and integrated cancer service level. Recording of patient data is resource intensive and units and the specialist centres should have appropriate and adequate support. This specifically includes data managers and functional data systems linked to the NCRS.
17 Clinical Research

Involvement in clinical research protocols should be considered for all patients. The most appropriate time to consider inclusion into trials is at the MDM. This is applicable at both unit and specialist centre level to allow consideration of both national and local protocols. The role of research staff is crucial with close links to the National Cancer Research Network.
### Urgent Referrals Criteria

(please tick category)

**UGI 1**
- Patients of any age with dyspepsia **AND** with any of the following:
  - Chronic GI bleeding
  - Dysphagia
  - Progressive unintentional weight loss
  - Persistent vomiting
  - Iron deficiency anaemia
  - Epigastric mass
  - Suspicious barium meal result

**UGI 2**
- Patients aged over 55 with unexplained recent onset dyspepsia

**UGI 3**
- Dyspepsia that occurs within 5 seconds of having commenced swallowing

**UGI 4**
- Unexplained weight loss (and no dyspepsia)

**UGI 5**
- Iron deficiency anaemia (and no dyspepsia)

**UGI 6**
- Persistent vomiting and weight loss (and no dyspepsia)

**UGI 7**
- Patients presenting with:
  - Unexplained upper abdominal pain and weight loss (+/- back pain)
  - An upper abdominal mass (+/- dyspepsia)

**UGI 8**
- Obstructive jaundice

**UGI 9**
- Dysphagia

**UGI 10**
- Unexplained upper abdominal pain and weight loss (+/- back pain)
- An upper abdominal mass (+/- dyspepsia)

**UGI 11**
- Patients presenting with:
  - Unexplained weight loss
  - Iron deficiency anaemia
  - Persistent vomiting

**UGI 12**
- Patients aged over 55 with unexplained recent onset dyspepsia

**UGI 13**
- Dyspepsia that occurs within 5 seconds of having commenced swallowing

**UGI 14**
- Unexplained weight loss (and no dyspepsia)

**UGI 15**
- Iron deficiency anaemia (and no dyspepsia)

**UGI 16**
- Persistent vomiting and weight loss (and no dyspepsia)

**UGI 17**
- Patients presenting with:
  - Unexplained upper abdominal pain and weight loss (+/- back pain)
  - An upper abdominal mass (+/- dyspepsia)

**UGI 18**
- Obstructive jaundice

**UGI 19**
- Dysphagia

---

### GP Details

- **Date of GP Decision to Refer:**
- **No of Pages Faxed:**

### Patient Details

- **Last Name:**
- **Address:**
- **Daytime Tel or Mobile:**
- **Date of Birth:**
- **Interpreter required?** Y / N
- **Hospital No:**

### Comments/Other Reasons for Urgent Referral
### Patient Awareness Questions:

1. Has the patient been made aware of the nature of their referral? 
   - Yes ☐ No ☐

2. Has the patient been supplied with supportive information about the Urgent Suspected Cancer referral process? 
   - Yes ☐ No ☐

3. Have you asked the patient if they will be available to attend an appointment within the next two weeks? 
   - Yes ☐ No ☐

4. Has the patient indicated to you that they would be available to attend an appointment within the next two weeks? 
   - Yes ☐ No ☐

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### SOUTH WEST LONDON CANCER NETWORK

**How to make urgent referrals for suspected upper GI cancers**

Please FAX / EMAIL this form to the Cancer Office at the relevant hospital, with or without an accompanying letter. E-Mails **MUST** be sent from a NHS.net address. **Please ensure that the referral reaches the hospital within 24 hours of the GP’s decision to refer.**

<table>
<thead>
<tr>
<th>Epsom and St Helier NHS Trust</th>
<th>Epsom and St Helier NHS Trust</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epsom General Hospital</strong></td>
<td><strong>St Helier Hospital</strong></td>
</tr>
<tr>
<td>Dorking Road, Epsom</td>
<td>Wrythe Lane, Carshalton</td>
</tr>
<tr>
<td>Surrey KT18 7EG</td>
<td>Surrey SM5 1AA</td>
</tr>
<tr>
<td>FAX: 020 8296 2741</td>
<td>FAX: 020 8296 2741</td>
</tr>
<tr>
<td>TEL: 020 8296 2742</td>
<td>TEL: 020 8296 2742</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Croydon Health Services NHS Trust</th>
<th>St George’s Healthcare NHS Trust</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Croydon University Hospital</strong></td>
<td><strong>St George’s Hospital</strong></td>
</tr>
<tr>
<td>London Road, Croydon</td>
<td>Blackshaw Road, Tooting</td>
</tr>
<tr>
<td>Surrey CR7 7YE</td>
<td>London SW17 0QT</td>
</tr>
<tr>
<td>FAX: 020 8401 3337</td>
<td>FAX: 020 8725 0778</td>
</tr>
<tr>
<td>TEL: 020 8401 3986</td>
<td>TEL: 020 8725 1111</td>
</tr>
<tr>
<td></td>
<td>E-MAIL: <a href="mailto:cancerreferraloffice@stgeorges.nhs.uk">cancerreferraloffice@stgeorges.nhs.uk</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kingston Hospital NHS Trust</th>
<th>Kingston Hospital NHS Trust</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kingston Hospital</strong></td>
<td><strong>Queen Mary’s Hospital</strong></td>
</tr>
<tr>
<td>Galsworthy Road</td>
<td>Roehampton Lane</td>
</tr>
<tr>
<td>Kingston KT2 7QB</td>
<td>London SW15 5PN</td>
</tr>
<tr>
<td>FAX: 020 8934 3306</td>
<td>FAX: 020 8812 7937</td>
</tr>
<tr>
<td>TEL: 020 8934 3305</td>
<td>TEL: 020 8487 6037 / 6032</td>
</tr>
</tbody>
</table>
North West London Referral Form

<table>
<thead>
<tr>
<th>NORTH WEST LONDON URGENT SUSPECTED UPPER GI CANCER REFERRAL FORM</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLEASE ENSURE THAT THIS FORM IS ATTACHED TO YOUR CHOOSE AND BOOK REFERRAL</td>
</tr>
<tr>
<td>Consultant/Hospital to which patient is being referred:</td>
</tr>
<tr>
<td>Patient details</td>
</tr>
<tr>
<td>NHS number:</td>
</tr>
<tr>
<td>Surname:</td>
</tr>
<tr>
<td>First Name:</td>
</tr>
<tr>
<td>Age / D.O.B:</td>
</tr>
<tr>
<td>Address:</td>
</tr>
<tr>
<td>Postcode:</td>
</tr>
<tr>
<td>Tel day:</td>
</tr>
</tbody>
</table>

Have you informed the patient that you suspect upper GI cancer?  Y / N
Have you given the patient the 2WW information leaflet  Y / N
Have you told the patient they will be seen within 2 weeks?  Y / N
Has the patient had a previous diagnosis of cancer?  Y / N (Specify if known)
Has the patient previously visited this hospital?  Y / N
Hospital number (if known): |
First language: |
Interpreter required?  Y / N

Symptoms and Clinical Findings

**NB:** 55 years + recent onset of dyspepsia, refer for gastroscopy first usually

<table>
<thead>
<tr>
<th>Gastroscopy / Barium swallow result (if available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia  □</td>
</tr>
<tr>
<td>Persistent vomiting &amp; weight loss  □</td>
</tr>
<tr>
<td>Unexplained iron deficiency anaemia  □</td>
</tr>
<tr>
<td>Unexplained weight loss  □</td>
</tr>
<tr>
<td>Unexplained abdominal pain and weight loss  □</td>
</tr>
<tr>
<td>Upper abdominal mass  □</td>
</tr>
<tr>
<td>Obstructive jaundice - US if possible  □</td>
</tr>
<tr>
<td>Duration of symptoms ..................................................</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Helicobacter Pylori Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive  □</td>
</tr>
<tr>
<td>Negative  □</td>
</tr>
<tr>
<td>Not Tested  □</td>
</tr>
</tbody>
</table>

**RISK FACTORS**

- Barrett’s oesophagus  □
- Known dysplasia  □
- Atrophic gastritis or intestinal metaplasia  □
- > 20 years peptic ulcer surgery  □
- Known smoker or ex-smoker  □
**Additional Clinical Information:** Include any investigations arranged or results obtained, and any other information you think relevant.

Continue on a separate sheet if necessary ensuring patient details and referring doctor's name are on additional sheets.

<table>
<thead>
<tr>
<th>North West London Hospitals NHS Trust</th>
<th>Imperial College Healthcare NHS Trust</th>
<th>Chelsea and Westminster NHS Foundation Trust</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fax: 020 8235 4188</td>
<td>Fax: 020 3312 1580</td>
<td>Fax: 020 3315 8814</td>
</tr>
<tr>
<td>Tel: 020 8235 4293</td>
<td>Tel: 020 3312 1527</td>
<td>Tel: 020 3315 2637</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ealing Hospital NHS Trust</td>
<td>Hillingdon Hospital NHS Trust</td>
<td>West Middlesex University Hospital NHS Trust</td>
</tr>
<tr>
<td>Fax: 020 8967 5005</td>
<td>2WW fax line: 01895 279807</td>
<td>Fax: 020 8321 5157</td>
</tr>
<tr>
<td>Tel: 020 8967 5000, x3921</td>
<td>Tel: 01895 279549</td>
<td>Tel: 020 8321 6776</td>
</tr>
<tr>
<td></td>
<td>Alternate Fax: 01895 279215</td>
<td></td>
</tr>
</tbody>
</table>
South East London Referral Form

**SOUTH EAST LONDON CANCER NETWORK**
Upper GI Urgent Suspected Cancer Referral

Please tick the box of the hospital clinic you are referring to and fax this form to the relevant Urgent Referral Team within 24 hours. Guidelines are on the reverse side.

- **Princess Royal**
  - Fax: 01689 863187
  - Tel: 01689 865676

- **Queen Elizabeth**
  - Fax: 020 8836 4035
  - Tel: 020 8836 5964/5

- **Guy’s & St Thomas’**
  - Fax: 020 7188 0923
  - Tel: 020 7188 0902

- **King’s College**
  - Fax: 020 3299 1515
  - Tel: 020 3299 1516

- **Lewisham**
  - Fax: 020 8333 3451
  - Tel: 020 8333 3450

- **Queen Mary’s**
  - Fax: 020 8308 9264
  - Tel: 020 8308 3258/3088

---

### SECTION 1 – PATIENT INFORMATION. PLEASE COMPLETE IN BLOCK CAPITALS.

<table>
<thead>
<tr>
<th>SURNAMEnumber</th>
<th>Patient visited this hospital before? Y / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRST NAME</td>
<td>NHS Hospital Number</td>
</tr>
<tr>
<td>Gender M / F</td>
<td>D.O.B. Patient aware the referral is urgent? Y / N</td>
</tr>
<tr>
<td>Address</td>
<td>First language</td>
</tr>
<tr>
<td>Post Code</td>
<td>Interpreter required? Y / N</td>
</tr>
<tr>
<td>Daytime Telephone</td>
<td>Home Telephone (if different) / Mobile No.</td>
</tr>
</tbody>
</table>

### SECTION 2 – PRACTICE INFORMATION. USE PRACTICE STAMP IF AVAILABLE.

<table>
<thead>
<tr>
<th>Referring GP</th>
<th>Date of referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practice Address</td>
<td>Telephone</td>
</tr>
<tr>
<td>Post Code</td>
<td>Fax</td>
</tr>
</tbody>
</table>

### SECTION 3 – CLINICAL INFORMATION. PLEASE TICK THE RELEVANT BOXES.

**Symptoms**

- [ ] Dysphagia
- [ ] Worsening dyspepsia
  - Age > 55 years, unexplained and persistent (4-6 weeks) recent-onset dyspepsia
- [ ] Cholestatic jaundice
- [ ] Unexplained upper ab pain and weight loss +/- back pain
- [ ] Chronic GI bleeding

**Clinical Examination & Results**

- [ ] Epigastric / abdominal mass
- [ ] Hepatomegaly
- [ ] Obstructive jaundice
- [ ] Ultrasound scan? Y / N
- [ ] Suspicious barium meal result
- [ ] Iron deficiency anaemia
  - Hb =
  - Ferritin =
- [ ] Known dysplasia, atrophic gastritis or intestinal metaplasia
- [ ] Barrett’s oesophagus
- [ ] Peptic ulcer surgery > 20 years ago

**Risk Factors**

- [ ] Known dysplasia, atrophic gastritis or intestinal metaplasia
- [ ] Barrett’s oesophagus
- [ ] Epigastric / abdominal mass
- [ ] Hepatomegaly
- [ ] Obstructive jaundice
- [ ] Ultrasound scan? Y / N
- [ ] Suspicious barium meal result
- [ ] Iron deficiency anaemia
  - Hb =
  - Ferritin =
- [ ] Known dysplasia, atrophic gastritis or intestinal metaplasia
- [ ] Barrett’s oesophagus
- [ ] Peptic ulcer surgery > 20 years ago

**History**

- [ ] Previous investigation of upper GI tract
  - Location
  - Diagnosis

**Additional information**

Continue on separate sheet, and attach patient computer record summary if available.
Refer urgently patients:

- Dysphagia
- Unexplained upper abdominal pain and weight loss, with or without back pain
- Upper abdominal mass with or without dyspepsia
- Obstructive jaundice (depending on clinical state)
- Patients of any age with dyspepsia and any of the following
  - Chronic gastrointestinal bleeding
  - Progressive unintentional weight loss
  - Persistent vomiting
  - Iron deficiency anaemia
  - Epigastric mass
  - Suspicious barium meal result
- Patients aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone.

Consider an urgent referral for patients presenting with:

- Persistent vomiting and weight loss in the absence of dyspepsia
- Unexplained weight loss or iron deficiency anaemia in the absence of dyspepsia
- Unexplained worsening of dyspepsia and
  - Barrett’s oesophagus
  - Known dysplasia, atrophic gastritis or intestinal metaplasia
  - Peptic ulcer surgery over 20 years ago.

Use this proforma to refer urgently (2 Week Wait)

Investigations in Primary Care:

- When referring, a full blood count may assist specialist assessment in the outpatient clinic. This should be carried out in accordance with local arrangements.
- For all patients with new-onset dyspepsia, consider a full blood count to detect iron deficiency anaemia.

Patient information and support:

Consider the information and support needs of patients and the people who care for them while they are waiting for the referral appointment. Resources for GPs to use are available from the Cancer Network on 020 7188 7090, or visit our website www.selcn.nhs.uk.

Approved by the South East London Cancer Network in July 2012

For comments or additional copies contact the Network on Tel 020 7188 7090 / Fax 020 7188 7120, or visit our website: www.selcn.nhs.uk.
Appendix 2: Inter-Trust Referral Forms

Hepatic metastases inter-Trust referral

To: HPB Team  A/o CONSULTANT NAME:  (If applicable)

<table>
<thead>
<tr>
<th>New patient</th>
<th>☐</th>
<th>Response to treatment</th>
<th>☐</th>
<th>Relapse</th>
<th>☐</th>
<th>Other</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient:</td>
<td></td>
<td></td>
<td></td>
<td>GP:</td>
<td></td>
<td>Address:</td>
<td></td>
</tr>
<tr>
<td>Surname:</td>
<td></td>
<td></td>
<td></td>
<td>GP Practice Code:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forename:</td>
<td></td>
<td></td>
<td></td>
<td>Dr:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Birth:</td>
<td></td>
<td></td>
<td></td>
<td>Address:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHS No:</td>
<td></td>
<td></td>
<td></td>
<td>Post code:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital No:</td>
<td></td>
<td></td>
<td></td>
<td>Tel. no:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Address:</td>
<td></td>
<td></td>
<td></td>
<td>Fax no:</td>
<td></td>
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<tr>
<td>Postcode:</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please include any of the below information if available but please do not delay referring the patient if it is not obtainable.

**Primary diagnosis:**

- Date of primary diagnosis:  KRAS status: mutant / wild type / not yet checked

**Primary Treated:**  Y / N  If not yet but planned – date:

- How Treated: Neo-adjuvant therapy  Surgery  Adjuvant therapy

**Date treated:**

**If Surgery was this an Elective / Emergency procedure (delete as applicable)**

**Metastatic disease suspected:** at primary diagnosis / metachronously

**Details of neo-adjuvant therapy: (if applicable)**

<table>
<thead>
<tr>
<th>Type:</th>
<th>Surgical details: e.g. operation type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start date:</td>
<td></td>
</tr>
<tr>
<td>Completion date:</td>
<td></td>
</tr>
<tr>
<td>Overall response:</td>
<td></td>
</tr>
</tbody>
</table>

**Surgical details:**

<table>
<thead>
<tr>
<th>Type:</th>
<th>Surgical details: e.g. operation type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start date:</td>
<td></td>
</tr>
<tr>
<td>Completion date:</td>
<td></td>
</tr>
<tr>
<td>Overall response:</td>
<td></td>
</tr>
</tbody>
</table>
Has patient had adjuvant chemotherapy? Y / N
If Y – please state regime:

Date started:

Date completed:

OR

Date due to complete:

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Pre chemo</th>
<th>Post chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>USS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pre op CEA: Date:
Post op CEA: Date:
Current CEA: Date:

Have pathology reports/slides been sent? Y / N
To:

Have imaging results been sent? Y / N
CD (DICOM compatible)/ Image link

FOR MDM DISCUSSION ALL IMAGING AND HISTOLOGY SHOULD BE PROVIDED

Reason for referral:
Advice Only Assessment for surgery Assessment for RFA
Other: pls state:

Question(s) to be answered by multi-disciplinary team meeting:

ESSENTIAL: patient’s eGFR: date:

Has patient been informed of referral?

Provisional diagnosis:

Patient fitness to travel to centre, requires transport?
Patient preference/concerns re treatment?

Refers by: at:

Contact details:
Fax no. please (ESSENTIAL for rapid feedback):

Date: CNS Name:
Additional information or attach referral letter: pls include any relevant past medical history

<table>
<thead>
<tr>
<th>Outcome: MDM Centre use only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient listed for mdm: Y / N: If Y date</td>
</tr>
<tr>
<td>If N pls state why?</td>
</tr>
<tr>
<td>Outcome of discussion sent to referee? Y / N</td>
</tr>
<tr>
<td>If Y date If N pls state why?</td>
</tr>
<tr>
<td>Completed by: (name in capitals) (signature)</td>
</tr>
</tbody>
</table>

FOR MDM DISCUSSION ALL IMAGING AND HISTOLOGY SHOULD BE PROVIDED
# Hepato-biliary and pancreatic inter-Trust referral

<table>
<thead>
<tr>
<th>New patient □</th>
<th>Response to treatment □</th>
<th>Relapse □</th>
<th>Other □</th>
<th>Please specify below*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>GP</td>
<td>GP Practice Code:</td>
<td>Dr:</td>
<td></td>
</tr>
<tr>
<td>Surname:</td>
<td></td>
<td>Address:</td>
<td></td>
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</tr>
<tr>
<td>Forename:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Birth:</td>
<td></td>
<td>Post code:</td>
<td>Tel. no:</td>
<td></td>
</tr>
<tr>
<td>NHS No:</td>
<td></td>
<td>Tel. no:</td>
<td>Fax no:</td>
<td></td>
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<tr>
<td>Hospital No:</td>
<td></td>
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</tr>
<tr>
<td>Address:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Please include any of the below information if available but please do not delay referring the patient if it is not obtainable.**

**Date of initial referral letter:**
*Applies to initial referral from GP, A&E, screening or other consultant*

<table>
<thead>
<tr>
<th>Date 1st seen:</th>
<th>seen by (Cons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority type:</td>
<td>□ 2ww □ Other (please state):</td>
</tr>
</tbody>
</table>

**Presenting symptoms**
- Abdominal mass
- Dark urine / pale stools
- Weight loss
- Jaundice
- Anaemia
- If Pain – site and type

**Relevant medical / surgical history**
- Gallstones
- Hypertension
- Weight loss
- Peptic Ulcer
- Other specify
  - Hx of cancer
  - if Y type & outcome
  - Pre-existing liver disease?
  - if Y type?

**Reason for referral:**
- Advice only (MDM) □
- MDM & consultation (OPD) □
- Transfer (urgent)* □
- For ERCP +/- stent □
- PTC+/- stent □
- EUS □
- Biopsy □
- Other □ pls state
Question(s) to be answered by multi-disciplinary team meeting:

Has patient been informed of diagnosis?

What diagnostics have been performed?

Provisional diagnosis:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Date</th>
<th>Histology</th>
<th>Type</th>
<th>Differentiation</th>
<th>Brushing</th>
<th>High Grade Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERCP</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Staging CT scan</td>
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<td>Biopsy</td>
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<tr>
<td>MRI</td>
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<td></td>
</tr>
</tbody>
</table>

FOR MDM DISCUSSION ALL IMAGING AND HISTOLOGY SHOULD BE PROVIDED

<table>
<thead>
<tr>
<th>Have pathology reports/slides been sent? (please send to HPB Oncology Office)</th>
<th>Have imaging results been sent? CD/ Image link (if CD, must be DICOM compatible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSENTIAL: patient’s eGFR:</td>
<td></td>
</tr>
<tr>
<td>Patient fitness to travel to centre:</td>
<td></td>
</tr>
<tr>
<td>Patient preference/concerns re treatment?</td>
<td></td>
</tr>
</tbody>
</table>

Referred by: at:

Contact details:
Tel: Fax:
Email:

Date: Day in patient pathway:
### Additional information or attach referral letter:

<table>
<thead>
<tr>
<th>Outcome:</th>
<th>Centre use only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient listed for MDM: Y / N: If Y date</td>
<td></td>
</tr>
<tr>
<td>If N pls state why?</td>
<td></td>
</tr>
<tr>
<td>Outcome of discussion sent to referee? Y / N</td>
<td></td>
</tr>
<tr>
<td>If Y date If N pls state why?</td>
<td></td>
</tr>
<tr>
<td>Completed by: (name in capitals) (signature)</td>
<td></td>
</tr>
</tbody>
</table>

FOR MDM DISCUSSION ALL IMAGING AND HISTOLOGY SHOULD BE PROVIDED
Hepatocellular carcinoma (HCC) inter-Trust referral

<table>
<thead>
<tr>
<th>New patient</th>
<th>Response to treatment</th>
<th>Relapse</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

*Please specify below*

| Patient
Surname:          | GP
Forename:         | GP Practice Code:
Date of Birth:    | Dr:
NHS No:           | Address:
Hospital No:      | Post code:
Address:          | Tel. no:
Postcode:         | Fax no:
Tel. no:          | Email:
Patient’s e-mail: |

Please include any of the below information if available but please do not delay referring the patient if it is not obtainable.

**Date of initial referral letter:**
*Applies to initial referral from GP, A&E, screening or other consultant*

**Date 1st seen:**
*seen by (Cons):*

**Priority type:** ☐ 2ww ☐ Other (please state):

**Clinical Presentation:**

<table>
<thead>
<tr>
<th>Known CLD diagnosis during surveillance</th>
<th>Constitutional symptoms Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decompenated liver disease Y/N</td>
<td>If yes please specify ↓</td>
</tr>
<tr>
<td>If yes: Please Specify ↓</td>
<td>Pain</td>
</tr>
<tr>
<td>Ascites</td>
<td>If pain Site &amp; Type....................</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Hepatic encephalopa hy</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Variceal bleed</td>
<td>Lethargy</td>
</tr>
</tbody>
</table>

**Relevant past medical history:**

<table>
<thead>
<tr>
<th>Known liver disease Y / N</th>
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</thead>
<tbody>
<tr>
<td>If yes aetiology: ↓</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>HBV</td>
</tr>
<tr>
<td>HCV</td>
</tr>
<tr>
<td>NASH</td>
</tr>
<tr>
<td>PBC</td>
</tr>
<tr>
<td>Haemochromatosis</td>
</tr>
<tr>
<td>Other; please state:</td>
</tr>
<tr>
<td>Significant cardiac disease:</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Reason for referral: Advice only (MDM) □ MDM &amp; consultation (OPD) □ Transfer (urgent)* □</td>
</tr>
<tr>
<td>Question(s) to be answered by multi-disciplinary team meeting:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Has patient been informed of diagnosis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>What diagnostics have been performed?</td>
</tr>
<tr>
<td>Provisional diagnosis:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ultrasound</th>
<th>Date:</th>
<th>Histology Type:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staging CT scan</td>
<td>Date:</td>
<td>Differentiation:</td>
</tr>
<tr>
<td>MRI</td>
<td>Date:</td>
<td>Brushing:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High Grade Dysplasia:</td>
</tr>
</tbody>
</table>

**FOR MDM DISCUSSION ALL IMAGING AND HISTOLOGY SHOULD BE PROVIDED**

<table>
<thead>
<tr>
<th>Have pathology reports/slides been sent?</th>
<th>Have imaging results been sent?</th>
</tr>
</thead>
<tbody>
<tr>
<td>(please send to HPB Oncology Office)</td>
<td>Image link/CD (if CD, must be DIACOM compatible)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient fitness to travel to centre:</th>
<th>Performance Status:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient preference/concerns re treatment?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Referred by (Cons):</th>
<th>at:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact details (telephone):</td>
<td></td>
</tr>
<tr>
<td>Fax no:</td>
<td>E-mail:</td>
</tr>
</tbody>
</table>

| Referral to King’s Date: | Day in patient pathway: |

**Blood Results:** MUST INCLUDE: eGFR, bilirubin, INR, Alb, ALT, AST, ALP, GGT, Hepatitis serology, auto-antibodies, CA19-9, CA125 & AFP.
Additional information or attach referral letter:

<table>
<thead>
<tr>
<th>Outcome: Centre use only</th>
</tr>
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<tbody>
<tr>
<td>Patient listed for MDM: Y / N: If Y date</td>
</tr>
<tr>
<td>If N pls state why?</td>
</tr>
<tr>
<td>Outcome of discussion sent to referee? Y / N</td>
</tr>
<tr>
<td>If Y date: If N pls state why?</td>
</tr>
<tr>
<td>Completed by: (name in capitals) (signature)</td>
</tr>
</tbody>
</table>

FOR MDM DISCUSSION ALL IMAGING AND HISTOLOGY SHOULD BE PROVIDED
# Gastrointestinal neuroendocrine tumour referral proforma

<table>
<thead>
<tr>
<th>Newly diagnosed patient ☐</th>
<th>Previously treated surgically ☐</th>
<th>Previously treated with chemotherapy ☐</th>
<th>Other ☐</th>
<th>Please specify below*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surname:</td>
<td></td>
<td>GP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forename:</td>
<td></td>
<td>Dr:</td>
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<td></td>
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<tr>
<td>Date of Birth:</td>
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<td>Address:</td>
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</tr>
<tr>
<td>NHS No:</td>
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<tr>
<td>Tel. no:</td>
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</tr>
<tr>
<td>Email:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please include any of the below information if available but please do not delay referring the patient if it is not obtainable.

**Date of initial referral letter:**

*Applies to initial referral from GP, A&E, screening or other consultant*

**Date 1st seen:**

seen by (Cons)

**Priority type:**

☐ 2ww  If 2WW give start date  ☐ Other (please state):

**Initial Presenting symptoms** (i.e. prior to any local treatment)

<table>
<thead>
<tr>
<th>Abdominal mass</th>
<th>Dyspepsia</th>
<th>Obstructed bowel</th>
<th>Nausea/Vomiting</th>
<th>Weight loss</th>
<th>Flushing</th>
<th>Jaundice</th>
<th>Diarrhoea</th>
<th>Anaemia</th>
<th>Pain</th>
</tr>
</thead>
</table>

**Relevant medical /surgical history**

- Heart disease
- Lung disease
- Neurological disease
- Peptic Ulcer
- + ve Family History
- Other specify
- Diabetes
- Hx of cancer

* if Y type & outcome

*Pre-existing liver disease?  If Y type?

<table>
<thead>
<tr>
<th>Chromogranin A</th>
<th>Urinary 5HiAA</th>
<th>GAWK B</th>
<th>Gut Hormones</th>
</tr>
</thead>
</table>

111
**Reason for referral:**
Advice only (MDM) □ MDM & consultation (OPD) □ Transfer (urgent)* □

Question(s) to be answered by multi-disciplinary team meeting:

Has patient been informed of diagnosis?

What diagnostics have been performed?

Provisional diagnosis:

<table>
<thead>
<tr>
<th>Ultrasound</th>
<th>Date:</th>
<th>Histology</th>
<th>Type:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreoscan</td>
<td>Date:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staging CT scan</td>
<td>Date:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>Date:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>Date:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FOR MDM DISCUSSION ALL IMAGING AND HISTOLOGY SHOULD BE PROVIDED

<table>
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<tr>
<th>Have pathology reports/slides been sent? (please send to HPB Oncology Office)</th>
<th>Have imaging results been sent? Please use IEP Image link for CT/MRI CD for all nuclear medicine imaging (CD must be DICOM compatible)</th>
</tr>
</thead>
</table>

**ESSENTIAL:** patient’s eGFR:

Patient fitness/willingness to travel to centre: Yes / No

Patient preference/concerns re treatment?

Referred by: at:

Contact details:
Tel: Fax:
Email:

Date: Day in patient pathway:
Additional information or attach referral letter: PLEASE SEND SCAN REPORTS as well as sending images.

<table>
<thead>
<tr>
<th>Outcome: Centre use only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient listed for MDM: Y / N: If Y date</td>
</tr>
<tr>
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</tr>
<tr>
<td>If Y date If N pls state why?</td>
</tr>
<tr>
<td>Completed by: (name in capitals) (signature)</td>
</tr>
</tbody>
</table>

FOR MDM DISCUSSION ALL IMAGING AND HISTOLOGY SHOULD BE PROVIDED
Appendix 3: Quality of Life – Management of the Side Effects of Cancer Therapies

For many years, quality of life after treatment of upper gastrointestinal malignancy was not an important priority for oncologists or surgeons. With advances in treatment over the last two decades, far more people, many cured, are surviving for significantly longer.

Common physical symptoms impinging on quality of life after surgery, radiotherapy and chemotherapy for upper gastrointestinal cancers include difficulties with swallowing, regurgitation, maintaining weight, abdominal pain, nausea, vomiting, diarrhoea, steatorrhoea and wind.

Active management of these symptoms with appropriate referral to specialist gastroenterologists should be considered within the context of the Survivorship programme.

Mouth Care

All patients receiving chemotherapy should take home adequate supplies of Corsodyl (mint flavoured) mouth wash (20 mls bd - qds), according to treatment regimen.

Elderly Patients

There is currently no formal protocol for dose reduction in elderly patients or those who are considered to be particularly frail. There is a clinical impression that elderly patients have a reduced bone marrow tolerance.

Miscellaneous Information

Antibiotics and antiemetics policies are detailed by individual Trust’s chemotherapy protocols, together with other therapeutic policies such as pain control and H₂ antagonist cover. Hydration intravenously is particularly important in cisplatin based chemotherapy and should also be used. Dose reductions for chemotherapy according to local policies

Peritoneal Drainage

An ultrasound to locate the point of maximum fluid is recommended in all patients.

a) Puncture site needs to be away from scars, tumour masses, distended bowel, liver and bladder, or other organs; right or left lower quadrant is usually safe.

b) In patients who have had multiple paracentesis, the ascites may become loculated.

c) Using aseptic technique, the puncture site down to the peritoneum should be well infiltrated with 2% lignocaine.

d) The catheter must be used according to the manufacturer’s instructions.

e) It is known that prolonged drainage can lead to catheter infection and peritonitis. In most cases free drainage of ascites should be allowed to occur, this has been shown to be safe for up to 5 litres of drainage. IV fluid replacement and clamping of the drain (to reduce flow) should not be used routinely. These measures may be considered if dehydrated, hypotensive, in the presence of renal impairment, or if >5 litres of fluid has been drained.
BP and pulse should be monitored closely. In the event of cardiovascular compromise the drain should be clamped and the doctor informed. The drain should remain in no longer than 12 hours, renal function should be checked the following day.

f) Fluid should be sent for MC&S and cytology if not done previously.

g) After catheter removal, a colostomy bag may be placed over the puncture site for a few days if necessary.

In patients with recurrent ascites, the Pleurex drainage system should be considered for palliation. When pleurex system is used, written information should be provided to local nursing teams and patient.

Indwelling Venous Catheters

To deliver infused 5-FU regimens an indwelling venous catheter is required. Occasionally patients with poor peripheral access also require dwelling devices.

- Skin tunnelled catheters
- PICC line (Peripherally Inserted Central Catheter)

Not all patients are suitable for PICC insertion, and patients require assessment of antecubital veins.

The choice of device depends on patient’s preference and availability. Patients requiring to commence chemotherapy urgently should be admitted and commenced on peripheral therapy, insertion of an indwelling catheter can then be arranged.

All patients require education in the safe care of their indwelling catheter, written information should be provided with contact telephone numbers in case of difficulty.

Line-associated Thrombosis

Patients who present with arm or neck swelling on the side of the line must be assumed to have line-associated clot until proven otherwise. Patients should be investigated with doppler ultrasound or contrast imaging to confirm the diagnosis. If significant swelling has occurred then anticoagulation and line removal can be considered before the diagnosis is confirmed. These patients should subsequently undergo imaging investigation.

Once a patient has developed a line-associated thrombosis, he/she should remain on anti-coagulation until a new line is inserted (this is most easily done with LMWH which can be stopped on the day prior to line insertion) and then maintained on warfarin throughout the duration of the new line. Substitution of infused 5FU with capecitabine should be considered, to avoid further line placement.

Some patients will develop pain associated with their indwelling catheter with no evidence of thrombosis. This pain is typically described as an ache occurring over the posterior aspect of the scapula. Although Doppler studies should be performed in these cases to exclude the presence of clot, in the majority they will prove to be negative.

Simple analgesics should be prescribed but if they are ineffective then line removal may be necessary.

Wigs

Scalp cooling is used to prevent alopecia with regimens containing anthracyclines. If patients develop alopecia, they should be offered a wig.

Scalp cooling is contraindicated if oxaliplatin in the regimen.
Appendix 4: LCA Specialist Palliative Care Referral Form

Specialist Palliative Care (SPC) Community and SPC Inpatient Unit Referral Form

<table>
<thead>
<tr>
<th>Specialist Palliative Care Community Teams &amp; Inpatient Units across South &amp; West London</th>
</tr>
</thead>
</table>
| Greenwich & Bexley Community Hospice  
  Bostall Hill, Abbey Wood SE2 0GB  
  Home care: Tel: 020 83205837 Fax: 020 83205839  
  Admissions: Tel: 020 8312244 Fax: 020 83122444 |
| Lewisham Macmillan Community Team  
  Lewisham High Street SE13 6LH  
  Tel: 020 8333 3017 Fax: 020 8333 3270 |
| St Christopher's Hospice  
  Lawrie Park Rd, London SE26 6DZ  
  Home care: Tel: 020 8776 5656 Fax: 020 87765798  
  Admissions: Tel: 020 87684582 Fax: 02086595051  
  St Christopher’s Bromley  
  Tel: 01689 825755 Fax: 01689 892999 |
| Guy’s & St Thomas’ Community Team  
  Guy’s Hospital, Great Maze Pond SE1 9RT  
  Tel: 020 71884754 Fax: 020 71884748 |
| Meadow House Hospice  
  Southall UB1 3HW  
  Tel: 020 89657159 Fax: 020 89657556 |
| St John’s Hospice  
  Grove End Road, St John’s Wood NW8 9NH  
  Tel: 020 78064040 Fax: 020 78064041 |
| Harlington Hospice  
  St Peter’s Way, Harlington UB3 5AB  
  Tel: 020 87590453 Fax: 020 87590600 |
| Michael Sobell House  
  Northwood, Middlesex HA6 2RN  
  Tel:01923 844531 Fax: 01923 844565 |
| St Luke’s Hospice  
  Kenton Road, Harrow HA3 0YG  
  Tel: 020 83828000 Fax: 020 83828080 |
| Harrow Community Team  
  Kenton Road, Harrow HA3 0YG  
  Tel: 020 83828084 Fax: 020 83828085 |
| Pembroke Palliative Care Centre  
  Exmoor Street, W10 6DZ  
  Tel: 020 8962 4410 Inpatient Fax: 020 89624422 Community Services Fax: 020 89624413 |
| St Raphael’s Hospice  
  London Road, North Cheam SM3 9DX  
  Tel: 020 80997777 Fax: 020 8099 1724 |
| Harlington Hospice  
  St Peter’s Way, Harlington UB3 5AB  
  Tel: 020 87590453 Fax: 020 87590600 |
| Hillingdon Community Team  
  Pold Heath Road, Uxbridge UB8 3NN  
  Tel:01895 279412 Fax: 01895 279452 |
| Princess Alice Hospice  
  West End Lane, Esher KT10 8NA  
  Tel: 01372 461804 Fax: 01372 472037 |
| Trinity Hospice  
  Claypath Common SW4 0RJ  
  Tel: 020 7787 1000 Ref & Admissions Nurse: 020 77871065 Fax: 020 7787 1067 |

For further information and advice on these services, please visit the Help the Hospices service directory at: http://www.helpthehospices.org.uk/about-hospice-care/find-a-hospice/uk-hospice-and-palliative-care-services/ and enter the postcode provided above.

Every LCA hospital has a Specialist Palliative Care team; if your patient is a hospital inpatient, please contact the team, via the relevant hospital switchboard.

FAX MESSAGE

<table>
<thead>
<tr>
<th>From:</th>
<th>To:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fax No:</td>
<td>Date:</td>
</tr>
<tr>
<td>No. of pages (incl cover sheet):</td>
<td></td>
</tr>
</tbody>
</table>

Additional Information

Confidentiality: The content of this fax and attached documents are confidential and intended for the use of the addressee designated above. If you are not the addressee, you are hereby notified that you may not disclose, reproduce or otherwise disseminate or make use of this information for yourself or any third party. If you have received this in error, please notify us on the telephone number given above.

PLEASE SEND COPIES OF RECENT CLINICAL CORRESPONDENCE WITH THIS FORM – including recent clinic letters, blood tests and most recent imaging

NB. INSUFFICIENT INFORMATION MAY DELAY PATIENT ASSESSMENT

PATIENT NAME .............................................. NHS No: ..............................................

LCA Palliative Care Group Revised April 2014
**Referral Form for SPC Community and Inpatient Units**  
(2/3)

### Essential Patient Details
- **Surname**
- **Male/Female**
- **Age**
- **Patient consent to palliative care involvement?** Yes ☐ No ☐
- **Is GP aware of referral?** Yes ☐ No ☐
- **First Name**
- **DoB**
- **Address**
- **Postcode**
- **Marital Status**
- **Ethnicity**
- **Tel**
- **Mob**
- **NHS number**
- **Hospital No.**

### Primary diagnosis(es)

### Communication
- **Fluent in English?** Yes ☐ No ☐ (If ‘no’ proceed with remaining questions)
- **First Language, if not English:**
- **Would interpreter be helpful to patient and Palliative Care staff?** Yes ☐ No ☐

### Next of Kin/Patient Representatives
- **Name**
- **Address**
- **Telephone**
- **Relationship to patient**

### District Nurse
- **Yes ☐ No ☐**
- **Name**
- **Address**
- **Telephone**
- **Fax**

### Main Carer (if different from above)
- **Name**
- **Telephone**
- **Relationship to patient**
- **Fax**

### Social Services
- **Yes ☐ No ☐**
- **Name**
- **Telephone**
- **Fax**

### General Practitioner
- **Name**
- **Address**
- **Postcode**
- **Telephone**
- **Fax/email**
- **CCG:**

### Reason for Referral
- **Pain/symptom control**
- **Emotional/psychological support**
- **Social/financial**
- **Assessment for hospice admission**
- **Carer support**
- **Other reason (please give details below):**

### Service requested
- **Home assessment and support**
- **Hospital assessment**
- **Day Care**
- **Outpatient service**
- **Hospice at Home**
- **Respite / symptom control / terminal care**

### The patient is currently
- **At Home**
- **In Hospital (see over)**
- **Other e.g. Nursing Home**
- **Please specify**
- **Does patient live alone?** Yes ☐ No ☐

### Any access issues (e.g. key safe):
- **MRSA Status**
- **Positive ☐ Negative ☐ Not known ☐**

### Any other communicable infection:

### Special device in situ?
- **Yes ☐ No ☐**
- **If yes, give details (e.g. trache / PEG / ICD / NIPPV)**

### Referrer’s Name (please print)
- **Contact number:**
- **Bleep no:**
- **Hospital/Surgery:**

### IS REFERRAL URGENT (assess within 2 working days)?
- **Yes ☐ No ☐**

**IF URGENT, PLEASE PHONE US FOR IMMEDIATE ADVICE**

---

LCA Palliative Care Group Revised April 2014

117
Referral Form for SPC Community and Inpatient Units (3/3)

<table>
<thead>
<tr>
<th>In-Patient details</th>
<th>Patient Name:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>NHS No:</td>
</tr>
<tr>
<td>Ward</td>
<td>Telephone</td>
</tr>
<tr>
<td>Key worker</td>
<td>Date of discharge (if known)</td>
</tr>
<tr>
<td>Consultant</td>
<td>Is Palliative Care team involved? Yes  No</td>
</tr>
</tbody>
</table>

Brief History of diagnosis(es) and Key treatments

<table>
<thead>
<tr>
<th>Date</th>
<th>Progression of disease and investigations/treatment</th>
<th>Consultant and hospital</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

Current palliative care problems

1.  
2.  
3.  
4.  
5.  
6.  

Patient Mobility: Bariatric Nursing required? Yes  No

Any other comments/information (including preferences expressed about care or other psychosocial or spiritual issues)

---

Referrer's expectation of current treatment (please circle) symptom control / life prolonging / curative

Prognosis: In your opinion, is the patient

Stable? Yes  No  Unstable? Yes  No  Deteriorating? Yes  No  Dying? Yes  No

Is death anticipated within: Months  Weeks  Days

Patient on Coordinate My Care? Yes  No  Unknown

On the GSF register? Yes  No  Unknown

DNACPR in place? Yes  No

Past Medical and Psychiatric History

Current Medication

Known Drug Sensitivities/Allergies:

Yes  No  Details:

Insight: Has patient been told diagnosis? Yes  No  Is the carer aware of patient's diagnosis? Yes  No  Does patient discuss the illness freely Yes  No

Please ensure patients are aware information will be held on computer according to the Data Protection Act.

Referrer's signature:  Name: (please print)
Job title:  Contact number:  Bleep no:
Surgery or Hospital:  Date:

LCA Palliative Care Group Revised April 2014

118
Appendix 5: LCA Key Worker Policy

Definition

A key worker is a person who, with the patient’s consent and agreement, takes a key role in coordinating the patient’s care and promoting continuity, ensuring the patient knows who to access for information and advice in relation to their cancer diagnosis. In addition, the key worker will facilitate patients making informed decisions about their treatment.

The implementation of the key worker role is a requirement of the National Cancer Peer Review Programme and detailed in the Manual for Cancer Services, originally published by the National Cancer Action Team (NCAT), and related site-specific Improving Outcomes Guidance, issued by the National Institute for Health and Care Excellence (NICE).

Principles and responsibilities

Designation

1. The key worker is a named clinical member of the site-specific multidisciplinary team (MDT), and acts as the point of contact between the patient and MDT.
2. The key worker is a healthcare professional.
3. The key worker is assigned by the core clinical nurse specialist of an MDT, agreed by the MDT and recorded within the patient record and multidisciplinary meeting proforma.
4. The name of the key worker, designation and contact details will also be recorded in the patient handheld record (PHR), if used, and included in all correspondence and in the patient medical records. All entries in the medical notes will comply with the NHS Litigation Authority standards.

Access

5. All cancer patients will be made aware of their allocated key worker, but have the right to ask for an alternative if they prefer. This will usually happen at diagnosis.
6. The key worker will provide a contact number to all the patients for whom they act as the key worker.

Multi-professional communication

7. If a more appropriate person is identified as a key worker at a point in the patient’s pathway, this will be discussed and agreed by the patient and the new key worker, and recorded in the patient’s notes. This situation is most likely to arise with referral to the specialist palliative care team. In such cases the specialist palliative care clinical nurse specialist will check if a key worker has already been identified for the patient by the relevant tumour MDT. The specialist palliative care clinical nurse specialist will then negotiate and document care responsibilities in the patient’s notes.
8. The key worker may change as patients pass through various stages of the care trajectory or when care is transferred to a different Trust. It is the responsibility of the key worker to hand over to the next one, to document this in the patient’s notes and to keep the patient informed.
9. The key worker will lead on patient communication issues and coordination of the pathway for patients referred to the team.
10. The key worker will ensure that the patient pathway is coordinated and that all relevant information is transferred to the appropriate professionals as the patient moves across care boundaries, e.g. on admission to and discharge from institutions, when care is transferred between teams.

11. The key worker has responsibility for ensuring holistic needs assessments (HNAs) are recorded/document in patient records.

**Patient communication and support**

12. Where possible, the key worker will be available to support the patient on diagnosis to signpost and provide them with information and contacts for the MDT, national information and support services, self-help groups and associated site-specific support.

13. If the key worker is not available at the time of diagnosis, the person who is providing support at the time will ensure that the patient is aware of the key worker role and provide the relevant contact details.

14. The key worker will be accessible to the patient as a constant point of contact, handing over to colleagues when unavailable and making sure that the patient has clear information about alternative contacts and cover arrangements.

15. The key worker will provide information, care and support throughout the patient journey *regardless of the patient’s condition*, liaising between health professionals to ensure continuity of care and a seamless service.

**Data/audit**

16. The key worker will contribute to the audit of the key worker role in their organisation.

**Annex A**

*NCAT peer review standard*

There should be an operational policy whereby a single named key worker for the patient’s care at a given time is identified by the MDT members for each individual patient and the name and contact number of the current key worker is recorded in the patient’s case notes. The responsibility for ensuring that the key worker is identified should be that of the nurse MDT member(s).

The above policy should have been implemented for patients who came under the MDT’s care after publication of these measures and who are under their care at the time of the peer review visit.

**Notes**

- According to the NICE supportive and palliative care guidance, a key worker is a person who, with the patient’s consent and agreement, takes a key role in coordinating the patient’s care and promoting continuity, e.g. ensuring that the patient knows who to access for information and advice. This is not intended to have the same connotation as the key worker in social work.

It may be necessary to agree a single key worker across both a cancer site-specific MDT and the specialist palliative care MDT for certain patients.
Appendix 6: Children’s Pathways

Children below the age of 16 years with a diagnosis of cancer or suspected cancer must be referred to the paediatric oncology team at the Principal Treatment Centre (PTC) and must not be managed exclusively by adult site-specific teams.

- All patients <1 year from both North and South Thames should be referred to Great Ormond Street Hospital.
- The joint PTC for children aged 1 year to 16 years for South Thames is the Royal Marsden Hospital, Sutton and St George’s Hospital.
- The PTC for North Thames (including North West London) is Great Ormond Street Hospital and University College London Hospital.

For certain tumour types that are uncommon in children (e.g. skin, melanoma, head and neck, thyroid, gastrointestinal, hepatobiliary), the paediatric oncology team should liaise with the appropriate site-specific MDT for advice about management and to agree surgical interventions. However, overall responsibility for managing the patient remains with the paediatric oncology team.

Contact details for the children’s PTCs are below.

**South Thames PTC contacts**

<table>
<thead>
<tr>
<th>The Royal Marsden NHS Foundation Trust</th>
<th>Lead Clinician – Dr Julia Chisholm <a href="mailto:julia.chisholm@rmh.nhs.uk">julia.chisholm@rmh.nhs.uk</a> 020 8661 3549 Paediatric oncology on-call registrar (new referrals) 020 8915 6248 (24-hour line)</th>
</tr>
</thead>
</table>

**North Thames PTC contacts**

<table>
<thead>
<tr>
<th>Great Ormond Street Hospital for Children NHS Foundation Trust (patients aged &lt;13 years)</th>
<th>Lead Clinician – Darren Hargrave <a href="mailto:darren.hargrave@nhs.net">darren.hargrave@nhs.net</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>University College London Hospitals NHS Foundation Trust (patients aged ≥13 years)</td>
<td>Lead Clinician – Dr Sara Stoneham <a href="mailto:sara.stoneham@uclh.nhs.uk">sara.stoneham@uclh.nhs.uk</a> 020 3447 9950</td>
</tr>
</tbody>
</table>
Appendix 7: Teenagers and Young Adults

Teenagers aged 16–18 should be managed at a PTC for teenager and young adult (TYA) cancers. Those aged 19–24 are given the choice of being managed at a PTC or TYA designated hospital.

- The PTC for TYA for South Thames is the Royal Marsden Hospital, Sutton.
- The PTC for North Thames (including North West London) is University College London Hospital.

All patients within the age range 16 to 24, regardless of place of care, should be referred to the TYA MDT at the relevant PTC.

### South Thames PTC contacts

<table>
<thead>
<tr>
<th>Organization</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Royal Marsden NHS Foundation Trust</td>
<td>Lead Clinician – Dr Julia Chisholm&lt;br&gt;<a href="mailto:julia.chisholm@rmh.nhs.uk">julia.chisholm@rmh.nhs.uk</a>&lt;br&gt;020 8661 3549&lt;br&gt;TCT Nurse Consultant for Adolescents &amp; Young Adults – Louise Soanes&lt;br&gt;<a href="mailto:lsoanes@nhs.net">lsoanes@nhs.net</a></td>
</tr>
</tbody>
</table>

### London Cancer Alliance TYA designated centre contacts allied to Royal Marsden Hospital PTC

<table>
<thead>
<tr>
<th>Organization</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint centre (Guy’s and St Thomas’ NHS Foundation Trust/King’s College Hospital NHS Foundation Trust)</td>
<td>Lead Clinician – Dr Robert Carr&lt;br&gt;<a href="mailto:Robert.carr@gstt.nhs.uk">Robert.carr@gstt.nhs.uk</a>&lt;br&gt;Lead Nurse – Gavin Maynard-Wyatt&lt;br&gt;<a href="mailto:Gavin.maynard-wyatt@gstt.nhs.uk">Gavin.maynard-wyatt@gstt.nhs.uk</a></td>
</tr>
<tr>
<td>Joint centre (Guy’s and St Thomas’ NHS Foundation Trust/King’s College Hospital NHS Foundation Trust)</td>
<td>Lead Clinician – Dr Donal McLornan&lt;br&gt;<a href="mailto:donal.mclornan@nhs.net">donal.mclornan@nhs.net</a>&lt;br&gt;Lead Nurse – Gavin Maynard-Wyatt&lt;br&gt;<a href="mailto:Gavin.maynard-wyatt@gstt.nhs.uk">Gavin.maynard-wyatt@gstt.nhs.uk</a></td>
</tr>
<tr>
<td>St George’s Healthcare NHS Trust</td>
<td>Lead Clinician – Dr Jens Samol&lt;br&gt;<a href="mailto:jens.samol@stgeorges.nhs.uk">jens.samol@stgeorges.nhs.uk</a>&lt;br&gt;Lead Nurse – Linda Shephard&lt;br&gt;<a href="mailto:Linda.shephard@stgeorges.nhs.uk">Linda.shephard@stgeorges.nhs.uk</a></td>
</tr>
</tbody>
</table>

### North Thames PTC contacts

<table>
<thead>
<tr>
<th>Organization</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>University College London Hospitals NHS Foundation Trust</td>
<td>Lead Clinician – Dr Rachael Hough&lt;br&gt;<a href="mailto:Rachael.hough@uclh.nhs.uk">Rachael.hough@uclh.nhs.uk</a>&lt;br&gt;TCT Nurse Consultant for Teenagers &amp; Young Adults – Wendy King&lt;br&gt;<a href="mailto:wendy.king@uclh.nhs.uk">wendy.king@uclh.nhs.uk</a></td>
</tr>
</tbody>
</table>
London Cancer Alliance TYA designated centre contacts allied to University College London Hospital PTC

| Chelsea and Westminster Hospital NHS Foundation Trust | Chelsea and Westminster (HIV and skin only) | Lead Clinician – Dr Mark Bower (interim)  
Mark.Bower@chelwest.nhs.uk  
Lead Nurse – Kate Shaw (interim)  
Kate.Shaw@chelwest.nhs.uk |
|---|---|---|
| Imperial College Healthcare NHS Trust | Charing Cross | Lead Clinician – Dr Josu de la Fuente (deputy)  
j.delafuente@imperial.ac.uk  
Lead Nurse – Sinead Cope  
sinead.cope@imperial.nhs.uk |
| East and North Hertfordshire NHS Trust | Mount Vernon Cancer Centre | Lead Clinician (MVCC) – Dr Gordon Rustin  
grustin@nhs.net  
Lead Nurse (MVCC) – Laura Miles  
laura.miles@nhs.net |
Appendix 8: NCSI Treatment Summary

Dear Dr X

Re: Add in patient name, address, date of birth and record number

Your patient has now completed their initial treatment for cancer and a summary of their diagnosis, treatment and on-going management plan are outlined below. The patient has a copy of this summary.

<table>
<thead>
<tr>
<th>Diagnosis:</th>
<th>Date of Diagnosis:</th>
<th>Organ/Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Local/Distant</td>
</tr>
</tbody>
</table>

Summary of Treatment and relevant dates:

<table>
<thead>
<tr>
<th>Treatment Aim:</th>
</tr>
</thead>
</table>

Possible treatment toxicities and / or late effects:

<table>
<thead>
<tr>
<th>Advising entry onto primary care palliative or supportive care register</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes / No</td>
</tr>
<tr>
<td>DS 1500 application completed</td>
</tr>
<tr>
<td>Yes/No</td>
</tr>
<tr>
<td>Prescription Charge exemption arranged</td>
</tr>
<tr>
<td>Yes/No</td>
</tr>
</tbody>
</table>

Alert Symptoms that require referral back to specialist team:

<table>
<thead>
<tr>
<th>Contacts for re referrals or queries:</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Hours:</td>
</tr>
<tr>
<td>Out of hours:</td>
</tr>
</tbody>
</table>

Other service referrals made: (delete as nec)

<table>
<thead>
<tr>
<th>District Nurse</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHP</td>
</tr>
<tr>
<td>Social Worker</td>
</tr>
<tr>
<td>Dietician</td>
</tr>
<tr>
<td>Clinical Nurse Specialist</td>
</tr>
<tr>
<td>Psychologist</td>
</tr>
<tr>
<td>Benefits/Advice Service</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Secondary Care Ongoing Management Plan: (tests, appointments etc)

Required GP actions in addition to GP Cancer Care Review (e.g. ongoing medication, osteoporosis and cardiac screening)

Summary of information given to the patient about their cancer and future progress:

Additional information including issues relating to lifestyle and support needs:

Completing Doctor:  
Signature:  
Date:

GP READ CODES FOR COMMON CANCERS (For GP Use only). Other codes available if required.
(Note: System codes are case sensitive so always ensure codes are transcribed exactly as below).

<table>
<thead>
<tr>
<th>System 1</th>
<th>(5 digit codes)</th>
<th>All other systems</th>
<th>Version 3 five byte codes (October 2010 release)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung Malignant Tumour</td>
<td>XaOKG</td>
<td>Malignant neoplasm of bronchus or lung</td>
<td>B22z.</td>
</tr>
<tr>
<td>Carcinoma of Prostate</td>
<td>X78Y6</td>
<td>Malignant neoplasm of prostate</td>
<td>B46..</td>
</tr>
<tr>
<td>Malignant tumour of rectum</td>
<td>XE1vW</td>
<td>Malignant neoplasm of Rectum</td>
<td>B141.</td>
</tr>
<tr>
<td>Bowel Intestine</td>
<td>X78gK</td>
<td>Malignant neoplasm of Colon</td>
<td>B13..</td>
</tr>
<tr>
<td>Large Bowel</td>
<td>X78gN</td>
<td>Malignant neoplasm of female breast</td>
<td>B34..</td>
</tr>
<tr>
<td>Female Malignant Neoplasia</td>
<td>B34..</td>
<td>Malignant neoplasm of male breast</td>
<td>B35..</td>
</tr>
<tr>
<td>Male Malignant Neoplasia</td>
<td>B35..</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histology/Staging/Grade:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour grade</td>
<td>X7A6m</td>
<td>Tumour staging</td>
<td>4M6..</td>
</tr>
<tr>
<td>Dukes/Gleason tumour stage</td>
<td>XaOLF</td>
<td>Gleason grading of prostate Ca</td>
<td>4M0..</td>
</tr>
<tr>
<td>Recurrent tumour</td>
<td>XaOR3</td>
<td>Recurrence of tumour</td>
<td>4M6..</td>
</tr>
<tr>
<td>Local Tumour Spread</td>
<td>X7818</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mets from 1º</td>
<td>XaFr.</td>
<td>Metastatic NOS</td>
<td>BB13.</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative Radiotherapy</td>
<td>5149.</td>
<td>Radiotherapy tumour palliation</td>
<td>5149.</td>
</tr>
<tr>
<td>Curative Radiotherapy</td>
<td>XalpH</td>
<td>Radiotherapy</td>
<td>7M371</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>x71bL</td>
<td>Chemotherapy</td>
<td>8BAD.</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Xa851</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment Aim:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curative procedure</td>
<td>Xallm</td>
<td>Curative treatment</td>
<td>8BJ0.</td>
</tr>
<tr>
<td>Palliative procedure</td>
<td>XaL3</td>
<td>Palliative treatment</td>
<td>8BJ1.</td>
</tr>
<tr>
<td><strong>Treatment toxicities/late effects:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporotic #</td>
<td>Xa1TO</td>
<td>At risk of osteoporosis</td>
<td>1409.</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>XaELC</td>
<td>Osteoporosis</td>
<td>N330.</td>
</tr>
<tr>
<td>Infection</td>
<td>Xa9ua</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ongoing Management Plan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow up arranged (&lt;1yr)</td>
<td>8H8..</td>
<td>Follow up arranged</td>
<td>8H8..</td>
</tr>
<tr>
<td>Follow up arranged (&gt;1yr)</td>
<td>XaL.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No FU</td>
<td>8HA1.</td>
<td>No follow up arranged</td>
<td>8HA1.</td>
</tr>
<tr>
<td>Referral PRN</td>
<td>8HAZ.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Referrals made to other services:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>District Nurse</td>
<td>XaBsn</td>
<td>Refer to District Nurse</td>
<td>8H72.</td>
</tr>
<tr>
<td>Social Worker</td>
<td>XaBsr</td>
<td>Refer to Social Worker</td>
<td>8H75.</td>
</tr>
<tr>
<td>Nurse Specialist</td>
<td>XaAgq</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SALT</td>
<td>XaBT6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 9: Mitotane Treatment in Adrenocortical Carcinoma – King’s College Hospital Standard Operating Procedure

This standard operating procedure is to be used in the day-to-day management of patients taking Mitotane (o,p’-DDD; Lysodren®, HRA Pharma, Paris), in conjunction with the formulary guidelines for King’s College Hospital.

Introduction

Mitotane (o,p’-DDD) is an adrenolytic substance derived from DDT. Mitotane is activated through metabolism within the tumour cell with the exact mechanism of action remaining to be elucidated. Mitotane inhibits CYP11A1 and CYP11B1 and induces oxidative adrenal cell damage resulting in specific destruction and necrosis of adrenal cells. An additional effect of mitotane may derive from its inhibition of the multidrug resistance (MDR) gene and of its product, the MDR-1/P-glycoprotein. Over-expression of MDR-1/P-glycoprotein results in reduced susceptibility to cytotoxic chemotherapy.

Mitotane was used for treating metastatic adrenocortical cancer (ACC) for the first time in 1960 and is currently considered the standard treatment option for locally invasive and metastatic disease. Its effects on the disease progression are highly variable. Sustained remissions are the exception, but possible. Tumour-related hormone excess will be significantly reduced in 30–70% of patients and partial or complete regression of metastases will be achieved in 15–60%.

Use of mitotane in clinical practice has recently been greatly facilitated by the introduction of an assay monitoring service, making it possible to achieve the necessary plasma levels. Further interest has been stimulated by the multicentre FIRM-ACT study in which mitotane is used in combination with two different chemotherapy regimens.

The European Network for the Study of Adrenal Tumours (ENSAT) staging system is now universally adopted.

Table A9.1: ENSAT staging for adrenocortical cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumour &lt;5cm</td>
</tr>
<tr>
<td>II</td>
<td>Tumour &gt;5cm</td>
</tr>
<tr>
<td>III</td>
<td>Tumour locally invasive and or positive nodes and or invasion of local organs</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

Mitotane treatment may be effective in treating the endocrine consequences of ACC in patients even if tumour regression cannot be demonstrated. Mitotane use has also been successfully used in patients with other causes of cortisol excess, including refractory pituitary and ectopic Cushing’s.

Indications for mitotane use in adrenocortical cancer

• All patients with recurrent or metastatic ACC should be considered for surgical debulking before or in addition to commencing mitotane.

• Mitotane may also be considered as adjuvant therapy in patients with Stage II or III ACC (Terzolo et al., 2007).

• Mitotane may also be used concurrently with chemotherapy (etoposide, cisplatin and doxorubicin).
Side effects

- **Gastrointestinal (GI) toxicity** (nausea, diarrhoea) may be present at low doses but may diminish during ongoing treatment. GI toxicity may be dose-limiting at higher mitotane doses.

- **Neurological toxicity** (fatigue, drowsiness, ataxia, dysarthria) mostly occurs if plasma mitotane levels exceed 20mg/L. Because mitotane is lipophilic, plasma levels may take a while to drop after dose reduction or treatment interruption, and neurological toxicity is only slowly reversible (usually taking several weeks).

- **Hepatic toxicity:** liver enzymes invariably increase, but during ongoing treatment levels usually remain 2–3 times above the upper limit of normal without reflecting serious impairment of liver function. LFTs should be routinely monitored monthly (AST, ALT, AlkPhos, gGT). If gGT >10 fold or AST/ALT >3 fold above ULN, treatment interruption should be considered, synthetic liver function checked, mitotane levels checked and reintroduction considered at lower dose.

- **Hypercholesterolaemia:** prior to treatment and at regular intervals, fasting lipids should be measured; mitotane-induced hypercholesterolaemia is responsive to statin treatment, if indicated.

- **Haematological side effects** are uncommon, but FBC is typically monitored at visits.

- **Adrenal insufficiency** is a predictable consequence of treatment and occurs within weeks/months after initiation of mitotane therapy. Adrenal replacement with glucocorticoids is prescribed routinely from initiation, with ongoing monitoring. Mineralocorticoid replacement may also be required. Hydrocortisone replacement should be initiated concurrently with mitotane treatment. Daily replacement doses of 40–60mg hydrocortisone should be used (e.g. 20-10-10mg or 20mg TDS), possibly requiring further increases during ongoing mitotane treatment. These high doses are required due to a substantial mitotane-induced increase in cortisol-binding globulin, and also due to a proposed antagonistic effect on glucocorticoid action. Mitotane induces the metabolism of dexamethasone and prednisolone, thus hydrocortisone is generally considered first-line glucocorticoid replacement. Inadequate steroid replacement may be mistaken for GI toxicity due to mitotane.

   Mineralocorticoid deficiency may also develop with ongoing mitotane treatment. Serum potassium, sodium, plasma renin activity, postural hypotension should be monitored, and patients may require fludrocortisone replacement (starting dose 100mcg OD).

- **Hypogonadism** may develop because of increases in sex hormone binding globulin (SHBG). Monitoring should consist of measurements of total testosterone and SHBG; testosterone replacement may be required.

- **Secondary hypothyroidism** has been described during mitotane treatment, thyroid stimulating hormone (TSH) is not informative and fT4 should be used for monitoring; thyroxine (T4) replacement may be required.
Mitotane (Lysodren®) treatment in clinical practice

- Mitotane is very lipophilic and accumulates in adipose tissue, from where it is slowly released back into the bloodstream. This means that plasma mitotane levels may substantially increase during ongoing treatment with the same dose. Thus, doses easily tolerated in the beginning may later cause significant side effects, emphasising the need for regular monitoring of plasma mitotane levels.

- Treatment should be monitored by measurement of plasma mitotane levels, aiming for the therapeutic range of 14–20mg/L. Concentrations below 10mg/L are ineffective and concentrations above 20mg/L are associated with increased toxicity (predominantly neurotoxicity). If tolerated, levels >20mg/L need not be of concern.

Therapeutic drug monitoring of mitotane

Therapeutic drug monitoring (TDM) is provided by HRA Pharma which also markets mitotane in Europe, and which has involved Parexel to deliver the Lysosafe Service. Mitotane plasma levels are provided free for patients on mitotane; the prescribing consultant has to register at www.Lysodren-Europe.com to register for Lysosafe to obtain documents, packaging etc. EDTA-containing plasma samples are placed on ice immediately and remain on ice for transportation. At King’s College Hospital, TDM is organised through the endocrine day-case unit, to whom results are dispatched.

Results of routine samples are fed back by fax and mail within a week; urgent samples can be processed within 1–2 days after receipt (overnight courier).

Treatment algorithms

Mitotane can be prescribed at conventional dosing (low-dose regimen) but may require several months to achieve steady state. A high-dose accelerated regimen has been reported to achieve a therapeutic level more quickly, without a greater number of side effects. The use of the higher dose regimen has been advocated in rapidly progressing disease but remains an individualised therapeutic decision (Faggiano et al., 2006). Individuals undergoing chemotherapy while mitotane is being initiated may be better started on the low-dose regimen.
### Table A9.2: Low-dose regimen

<table>
<thead>
<tr>
<th>Week 1 (in 2–3 divided doses)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1g</td>
<td>1g</td>
<td>1.5g</td>
<td>1.5g</td>
<td>1.5g</td>
<td>2g</td>
<td>2g</td>
<td></td>
</tr>
<tr>
<td><strong>Week 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 8</td>
<td>2g</td>
<td>2.5g</td>
<td>2.5g</td>
<td>2.5g</td>
<td>3g</td>
<td>3g</td>
<td>3g</td>
</tr>
</tbody>
</table>

Sampling intervals: every 4 weeks until steady state (6–12 months) (optional reduction in frequency after 1 year to 3-monthly).

Dose adjustment at least every 4 weeks until steady state according to side effects and plasma mitotane level.

<table>
<thead>
<tr>
<th>Plasma mitotane level</th>
<th>Central nervous system (CNS) (Grade 2) and/or GI side effects (Grade 3/4)</th>
<th>Grade 3/4 Central Nervous System (CNS) side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

**Treatment dose decision**

- **<14mg/l**
  - Increase daily dose by 1g*
  - Reduce daily dose by 1g
  - Stop mitotane†

- **14–20mg/l**
  - Maintain dose
  - Reduce daily dose by 1.5g
  - Stop mitotane†

- **>20mg/l**
  - Reduce daily dose to 50–80% of the most recent dose
  - Stop mitotane†
  - Stop mitotane†

* Maximum daily mitotane dose permitted is 12g.
† Until recovery of side effects and restart with a lower dose (50–80 % of the most recent dose).

### Table A9.2: High-dose regimen

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5g</td>
<td>3g</td>
<td>4.5g</td>
<td>6g</td>
<td>6g</td>
<td>6g</td>
<td>6g</td>
<td></td>
</tr>
<tr>
<td><strong>Week 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 8</td>
<td>6g</td>
<td>6g</td>
<td>6g</td>
<td>6g</td>
<td>6g</td>
<td>6g</td>
<td>6g</td>
</tr>
</tbody>
</table>

From day 15 onwards drop dose down to 4.5g/daily (1.5g TDS) and await result of plasma mitotane level

Sampling intervals: every 2 weeks to week 12; every 4 weeks until steady state (e.g. 6–12 months), (optional reduction in frequency after 1 year to 3-monthly).

Dose adjustment at least every 4 weeks until steady state according to side effects and plasma mitotane level.

<table>
<thead>
<tr>
<th>Plasma mitotane level</th>
<th>CNS (Grade 2) and/or GI side effects (Grade 3/4)</th>
<th>Grade 3/4 CNS side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

**Treatment dose decision**

- **<14mg/l**
  - Increase daily dose by 1.5g for 1 week, then another 1.5g in the second week*
  - Reduce daily dose by 1.5g
  - Stop mitotane†

- **14–20mg/l**
  - Maintain dose
  - Reduce daily dose by 1.5g
  - Stop mitotane†

- **>20mg/l**
  - Reduce daily dose to 50–80% of the most recent dose
  - Stop mitotane†
  - Stop mitotane†

* Maximum daily mitotane dose permitted is 12g.
† Until recovery of side effects and restart with a lower dose (50–80 % of the most recent dose).
Monitoring of mitotane treatment

Monitoring visits should occur every 4 weeks (low-dose regimen) or 2 weeks (high-dose regimen) initially. See sample mitotane monitoring form (Annex 1), and cumulative visit form (Annex 2).

Visits are to determine:

1. Symptoms of toxicity and performance status:
   - ask for potential disease-related and mitotane-related symptoms
   - record body weight

2. Biochemical/haematological tests for toxicity (FBC, DAX, TFT)

3. Mitotane level (minimum monthly for first year, 3-monthly thereafter)

4. Assessment of tumour markers:
   - DHEAS, androstenedione, 17-hydroxyprogesterone, testosterone
   - urine steroid profile

5. Adequacy of steroid replacement:
   - record dose of hydrocortisone
   - check and verify the steroid emergency card/bracelet
   - check for symptoms suggestive of glucocorticoid under-replacement
   - patients benefit from the prescription of a hydrocortisone emergency kit
   - plasma renin activity (EDTA plasma)
   - plasma ACTH (should be in the normal range)

6. Efficacy of treatment with imaging typically at every 3 months, initially 2 months after achieving therapeutic mitotane plasma levels

7. Presence of other cancer-related complications.

Roles of the hospital and GP

The hospital will be responsible for the prescription, monitoring and pharmacovigilance associated with mitotane therapy. Visits for monitoring are likely to continue on a monthly basis for most patients with a hospital prescription for mitotane.

GPs are requested to:

- report adverse events to the clinical nurse specialists (020 3299 3034)
- discuss treatment strategy as appropriate with the consultant (020 3299 2996)
- continue prescription for hydrocortisone, fludrocortisone, and anti-emetics as required.

In certain circumstances, the stability of the patient’s condition may lead to consideration of a shared care agreement with 3-monthly hospital visits, in which case prescriptions issued by the GP might be considered appropriate.
Annex 1: Mitotane monitoring form

<table>
<thead>
<tr>
<th>Name</th>
<th>Hospital number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit date</td>
<td>Mitotane start date</td>
</tr>
<tr>
<td>Current total daily dose</td>
<td>Last dose change (date)</td>
</tr>
<tr>
<td>Hydrocortisone dose</td>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Fludrocortisone dose</td>
<td>Systolic BP</td>
</tr>
<tr>
<td>Steroid card (Y / N)</td>
<td>Other drugs</td>
</tr>
<tr>
<td>HC emergency pack (Y / N)</td>
<td></td>
</tr>
</tbody>
</table>

Adverse effects
Grade from 0 (none) to 4 (severe)

<table>
<thead>
<tr>
<th>Common</th>
<th>Evidence of dose toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Cortisol deficiency</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Dysarthria</td>
</tr>
<tr>
<td>Reduced energy</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
</tr>
</tbody>
</table>

MONTHLY (unless otherwise indicated)
Mitotane level
Target mitotane level 14–20 (mg/L)

<table>
<thead>
<tr>
<th>3-monthly</th>
<th>cortisol (pre-dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td></td>
</tr>
<tr>
<td>Renin</td>
<td></td>
</tr>
<tr>
<td>Aldosterone</td>
<td></td>
</tr>
<tr>
<td>testosterone</td>
<td></td>
</tr>
<tr>
<td>SHBG</td>
<td></td>
</tr>
<tr>
<td>DHEAS</td>
<td></td>
</tr>
<tr>
<td>Androstenedione</td>
<td></td>
</tr>
<tr>
<td>17OHP</td>
<td></td>
</tr>
<tr>
<td>progesterone</td>
<td></td>
</tr>
<tr>
<td>cholesterol</td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td></td>
</tr>
<tr>
<td>free T4</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td></td>
</tr>
<tr>
<td>steroid profile</td>
<td></td>
</tr>
</tbody>
</table>

steroid profile comment

Advice (please record changes to medical treatment advised)

SJBA v 1.2
## Annex 2: Cumulative mitotane monitoring form

<table>
<thead>
<tr>
<th>Name</th>
<th>Hospital number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>Visit Number</th>
<th>Hospital number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weeks on Rx</th>
<th>Mitotane dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hb</th>
<th>wbc</th>
<th>plt</th>
<th>Na</th>
<th>K</th>
<th>Creat</th>
<th>Alk Phos</th>
<th>AST</th>
<th>gGT</th>
<th>cortisol (pre-dose)</th>
<th>ACTH</th>
<th>Renin</th>
<th>Aldosterone</th>
<th>testosterone</th>
<th>SHBG</th>
<th>DHEAS</th>
<th>Androstenedione</th>
<th>17OHP</th>
<th>progesterone</th>
<th>cholesterol</th>
<th>Triglyceride</th>
<th>free T4</th>
<th>TSH</th>
<th>urine steroid metabolites (specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Annex 3: Karnofsky Index score

100  normal, no complaints; no evidence of disease
90   able to carry on with normal activities; minor symptoms
80   normal activity with effort; some symptoms
70   unable to carry on with normal activities, but complete self-care
60   requires occasional assistance, but still cares for most of own needs
50   requires considerable assistance and frequent care
40   disabled: requires special care and assistance
30   severely disabled: hospitalised, death not imminent
20   very sick: active supportive care needed
10   moribund: fatal processes are progressing rapidly
0    dead

Annex 4: ECOG index for Performance Status

0    able to carry out all normal activity without restriction
1    restricted in physically strenuous activity but ambulatory and able to do light work
2    ambulatory and capable of all self-care but unable to carry out any work. 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 out any self-care; totally confined to bed or chair
### Annex 5: WHO recommendations for grading of acute and subacute toxic effects

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBC (1,000/mm)</strong></td>
<td>≥4.0</td>
<td>3.0–3.9</td>
<td>2.0–2.9</td>
<td>1.0–1.9</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td><strong>Neut (1,000/mm)</strong></td>
<td>≥2.0</td>
<td>1.5–1.9</td>
<td>1.0–1.4</td>
<td>0.5–0.9</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td><strong>PLTS (1,000/mm)</strong></td>
<td>≥100</td>
<td>75.0–99.9</td>
<td>50.0–74.9</td>
<td>25.0–49.9</td>
<td>&lt;25.0</td>
</tr>
<tr>
<td><strong>Hb</strong></td>
<td>≥11.0</td>
<td>9.5–10.9</td>
<td>8.0–9.4</td>
<td>6.5–7.9</td>
<td>&lt;6.5</td>
</tr>
<tr>
<td><strong>Haemorrhage (clinical)</strong></td>
<td>none</td>
<td>mild, no transfusion</td>
<td>gross, 1–2 units blood</td>
<td>gross, 3–4 units blood</td>
<td>massive, &gt;4 units blood</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>none</td>
<td>no active Rx</td>
<td>localised infection requires active Rx</td>
<td>systemic infection requires active Rx</td>
<td>life threatening, sepsis</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>none</td>
<td>able to eat</td>
<td>unable to eat</td>
<td>intractable unable to eat</td>
<td>dehydrated and/or electrolyte imbalance</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>none</td>
<td>1 episode in 24 hours, able to eat and take fluids</td>
<td>≥2 episodes in 24 hours, able to retain fluids/food</td>
<td>intractable, unable to retain fluids/food</td>
<td>dehydrated and/or electrolyte imbalance</td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td>none</td>
<td>transient ≤2 days</td>
<td>tolerable &gt;2 days</td>
<td>intolerable requiring therapy</td>
<td>haemorrhagic, dehydrated and/or electrolyte imbalance</td>
</tr>
<tr>
<td><strong>Stomatitis</strong></td>
<td>none</td>
<td>soreness, erythema</td>
<td>ulcers – can eat solid</td>
<td>ulcers – requires liquid diet only</td>
<td>requires parenteral support</td>
</tr>
<tr>
<td><strong>Billirubin</strong></td>
<td>&lt;1.5 x N</td>
<td>1.5–2.5 x N</td>
<td>2.6–5.0 x N</td>
<td>5.1–10 x N</td>
<td>&gt;10 x N</td>
</tr>
<tr>
<td><strong>SGOT SGPT</strong></td>
<td>&lt;1.5 x N</td>
<td>1.5–2.5 x N</td>
<td>2.6–5.0 x N</td>
<td>5.1–10 x N</td>
<td>&gt;10 x N</td>
</tr>
<tr>
<td><strong>Alc Phos</strong></td>
<td>&lt;1.5 x N</td>
<td>1.5–2.5 x N</td>
<td>2.6–5.0 x N</td>
<td>5.1–10 x N</td>
<td>&gt;10 x N</td>
</tr>
<tr>
<td><strong>Liver clinical</strong></td>
<td>no change</td>
<td>–</td>
<td>–</td>
<td>pre-coma</td>
<td>hepatic coma</td>
</tr>
<tr>
<td><strong>BUN</strong></td>
<td>&lt;1.5 x N</td>
<td>1.5–2.5 x N</td>
<td>2.6–5.0 x N</td>
<td>5.1–10 x N</td>
<td>&gt;10 x N</td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td>&lt;1.25</td>
<td>1.25–2.0 x N</td>
<td>2.1–3.0 x N</td>
<td>3.1–6.0 x N</td>
<td>&gt;6.0 x N</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>no change</td>
<td>1+, &lt;0.3g%, &lt;3g/l</td>
<td>2–3+, 0.3–1.0%, 3–10g/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Haematuria</strong></td>
<td>neg.</td>
<td>micro, cult. neg.</td>
<td>gross, cult. neg.</td>
<td>gross + clots</td>
<td>life-threatening</td>
</tr>
<tr>
<td><strong>Hair</strong></td>
<td>no loss</td>
<td>mild hair loss</td>
<td>pronounced or total hair loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>none</td>
<td>mild</td>
<td>moderate</td>
<td>severe</td>
<td>intractable</td>
</tr>
<tr>
<td><strong>Pulmonary (clin.)</strong></td>
<td>no change</td>
<td>mild symptoms, not interfering with normal function</td>
<td>exertional dyspnea</td>
<td>dyspnoea at rest</td>
<td>complete bed rest required</td>
</tr>
<tr>
<td>Grade</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Cardiac</td>
<td>none or normal or no change</td>
<td>sinus tachycardia &gt;110;</td>
<td>unifocal PVCs;</td>
<td>multifocal PVCs;</td>
<td>ventricular tachycardia;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or mild ST-T changes;</td>
<td>or severe ST-T changes;</td>
<td>or pericarditis;</td>
<td>or atrial fibrillation;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or orthostatic symptoms w/o BP changes;</td>
<td>or systolic BP falls &lt;20 with symptoms;</td>
<td>or BP falls &gt;20 but &lt;50;</td>
<td>or tamponade;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or systolic increase &gt;15 and &gt;150;</td>
<td>or systolic increase &gt;20 and &gt;170;</td>
<td>or systolic increase &gt;25 and &gt;190;</td>
<td>or BP falls &gt;50 or needs Rx;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or diastolic increase &gt;10 and &gt;95;</td>
<td>or diastolic increase &gt;15 and &gt;105;</td>
<td>or diastolic increase &gt;20 and &gt;115;</td>
<td>or ejection fraction decrease &gt;40%;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or ejection fraction decrease 10–19%</td>
<td>or ejection fraction decrease 20–29%</td>
<td>or ejection fraction decrease 30–39%;</td>
<td>or clinical CHF req Rx but well controlled</td>
</tr>
<tr>
<td>Servomotor</td>
<td>normal or no change or none</td>
<td>mild weakness/lethargy but normal function;</td>
<td>moderate weakness/lethargy with decrease in normal function;</td>
<td>difficulty walking or severe weakness/lethargy or foot drop and not able to function;</td>
<td>paralysis or hospitalisation; or generalised seizure activity or mute</td>
</tr>
<tr>
<td>Neuro-sensory</td>
<td>normal or no change or none</td>
<td>minor paraesthesia numbness;</td>
<td>noticeable paraesthesia;</td>
<td>disabling paraesthesia unable to use buttons;</td>
<td>loss of sensation and bed-ridden; or unable to walk; or deaf or blind</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or mild decrease DTRs;</td>
<td>or moderate decrease DTRs;</td>
<td>or loss of DTRs;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or mild ataxia;</td>
<td>or moderate ataxia;</td>
<td>or severe ataxia;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or decrease acuity on audiogram;</td>
<td>or decrease hearing clinically detectable;</td>
<td>or difficulty walking;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or mild tinnitus;</td>
<td>or moderate tinnitus;</td>
<td>or clinical significant hearing loss needing hearing aid;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or vertigo;</td>
<td>or vertigo;</td>
<td>or severe tinnitus;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or visual change;</td>
<td>or visual change;</td>
<td>or visual change;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or headaches &lt;3/week and mild</td>
<td>or headaches 3–7/week and moderate</td>
<td>or headaches &gt;7/week or continuous and severe</td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>-------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Neuro-psychiatric</td>
<td>normal or no change</td>
<td>mild depression or personality change but normal function</td>
<td>moderate depression or personality change with disruption of normal function</td>
<td>severe depression or behaviour change</td>
<td>suicidal or attempted suicide or psychosis</td>
</tr>
<tr>
<td>Neuro-clinical</td>
<td>normal or no change</td>
<td>mild confusion; or somnolence; or disorientation; or impaired thinking; but normal function</td>
<td>moderate confusion etc. with reduced function</td>
<td>severe confusion etc. and confined due to dysfunction</td>
<td>coma</td>
</tr>
<tr>
<td>Skin</td>
<td>no change</td>
<td>erythema</td>
<td>dry desquamation, vesiculation, pruritus</td>
<td>moist desquamation, ulceration</td>
<td>exfoliative dermatitis, necrosis requiring surgical intervention</td>
</tr>
<tr>
<td>Allergy</td>
<td>none</td>
<td>transient rash, drug fever &lt;38c, &lt;100.4f</td>
<td>urticaria, drug fever ≥38c, 100.4f mild bronchospasm</td>
<td>serious sickness bronchospasm, requiring parenteral meds</td>
<td>anaphylaxis</td>
</tr>
<tr>
<td>Fever</td>
<td>none</td>
<td>&lt;38c, &lt;100.4f</td>
<td>38–40c, 100.4–104f</td>
<td>&gt;40c, &gt;104f</td>
<td>fever + hypotension</td>
</tr>
<tr>
<td>Focal</td>
<td>none</td>
<td>pain</td>
<td>pain + phlebitis</td>
<td>ulceration</td>
<td>surgery indicated</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>none</td>
<td>arm</td>
<td>thrombophlebitis leg</td>
<td>hospitalisation</td>
<td>Embolus</td>
</tr>
<tr>
<td>Serum glucose (mg/100ml)</td>
<td>≤140</td>
<td>&gt;140</td>
<td>symptomatic hyperglycaemia</td>
<td>insulin necessary</td>
<td>ketoacidosis coma</td>
</tr>
<tr>
<td>Weight gain/loss</td>
<td>&lt;5%</td>
<td>5–10%</td>
<td>10–20%</td>
<td>&gt;20%</td>
<td></td>
</tr>
<tr>
<td>Lack of appetite or inability to eat or consume fluids after treatment</td>
<td>&lt;12 hours</td>
<td>&gt;12 hours</td>
<td>&gt;24 hours and persists after repeated treatments (2 weeks)</td>
<td>Grade 3 toxicity after dose reduction</td>
<td></td>
</tr>
<tr>
<td>Weight loss from baseline</td>
<td>&lt;5%</td>
<td>5–10%</td>
<td>&gt;10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain from baseline/ fluid retention</td>
<td>&gt;5% &lt;10%</td>
<td>≥10 &lt;15%</td>
<td>&gt;15% &lt;20% or symptomatic fluid accumulation (ascites, effusion)</td>
<td>≥20%</td>
<td></td>
</tr>
<tr>
<td>Fatigue in bed after treatment</td>
<td>&lt;6 hours’ duration</td>
<td>6–12 hours</td>
<td>12–24 hours</td>
<td>&gt;24 hours</td>
<td></td>
</tr>
</tbody>
</table>
### References


Appendix 10: LCA Holistic Needs Assessment Tool

The tool can be downloaded from the LCA website.

### London Holistic Needs Assessment

For each item below, please tick yes or no if they have been a concern for you during the last week, including today. Please also tick yes if you wish to speak about it with your healthcare professional.

Choose not to complete the assessment today by ticking this box.

#### Practical concerns

<table>
<thead>
<tr>
<th>Date:</th>
<th>Practical concerns</th>
<th>Physical concerns</th>
<th>Yes</th>
<th>No</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
<td>Caring responsibilities</td>
<td>High temperature</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Date:</td>
<td>Housing or finances</td>
<td>Wound care</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Date:</td>
<td>Transport or parking</td>
<td>Passing urine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Work or education</td>
<td>Constipation or diarrhoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Information needs</td>
<td>Indigestion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Difficulty making plans</td>
<td>Nausea and/or vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Grocery shopping</td>
<td>Cough</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Preparing food</td>
<td>Changes in weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Bathing or dressing</td>
<td>Eating or appetite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Laundry or housework</td>
<td>Changes in taste</td>
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</table>

#### Family concerns

<table>
<thead>
<tr>
<th>Date:</th>
<th>Family concerns</th>
<th>Yes</th>
<th>No</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
<td>Relationship with children</td>
<td>Feeling swollen</td>
<td></td>
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</tr>
<tr>
<td>Date:</td>
<td>Relationship with partner</td>
<td>Breathlessness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Relationship with others</td>
<td>Pain</td>
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#### Emotional concerns

<table>
<thead>
<tr>
<th>Date:</th>
<th>Emotional concerns</th>
<th>Yes</th>
<th>No</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
<td>Loneliness or isolation</td>
<td>Tingling in hands or feet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Sadness or depression</td>
<td>Hot flushes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Worry, fear or anxiety</td>
<td>Moving around or walking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Anger, frustration or guilt</td>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Memory or concentration</td>
<td>Sleep problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Hopelessness</td>
<td>Communication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td>Sexual concerns</td>
<td>Personal appearance</td>
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#### Spiritual concerns

<table>
<thead>
<tr>
<th>Date:</th>
<th>Spiritual concerns</th>
<th>Yes</th>
<th>No</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
<td>Other medical condition</td>
<td>Other medical condition</td>
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</tbody>
</table>

#### For health professional use

**Pathway point:**

**Diagnosis:**

**Date of diagnosis:**

**Date:**

**Preferred name:**

**Hospital/NHS number:**

### Care Plan

During my holistic needs assessment, these issues were identified and discussed:

<table>
<thead>
<tr>
<th>Number</th>
<th>Issue</th>
<th>Summary of discussion</th>
<th>Actions required/by (name and date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breathing problem</td>
<td>Possible causes identified, coping strategies discussed, printed information provided</td>
<td>Referral to anxiety management programme, CNS to complete by 24th Dec</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other actions/outcomes e.g. additional information given, health promotion, smoking cessation, ‘My actions’:

**Signed (patient):**

**Date:**

**Signed (healthcare professional):**

**Date:**

**For health professional use**

**Date of diagnosis:**

**Diagnosis:**

**Pathway point:**
Acknowledgements

Our thanks to the following healthcare professionals, patients and carers who have provided input into the LCA Hepato-pancreato-biliary Cancer Clinical Guidelines:

LCA HPB Pathway Group
LCA Survivorship Group
LCA Chemotherapy Closer to Home and Medicines Optimisation Pathway Group
LCA Radiotherapy Pathway Group
LCA Colorectal Pathway Group

Patient representatives
Pan-London Patient Experience Group
Pancreatic Cancer UK

LCA Project Managers
Tim Bill, LCA OG Project Manager
Felicity Surridge, LCA HPB Project Manager