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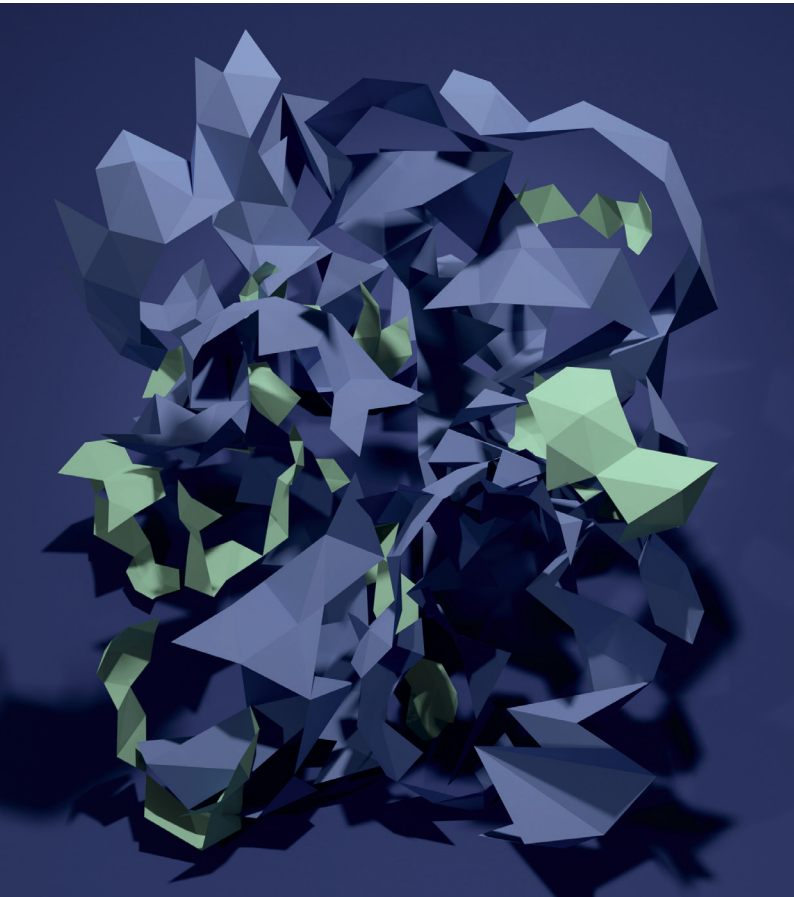
# Upper Gastrointestinal Cancers

## Pocket Guideline 2023



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# ESMO POCKET GUIDELINES

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## ESMO CLINICAL PRACTICE GUIDELINES

**Hepatocellular carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up**
*Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, Nault J-C, Neumann U, Ricke J, Sangro B, Schirmacher P, Verslype C, Zech CJ, Arnold D and Martinelli E, on behalf of the ESMO Guidelines Committee*
Ann Oncol 2018;29(Suppl 4):iv238-55
https://www.annalsofoncology.org/article/S0923-7534(19)31711-9/fulltext

**eUpdate – Hepatocellular carcinoma treatment recommendations (March 2021)**
*ESMO Guidelines Committee*
https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/hepatocellular-carcinoma/eupdate-hepatocellular-carcinoma-treatment-recommendations

**eUpdate – Hepatocellular carcinoma algorithm (March 2021)**
*ESMO Guidelines Committee*
https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/hepatocellular-carcinoma/eupdate-hepatocellular-carcinoma-algorithm

**Hereditary gastrointestinal cancers: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up**
*Stjepanovic N, Moreira L, Carneiro F, Balaguer F, Cervantes A, Balmaña J and Martinelli E, on behalf of the ESMO Guidelines Committee*
Ann Oncol 2019;30(10):1558-71
https://www.annalsofoncology.org/article/S0923-7534(19)60977-4/fulltext

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**Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up**
*Obermannová R, Alsina M, Cervantes A, Leong T, Lordick F, Nilsson M, van Grieken NCT, Vogel A and Smyth EC, on behalf of the ESMO Guidelines Committee*
Ann Oncol 2022;33(10):992-1004
https://www.annalsofoncology.org/article/S0923-7534(22)01850-6/fulltext

**Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up**
*Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, Vogel A and Smyth EC, on behalf of the ESMO Guidelines Committee*
Ann Oncol 2022;33(10):1005-20
https://www.annalsofoncology.org/article/S0923-7534(22)01851-8/fulltext

**ESMO Gastric Cancer Living Guideline v1.1 (July 2023)**
*Lordick F, Candia Montero L, Castelo-Branco L, Pentheroudakis G, Sessa C and Smyth E, on behalf of the Clinical Practice Guideline author group*
https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline

**Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up**
*Vogel A, Bridgewater J, Edeline J, Kelley RK, Klümpen HJ, Malka D, Primrose JN, Rimassa L, Stenzinger A, Valle JW and Ducreux M, on behalf of the ESMO Guidelines Committee*
Ann Oncol 2023;34(2):127-40
https://www.annalsofoncology.org/article/S0923-7534(22)04699-3/fulltext

**Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up**
*Conroy T, Pfeiffer P, Vilgrain V, Lamarca A, Seufferlein T, O'Reilly EM, Hackert T, Golan T, Prager G, Haustermans K, Vogel A and Ducreux M, on behalf of the ESMO Guidelines Committee*
Ann Oncol 2023; in press
https://www.annalsofoncology.org/article/S0923-7534(23)00824-4/fulltext

# ESMO GUIDE TO EVALUATION OF DATA

ESMO POCKET GUIDELINES PROVIDE YOU WITH A CONCISE SUMMARY OF THE FUNDAMENTAL RECOMMENDATIONS MADE IN THE PARENT GUIDELINES IN AN EASILY ACCESSIBLE FORMAT.

This quick reference booklet provides you with the most important content of the ESMO Clinical Practice Guidelines (CPGs) on the management of upper gastrointestinal (GI) cancers (including hepatocellular carcinoma, hereditary GI cancers, oesophageal cancer, gastric cancer, biliary tract cancer and pancreatic cancer). Key content includes diagnostic criteria, staging of disease, treatment plans and follow-up. The ESMO CPGs on upper GI cancers are intended to provide you with a set of recommendations for the best standards of care for upper GI cancers, using evidence-based medicine. Implementation of ESMO CPGs facilitates knowledge uptake and helps you to deliver an appropriate quality of focused care to your patients.

The approval and licensed indication of drugs mentioned in this pocket guideline may vary in different countries. Please consult your local prescribing information. This booklet can be used as a quick reference guide to access key content on evidence-based management of upper GI cancers.

Please visit http://www.esmo.org or http://oncologypro.esmo.org to view the full guidelines.

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**GLOSSARY**

# HEPATOCELLULAR CARCINOMA

## SURVEILLANCE

- Cost-effectiveness studies suggest that surveillance of hepatocellular carcinoma (HCC) is warranted in all cirrhotic patients, irrespective of its aetiology, as long as liver function and comorbidities allow for curative or palliative treatments
- Surveillance of non-cirrhotic, hepatitis-infected patients is also advocated, especially in chronic hepatitis B virus (HBV) carriers and those with hepatitis C virus (HCV) infection and advanced fibrosis
- Surveillance of patients at risk for HCC should be carried out by abdominal ultrasound every 6 months with or without $\alpha$-fetoprotein (AFP)

## DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

- The diagnosis of HCC is based on histological analysis and/or contrast-enhanced imaging findings, shown in the table on the next page

### Diagnosis by imaging

- Pathological proof is not mandatory in cirrhotic livers with specific imaging criteria
- Diagnosis requires identification of typical vascular hallmarks of HCC (hypervascularity in the arterial phase with washout in the portal venous or delayed phase) in a nodule of > 1 cm diameter using multiphasic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI)
  - Multiphasic MRI is more sensitive than multiple detector CT
- MRI with diffusion-weighted imaging and hepatobiliary contrast agents may identify high-risk nodules (either HCC not displaying the typical imaging hallmark features or high-grade dysplastic nodules)
  - Switching to palliative treatments after identification of potential premalignant nodules by these new techniques should be avoided
- Contrast-enhanced ultrasound is suitable for diagnosing HCC in the setting of liver cirrhosis, with hallmarks of arterial hyperenhancement followed by late (> 60 seconds) washout of a mild degree
- When tumour biopsy fails to demonstrate a correlate for a focal lesion, a second tumour biopsy, a different contrast-enhanced imaging modality or (if amenable) direct resection of the lesion may be considered, according to tumour size
- Serum AFP, angiography and [$^{18}$F]2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) scan are not recommended

## DIAGNOSTIC WORK-UP

| HISTORY AND CLINICAL EXAMINATION |
|---|
| Risk factors for chronic liver disease: IV drug abuse, alcohol intake, metabolic syndrome (obesity, diabetes, arterial hypertension) |
| Signs and symptoms of chronic liver disease (jaundice, ascites, encephalopathy, bleeding, splenomegaly) |
| PS (distinguish cancer-related symptoms of recent onset with long-standing symptoms associated with cirrhosis) and nutritional state |
| **LABORATORY ANALYSIS** |
| Aetiology of liver disease: HBV (at least HBsAg and anti-HBc), HCV (at least anti-HCV), iron status, autoimmune disease |
| Liver function: Prothrombin, albumin, bilirubin |
| Complete blood cell count including platelets |
| Tumour marker: Serum AFP |
| **ASSESSMENT OF PORTAL HYPERTENSION** |
| Upper endoscopy: Varices and/or hypertensive gastropathy |
| Optional: Transjugular measurement of hepatic-venous pressure gradient |
| **IMAGING STUDIES** |
| Liver dynamic (multiple phase) MRI or CT studies for diagnosis and evaluation of tumour extent inside the liver (number and size of nodules, vascular invasion, extrahepatic spread) |
| CEUS can also be used for the non-invasive diagnosis of HCC if CT scan or MRI are not possible, but is not considered appropriate for tumour staging |
| CT of the chest, abdomen and pelvis to rule out extrahepatic spread |
| **TUMOUR BIOPSY** |
| Required for nodules with non-diagnostic imaging |
| Required to diagnose HCC in non-cirrhotic liver |
| Should be carried out according to national or institutional policy in all clinical trials and may support centre-based innovative treatment approaches |
| Ideally, should evaluate tumour and non-tumour tissue when used for scientific purposes |

**AFP, α-fetoprotein; CEUS, contrast-enhanced ultrasound; CT, computed tomography; HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IV, intravenous; MRI, magnetic resonance imaging; PS, performance status**

### Diagnosis by pathology

- Assessment follows the tumour–node–metastasis (TNM) classification
- Histopathological diagnosis of tumour biopsies relies on standard (haemotoxylin and eosin) and special (e.g. reticulin) stains
  - Histological analyses may be supplemented by immunohistochemistry (IHC)

- Combined HCC and cholangiocarcinoma should be distinguished from HCC due to the different therapeutic modalities; however, the mixed differentiation features might not be visible in a biopsy
- Significant cytokeratin 19 (CK19) expression indicates a poor prognosis
- In highly differentiated HCC, definitive signs of malignancy are often absent and additional histological (trabecular alterations, capsule formation) and cytological criteria ("nuclear crowding", increased cytoplasmic basophilia) support the diagnosis
- In unclear cases, IHC is recommended. Capillarisation of sinusoids can be assessed using cluster of differentiation 34 (CD34) IHC
- Additional IHC markers for highly differentiated HCC, including glutamine synthetase, glypican 3, general stress protein CTC, enhancer of zeste homologue 2 (EZH2) and heat shock protein 70 (HSP70), can improve diagnosis
  - A combination of glutamine synthetase, glypican 3 and HSP70 forms a diagnostic panel and the use of further markers may increase its sensitivity

**STAGING AND RISK ASSESSMENT**

- Staging includes assessment of tumour extent, AFP level, liver function, portal pressure and clinical performance status (PS), as shown in the table on page 12
- Contrast-enhanced MRI or helical CT are recommended to evaluate tumour extent, with CT of the chest, abdomen and pelvis to rule out extrahepatic spread
- Routine preoperative bone scintigraphy is not recommended
- FDG-PET scanning is not recommended, although higher FDG uptake may be associated with poor differentiation, tumour size, serum AFP levels and microvascular invasion
- Liver function is assessed by the Child–Pugh scoring system (serum bilirubin, serum albumin, ascites, prothrombin time and hepatic encephalopathy)
  - The albumin–bilirubin (ALBI) score can distinguish between good- (ALBI 1) and poor- (ALBI 2) prognosis patients
- Oesophageal varices and/or splenomegaly with blood platelet counts of $100 \times 10^9$ cells/L suggest clinically important portal hypertension, which can also be measured invasively by the transjugular route (hepatic venous pressure gradient $> 10$ mmHg)
- Several staging systems have been developed for HCC
- The TNM system provides a means of standardising histopathological reports in patients treated by resection or transplantation
  - The eighth edition of the TNM system is shown in the table on the next page

## UICC EIGHTH EDITION STAGING SYSTEM FOR HCC

| PRIMARY TUMOUR (T) | |
|---|---|
| TX | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour |
| T1a | Solitary tumour ≤ 2 cm in greatest dimension with or without vascular invasion |
| T1b | Solitary tumour > 2 cm in greatest dimension without vascular invasion |
| T2 | Solitary tumour with vascular invasion > 2 cm dimension or multiple tumours, none > 5 cm in greatest dimension |
| T3 | Multiple tumours, any > 5 cm in greatest dimension |
| T4 | Tumour(s) involving a major branch of the portal or hepatic vein with direct invasion of adjacent organs (including the diaphragm), other than the gallbladder or with perforation of visceral peritoneum |
| **REGIONAL LYMPH NODES (N)** | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |
| **DISTANT METASTASIS (M)** | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

| STAGE – LIVER | | | |
|---|---|---|---|
| Stage IA | T1a | N0 | M0 |
| Stage IB | T1b | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage IIIA | T3 | N0 | M0 |
| Stage IIIB | T4 | N0 | M0 |
| Stage IVA | Any T | N1 | M0 |
| Stage IVB | Any T | Any N | M1 |

**HCC, hepatocellular carcinoma; M, metastasis; N, node; T, tumour; UICC, Union for International Cancer Control**

**Brierley JD et al, eds. TNM Classification of Malignant Tumours, 8th edition. Oxford: John Wiley & Sons, Inc. 2016. Reprinted with permission from John Wiley & Sons, Ltd**

- The Barcelona Clinic Liver Cancer (BCLC) staging system, shown in the table on the next page, is a commonly accepted staging system for prognostic prediction and treatment allocation
- Coexistent liver disease is not an independent prognostic factor but therapy for treatable conditions may improve liver function and prognosis

## BCLC STAGING AND TREATMENT OPTIONS

| BCLC STAGE | | TREATMENT (STANDARD OF CARE) | INDICATION CONSTRAINTS BASED ON TUMOUR BURDEN AND LIVER FUNCTION | ALTERNATIVE TREATMENT |
|---|---|---|---|---|
| 0-A | Single tumour any size or ≤ 3 nodules ≤ 3 cm<br>Preserved liver function<br>ECOG PS 0 | Resection | Adequate size and function of remnant liver | SBRT<br>HDR brachytherapy<br>SIRT |
| | | Transplantation | Size ≤ 5 cm, number ≤ 3 | |
| | | Thermal ablation | Size ≤ 3 cm, not adjacent to vessels or bile duct | |
| | | TACE | Contraindications against resection and thermal ablation. Bridging to transplantation | |
| B | Multinodular<br>Preserved liver function<br>ECOG PS 0 | TACE | Size 5-10 cm, tumour nodules accessible to supraselective catheterisation | Transplantation<br>Resection<br>Systemic therapy (not suitable for local therapies)<br>SIRT (liver-confined, good liver function, no systemic therapy feasible) |
| C | Portal invasion Extrahepatic spread<br>Preserved liver function<br>ECOG PS 0-2 | Atezolizumab–bevacizumab (first line)<br>Option:<br>Sorafenib (first line)<br>Lenvantinib (first line)* | Child–Pugh A | SIRT (liver-confined, good liver function, no systemic therapy feasible) |
| | | Standard after sorafenib:<br>Cabozantinib<br>Regorafenib†<br>Ramucirumab‡<br>Option after atezolizumab–bevacizumab or lenvantinib:<br>Sorafenib<br>Lenvantinib<br>Cabozantinib<br>Regorafenib†<br>Ramucirumab‡ | Child–Pugh A<br>Tolerability to sorafenib (regorafenib)<br>AFP ≥ 400 ng/mL for ramucirumab | |
| D | End-stage liver function<br>ECOG PS 3-4 | BSC | | |

*Non-inferiority to sorafenib established; no evaluable benefit

†Regorafenib is not recommended in TKI-naive patients

‡Ramucirumab is only recommended in patients with an AFP level ≥ 400 ng/mL

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; HDR, high dose rate; PS, performance status; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation; TKI, tyrosine kinase inhibitor

- Liver decompensation (including jaundice, variceal haemorrhage, ascites or encephalopathy) is a contraindication for locoregional therapy that may induce subclinical liver damage, such as resection, percutaneous ablation or transarterial therapies
  - Systemic therapy benefits have not been established in these patients

## MANAGEMENT OF EARLY AND INTERMEDIATE HEPATOCELLULAR CARCINOMA

- Treatment modalities for patients with HCC according to BCLC stage are shown in the figure on pages 18 and 19

### Liver resection

- Liver resection (LR) is recommended for patients with single tumours and well preserved liver function provided a resection with no residual tumour at the margin (R0) can be achieved without causing postoperative liver failure due to insufficient reserve in the liver remnant
- Child–Pugh A patients without significant portal hypertension are considered good candidates for minor or major LRs
- Carefully selected patients with Child–Pugh B and/or portal hypertension may be candidates for minor surgical resection
- Child–Pugh C patients are not suitable for surgical therapy
- In patients with liver cirrhosis, LR should preferably be carried out as a laparoscopic resection
- Surgical resection in cirrhotic HCC patients with advanced tumour burden and macrovascular invasion is not recommended
- After LR, there is no clear recommendation regarding the extent of surgical resection (anatomical resection versus non-anatomical wedge resection)

### Orthotopic liver transplantation

- Orthotopic liver transplantation (OLT) is recommended for patients meeting Milan criteria (one lesion < 5 cm or up to three lesions, each < 3 cm; no extrahepatic manifestations; no evidence of macrovascular invasion) and where < 10% recurrence and 70% 5-year survival rates are expected

- The University of California San Francisco (UCSF) criteria (one tumour ≤ 6.5 cm or up to three nodules with the largest ≤ 4.5 cm and the total tumour diameter ≤ 8 cm) may also be considered for OLT in patients with HCC beyond Milan criteria
- When a long waiting time (> 3 months) is anticipated, resection, local ablation or transarterial chemoembolisation (TACE) may be considered to minimise the risk of tumour progression and to offer a "bridge" to transplant

### Adjuvant therapy

- Adjuvant therapy is not recommended for patients with HCC after OLT, LR or local ablation outside of clinical trials

### Thermal tumour ablation

- Radiofrequency ablation (RFA) or microwave ablation (MWA) may be recommended as first-line treatment in very early-stage HCC (BCLC 0)
- In early-stage HCC (up to three lesions ≤ 3 cm), RFA is an alternative first-line option to LR, irrespective of liver function
- The potential advantage of MWA compared with RFA is not well studied

### High conformal, high dose rate radioablation (stereotactic body radiotherapy; high dose rate brachytherapy)

- High conformal high dose rate radioablation and stereotactic body radiotherapy (SBRT) are alternative options for tumours with a high risk of local failure after thermal ablation due to location
- External beam radiotherapy (EBRT) can be used to control pain in patients with bone metastases
- Ablation recommendations should be proposed by the local multidisciplinary team, based on liver function, tumour size, tumour location and the centre's medical expertise

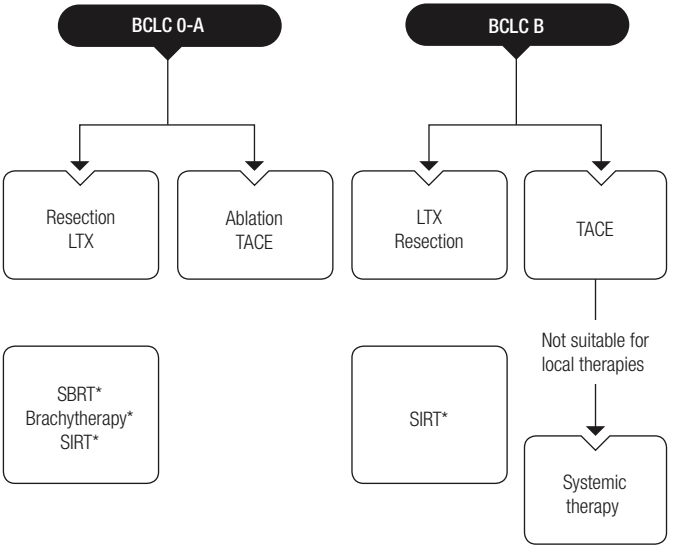
### Transarterial therapies

- Absolute contraindications for intra-arterial infusion of chemotherapy (ChT), embolising material or yttrium-90 radioactive particles are: Decompensated cirrhosis, extensive tumour burden, reduced portal vein (PV) flow, renal failure or any technical contraindication to transarterial therapy

### Transarterial chemoembolisation

- TACE prolongs overall survival (OS) in BCLC A to early intermediate BCLC B asymptomatic patients with maintained liver function and a small tumour burden who are not amenable to surgery or local ablation

## MANAGEMENT OF HCC ACCORDING TO BCLC STAGE



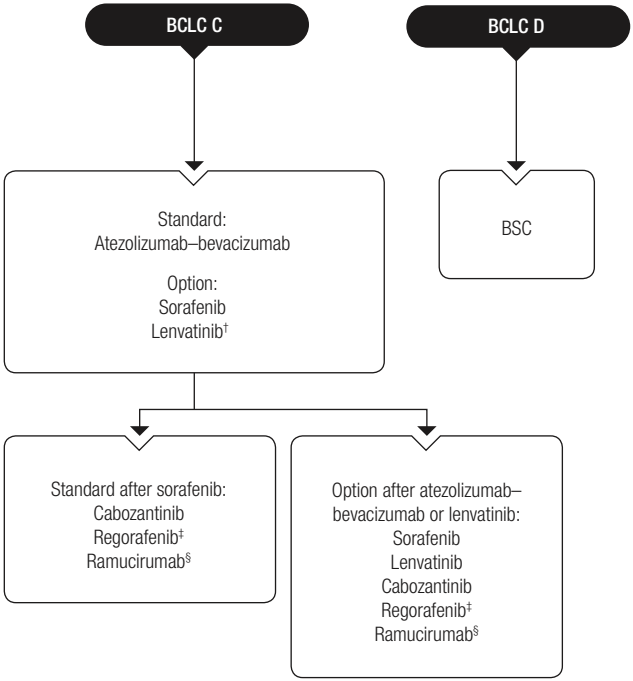

*See table on page 15 for indication constraints based on tumour burden and liver function

†Non-inferiority to sorafenib established; no evaluable benefit

‡Regorafenib is not recommended in TKI-naive patients

§Ramucirumab is only recommended in patients with an AFP level ≥ 400 ng/mL

AFP, $\alpha$-fetoprotein: BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; HCC, hepatocellular carcinoma; LTX, liver transplantation; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation; TKI, tyrosine kinase inhibitor


BCLC C
BCLC D
Standard:
Atezolizumab–bevacizumab
Option:
Sorafenib
Lenvatinib†
BSC
Standard after sorafenib:
Cabozantinib
Regorafenib‡
Ramucirumab§
Option after atezolizumab–
bevacizumab or lenvatinib:
Sorafenib
Lenvatinib
Cabozantinib
Regorafenib‡
Ramucirumab§

- Outside clinical trials, the use of therapeutic algorithms based on prognostic scores of unknown predictive values is not recommended for candidate selection for TACE
- Conventional lipiodol-based TACE is the standard of practice, but doxorubicin-eluting beads (DEB)-TACE may minimise the systemic side-effects of ChT
- The optimal duration and frequency of TACE treatment has not been defined but it should not be repeated where there is a failure to achieve either substantial necrosis after the second session or remission at initially responding sites
- The sequential or concomitant combination of TACE with systemic agents, such as sorafenib, cannot be recommended in clinical practice

### Selective internal radiotherapy

- Selective internal radiotherapy (SIRT) is not recommended as first-line therapy for patients with HCC with intermediate- or advanced-stage disease
  - The Phase III SARAH, SIRVENIB and SORAMIC trials, conducted in patients free from extrahepatic metastasis and with preserved liver function, failed to show a benefit of SIRT ± sorafenib over sorafenib alone
- SIRT may be considered in exceptional circumstances, e.g. for patients with liver-confined disease and preserved liver function in whom neither TACE nor systemic therapy are possible or for the treatment of small tumours in patients waiting for liver transplantation

## MANAGEMENT OF ADVANCED HEPATOCELLULAR CARCINOMA

### Systemic therapies for advanced hepatocellular carcinoma

#### *ChT*

- ChT has not been shown to improve survival in randomised trials and is not recommended as a standard of care

#### *Targeted first-line therapies*

#### Sorafenib

- Sorafenib is the standard of care for patients with advanced HCC (BCLC C) and those with intermediate-stage disease (BCLC B) not eligible for, or progressing despite, locoregional therapies
- It is recommended for patients with well-preserved liver function (Child–Pugh A) and Eastern Cooperative Oncology Group (ECOG) PS 0-2
- No predictive biomarkers of responsiveness to sorafenib have been identified
- The recommended daily dose of sorafenib is 800 mg, with a median treatment duration of 5-6 months, but early prevention of toxicities can enhance tolerability
- Clinically symptomatic coronary or peripheral vascular disease is a formal contraindication

Lenvatinib

- Lenvatinib is non-inferior in efficacy to sorafenib and can be considered as a first-line systemic treatment in ECOG PS 0-1 patients with advanced HCC without main PV invasion

*Targeted second-line therapies*

Regorafenib

- Regorafenib is the standard of care for patients with advanced HCC who have tolerated sorafenib but progressed and is recommended for patients with well-preserved liver function and ECOG PS 0-1

Cabozantinib

- Cabozantinib can be considered for patients with well-preserved liver function and ECOG PS 0-1 who have progressive disease following one or two systemic therapies

Ramucirumab

- Ramucirumab can be considered as second-line treatment for patients with baseline AFP ≥ 400 ng/mL, well-preserved liver function and ECOG PS 0-1

*Immunotherapies*

- Immunotherapy, in the form of combination regimens (atezolizumab–bevacizumab) or monotherapy, has been evaluated in untreated patients with BCLC B or C stage HCC
  - Atezolizumab–bevacizumab has shown superiority compared with sorafenib and is recommended as standard of care for the first-line treatment of patients with advanced HCC
  - The first-line Phase III CheckMate 459 trial, comparing sorafenib with nivolumab as a first-line treatment option, failed to meet the primary endpoint of OS
  - The second-line Phase III KEYNOTE-240 trial of pembrolizumab also failed to meet its co-primary endpoints of OS and progression-free survival (PFS), compared with placebo plus best supportive care

**ONGOING RESEARCH IN PERSONALISED THERAPY FOR HEPATOCELLULAR CARCINOMA**

- Molecular profiling is not recommended as a standard practice but tissue should be obtained in all research studies for exploring biomarkers of response
- The most common recurrent mutations in HCC are in the telomerase reverse transcriptase *(TERT)* promotor, catenin β1 *(CTNNB1)*, tumour suppressor protein p53 *(TP53)* and epigenetic regulators including AT-rich interactive domain-containing protein 1A *(ARID1A)* and 2 *(ARID2)*

## FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

- Viable tumour must be assessed using dynamic CT or MRI and should be defined as uptake of contrast agent in the arterial phase
- Modified Response Evaluation Criteria in Solid Tumours (mRECIST), as shown in the table below, require further prospective validation but may be used in daily clinical practice to consider tumour diameters and lesion viability in therapy decision making and are recommended for the assessment of response/progression to locoregional and systemic therapies

### RESPONSE ASSESSMENT BY RECIST V1.1 AND mRECIST FOR HCC

| | RECIST | mRECIST |
|---|---|---|
| CR | Disappearance of all target lesions | Disappearance of any intratumoural arterial enhancement in all target lesions |
| PR | ≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions | ≥ 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions |
| SD | Any cases that do not qualify for either PR or PD | Any cases that do not qualify for either PR or PD |
| PD | An increase of ≥ 20% in the sum of the diameters of target lesions (lymph nodes of 1.5 cm diameter), taking as reference the smallest sum of the diameters of target lesions recorded since treatment started<br>Development of new ascites | An increase of ≥ 20% in the sum of the diameters of viable (enhancing) target lesions (lymph nodes of 2 cm diameter), taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started<br>Development of new ascites with positive cytology |

**CR, complete response/remission; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumours; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease**

- There is limited evidence that OS can be predicted more accurately by mRECIST compared with Response Evaluation Criteria in Solid Tumours (RECIST) v1.1
- Response assessment following radioembolisation should be carried out by multiple phase MRI or CT at approximately 3-4 month intervals and can be captured by European Association for the Study of the Liver (EASL) criteria and mRECIST
- In the context of immunotherapy, serum tumour markers (such as AFP levels) may be helpful, particularly when disease is not easily measurable, but they should not be used as the sole basis for treatment decisions

- Follow-up of patients who underwent radical therapy (resection or RFA) should comprise the clinical evaluation of liver decompensation and the early detection of recurrence by dynamic CT or MRI every 3 months during the first year and surveillance every 6 months thereafter
- Patients with more advanced stages of HCC who are treated with TACE or systemic agents are evaluated clinically for signs of liver function and for tumour progression by dynamic CT or MRI every 3 months to guide therapy decisions

# HEREDITARY GASTROINTESTINAL CANCERS

## HEREDITARY GASTRIC CANCER

- Hereditary gastric cancer is diagnosed according to the figure on pages 26 and 27

### Hereditary diffuse gastric cancer

*Clinical and molecular diagnosis*

- Genetic testing for cadherin 1 *(CDH1)* is recommended in families with clinical criteria of hereditary diffuse gastric cancer (DGC)
- Testing of germline *CDH1* alterations is recommended in families fulfilling one of the following criteria, according to the International Gastric Cancer Linkage Consortium (IGCLC) guidelines:
  - Two or more documented cases of gastric cancer at any age in first- or second-degree relatives, with at least one confirmed DGC
  - Personal history of DGC before 40 years of age
  - Personal or family history (first- or second-degree relatives) of DGC and lobular breast cancer (LBC), one diagnosed before 50 years of age
- Genetic testing can be considered in families with bilateral or multiple cases of LBC before 50 years of age, families with clustering of DGC and cleft lip or cleft palate and any patient diagnosed with *in situ* or pagetoid spread of signet ring cells
- Testing from late teens or early 20s is favoured in families with early-onset DGC
- Germline testing should include both DNA sequencing and large rearrangement analysis

*Surveillance and risk reduction*

Endoscopic surveillance and prophylactic surgery

- Asymptomatic carriers of *CDH1* pathogenic germline mutations should be offered prophylactic gastrectomy or, for selected groups, annual endoscopic surveillance
- Annual endoscopic surveillance is recommended for individuals aged < 20 years, those declining gastrectomy and those with familial DGC and a variant of uncertain significance in *CDH1*
- A minimum of 30 random biopsies is recommended
- Any endoscopically detected malignant lesion should prompt referral for gastrectomy
- Total gastrectomy is recommended between 20 and 30 years of age
- In biopsy-positive individuals, a curative total gastrectomy is advised, regardless of age

### Breast cancer surveillance

- Annual breast magnetic resonance imaging (MRI) with mammography, starting at age 30 years, is recommended in women with a *CDH1* mutation
- Annual clinical breast examination and breast cancer awareness by the patient and physician are essential

### Familial intestinal gastric cancer

#### *Clinical and molecular diagnosis*

- Criteria for familial intestinal gastric cancer (FIGC) for high-incidence countries proposed by the IGCLC are analogous to the Amsterdam criteria, and are used to identify individuals at risk of Lynch syndrome (LS) based on age and family history of cancer, as shown in the table below

**AMSTERDAM CRITERIA II GUIDELINES**

| Amsterdam criteria II |
| --- |
| At least three relatives must have a cancer associated with LS (CRC, cancer of the endometrium, small bowel, ureter or renal–pelvis); all of the following criteria should be present:<br>• One must be an FDR of the other two<br>• At least two successive generations must be affected<br>• At least one relative with a cancer associated with LS should be diagnosed before age 50 years<br>• FAP should be excluded in the CRC case(s) (if any)<br>• Tumours should be verified whenever possible |

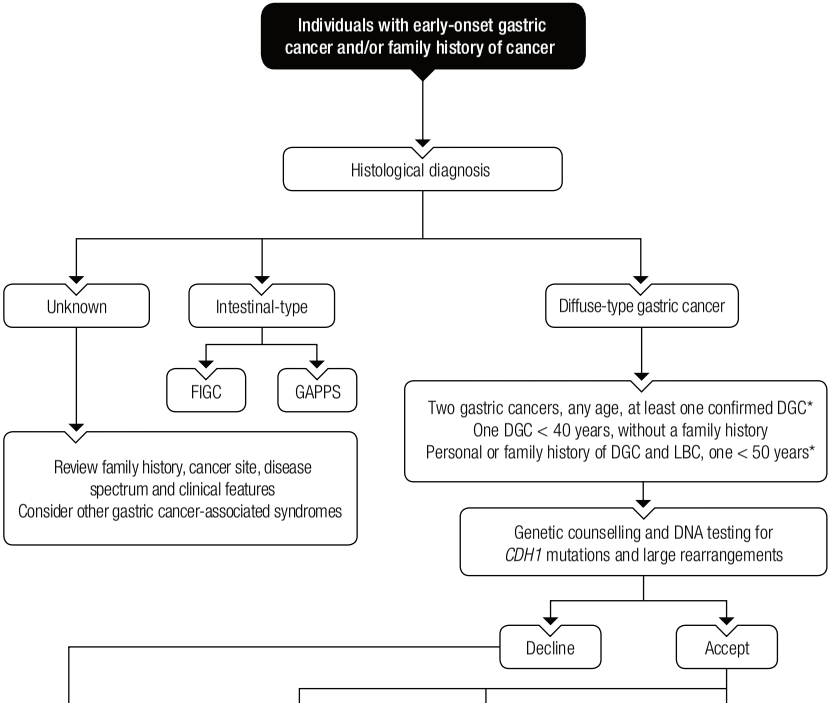
**CRC, colorectal cancer; FAP, familial adenomatous polyposis; FDR, first-degree relative; LS, Lynch syndrome**
**Vasen HF et al. Gastroenterology 1999;116(6):1453-6. Reprinted with permission from Elsevier**

- FIGC criteria for low-incidence countries include:
  - At least two first- or second-degree relatives affected by intestinal gastric cancer, one of them diagnosed before 50 years of age
  - Three or more relatives with intestinal gastric cancer at any age
- The diagnosis is considered when there is a family history of intestinal-type gastric cancer in families without polyposis
- The genetic cause of FIGC is unknown

#### *Surveillance and risk reduction*

- No robust recommendations can be made for the management of individuals at risk
- Eradication of *Helicobacter pylori* is advised in family members of patients with intestinal gastric cancer below 40 years of age or in families with clustering of FIGC

## DIAGNOSTIC WORK-UP OF HEREDITARY GASTRIC CANCER



***Including first- or second-degree relatives**

**BC, breast cancer; *CDH1*, cadherin 1; *CTNNA1*, catenin $\alpha$1; DGC, diffuse gastric cancer; FIGC, familial intestinal gastric cancer; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; LBC, lobular breast cancer; MDT, multidisciplinary team**

### Gastric adenocarcinoma and proximal polyposis of the stomach

*Clinical and molecular diagnosis*

- Clinical criteria are required for the diagnosis of gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS):
  - Gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis
  - > 100 polyps carpeting the proximal stomach in the index case, or > 30 polyps in a first-degree relative (FDR) of another case
  - Mainly fundic gastric polyps, some with regions of dysplasia (or a family member with either dysplastic fundic gastric polyps or gastric adenocarcinoma)
  - Autosomal dominant pattern of inheritance
  - Exclusions include other hereditary gastric polyposis syndromes and use of proton-pump inhibitors
- GAPPS is considered to be a familial adenomatous polyposis (FAP) variant with a predominant gastric phenotype

*Surveillance and risk reduction*

- Management includes endoscopic surveillance with random biopsies or preferably polypectomies directed to large and/or irregular polyps and, eventually, prophylactic gastrectomy
- Due to lack of data, individualised management is advised

## HEREDITARY PANCREATIC CANCER

### Clinical and molecular diagnosis

- Diagnosis is based on the clinical criteria of the different associated syndromes, including hereditary breast or ovarian cancer, familial atypical multiple mole melanoma, LS, FAP, ataxia telangiectasia, Peutz–Jegher syndrome (PJS) and hereditary pancreatitis (HP), followed by confirmation with genetic testing
- The most common cause of hereditary pancreatic cancer (PC) is *BRCA2* mutation
- The cause of hereditary PC is often not identified and familial PC applies to families with two or more FDRs with PC who do not fulfil the criteria for any other inherited tumour syndrome
- Multigene panel testing, covering *BRCA1, BRCA2,* partner and localiser of *BRCA2 (PALB2)* and cyclin-dependent kinase inhibitor 2A *(CDKN2A),* is recommended for families with a strong clustering of PC

### Surveillance of patients at high risk for pancreatic cancer

- The International Cancer of the Pancreas Screening (CAPS) Consortium consensus recommends surveillance for patients at high risk for PC:
  - Individuals with at least three blood relatives diagnosed with PC, with at least one affected FDR
  - Individuals with at least two affected FDRs with PC
  - Patients with PJS, regardless of a family history of PC
  - *CDKN2A/p16* carriers with one affected FDR
  - *BRCA2* mutation carriers with one affected FDR (or two affected family members, no FDR) with PC
  - *PALB2* mutation carriers with one affected FDR
  - Mismatch repair gene mutation carriers (LS) with one affected FDR
- Annual endoscopic ultrasonography and/or pancreatic MRI are the procedures of choice for surveillance
- Surveillance programmes generally begin at age 50 years (or 10 years earlier than the age of the youngest affected relative)
- For patients with HP or PJS, starting surveillance at ages 30 and 40 years, respectively, is recommended

### Surgical management in patients at high risk for pancreatic cancer

- For suspicious lesions, there is no consensus as to the extent of pancreatic resection (partial or total pancreatectomy) and surgical intervention must be individualised
- In gene mutation carriers without any precursor lesion, prophylactic pancreatectomy is not indicated

# OESOPHAGEAL CANCER

## DIAGNOSIS

- The recommended diagnostic and staging investigations for oesophageal cancer are shown in the table below

### DIAGNOSTIC AND STAGING INVESTIGATIONS IN OESOPHAGEAL CANCER

| PROCEDURE | PURPOSE |
|---|---|
| CBC | Assess for iron deficiency anaemia |
| Renal and liver function | Assess renal and liver function to determine appropriate therapeutic options |
| Endoscopy and biopsy | Obtain tissue for diagnosis, histological classification and molecular biomarkers, e.g. PD-L1 and HER2 status (AC) |
| EUS | Accurate assessment of T and N stage in potentially resectable tumours |
| Bronchoscopy with endobronchial ultrasonography | Assess tumour growth towards central airways; complementary to EUS, especially when tumour stricture precludes EUS |
| CT of thorax + abdomen ± pelvis | Staging of tumour – to detect local/distant lymphadenopathy and metastatic disease |
| PET-CT, if available | Staging of tumour – to detect local/distant lymphadenopathy and metastatic disease |
| Laparoscopy ± washings | Exclude occult metastatic disease involving peritoneum/ diaphragm, especially in locally advanced (T3/T4) ACs of the OGJ infiltrating the anatomical cardia |

**AC, adenocarcinoma; CBC, complete blood count; CT, computed tomography; EUS, endoscopic ultrasound; HER2, human epidermal growth factor receptor 2; N, node; OGJ, oesophagogastric junction; PD-L1, programmed death-ligand 1; PET, positron emission tomography; T, tumour**

- Upper intestinal endoscopy should be carried out in patients with new dysphagia, gastrointestinal bleeding, recurrent aspiration or emesis and weight loss and/or loss of appetite
- Diagnosis of oesophageal cancer is via histopathological assessment of ≥ 6 endoscopic biopsies
  - Multiple biopsies are necessary for adequate representation of the tumour and sufficient tissue for molecular analysis
  - Biopsies should be taken from all suspicious areas

### Pathology

- Histology should be reported according to the World Health Organization (WHO) criteria [Nagtegaal ID et al. Histopathol 2020;76(2):182-8]
- Differentiation between oesophageal squamous cell carcinoma (SCC) and oesophageal adenocarcinoma (AC) is of prognostic and therapeutic relevance
  - Immunohistochemistry (IHC) staining is recommended in poorly differentiated and undifferentiated cancers when it is not possible to differentiate between SCC and AC using morphological characteristics
- For oesophageal SCC, programmed death-ligand 1 (PD-L1) expression by IHC according to the tumour proportion score (TPS) or combined positive score (CPS) is a validated predictive biomarker in patients who are candidates for first-line treatment with immune checkpoint inhibitor (ICI) therapy
- Molecular pathology assessment in oesophageal and oesophagogastric junction (OGJ) AC should follow the recommendations provided in the ESMO Clinical Practice Guideline (CPG) for gastric cancer (https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/gastric-cancer)

## STAGING AND RISK ASSESSMENT

- Initial staging and risk assessment should include a physical examination and endoscopy, as well as a contrast-enhanced computed tomography (CT) or [$^{18}$F]2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)-CT scan of the thorax, abdomen ± pelvis
- Endoscopic ultrasound (EUS) can be used for tumour (T) and node (N) staging
  - EUS has low accuracy for T1 tumours; in these cases, endoscopic resection offers more precise staging as well as therapeutic benefit
- Bronchoscopy with endobronchial ultrasonography is a useful complement to EUS for assessment of tumour growth towards the central airways, especially when tumour stricture precludes the use of EUS
- FDG-PET should be carried out in patients who are candidates for oesophagectomy, as the finding of distant metastases can help to avoid futile surgery
- In locally advanced (T3 or T4) ACs of the OGJ that cross the diaphragm to infiltrate the anatomical cardia, laparoscopy should be carried out to rule out peritoneal metastases
- The tumour–node–metastasis (TNM) stage should be recorded according to the eighth edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) guidelines and staging manual, as shown in the tables on the next pages

## TNM STAGING OF OESOPHAGEAL CANCER ACCORDING TO THE AJCC/UICC EIGHTH EDITION

| PRIMARY TUMOUR (T) | | REGIONAL LYMPH NODES (N)* | | DISTANT METASTASIS (M) | |
|---|---|---|---|---|---|
| TX | Primary tumour cannot be assessed | NX | Regional lymph nodes cannot be assessed | M0 | No distant metastasis |
| T0 | No evidence of primary tumour | N0 | No regional lymph node metastasis | M1 | Distant metastasis |
| Tis | Carcinoma *in situ*/high grade dysplasia | N1 | Metastasis in 1-2 regional lymph nodes | | |
| T1 | Tumour invades lamina propria, muscularis mucosae or submucosa | N2 | Metastasis in 3-6 regional lymph nodes | | |
| T1a | Tumour invades lamina propria or muscularis mucosae | N3 | Metastasis in ≥ 7 regional lymph nodes | | |
| T1b | Tumour invades submucosa | | | | |
| T2 | Tumour invades muscularis propria | | | | |
| T3 | Tumour invades adventitia | | | | |
| T4 | Tumour invades adjacent structures | | | | |
| T4a | Tumour invades pleura, pericardium, azygos vein, diaphragm or peritoneum | | | | |
| T4b | Tumour invades other adjacent structures such as aorta, vertebral body or trachea | | | | |

***The regional lymph nodes, irrespective of the site of the primary tumour, are those in the oesophageal drainage area including coeliac axis nodes and paraesophageal nodes in the neck but not the supraclavicular nodes**

**AJCC, American Joint Committee on Cancer; M, metastasis; N, node; T, tumour; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control**

**Brierley JD et al (eds). TNM Classification of Malignant Tumours, 8th edition. John Wiley & Sons, Inc.; 2016. Reprinted with permission**

**ANATOMIC STAGE/PROGNOSTIC GROUPS FOR OESOPHAGEAL CANCER ACCORDING TO THE AJCC/UICC EIGHTH EDITION**

| STAGE GROUPING | T STAGE | N STAGE | M STAGE |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1a | N0 | M0 |
| Stage IB | T1b | N0 | M0 |
| Stage IIA | T2 | N0 | M0 |
| Stage IIB | T1 | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T1 | N2 | M0 |
| | T2 | N1 | M0 |
| Stage IIIB | T2 | N2 | M0 |
| | T3 | N1, N2 | M0 |
| | T4a | N0, N1 | M0 |
| Stage IVA | T4a | N2 | M0 |
| | T4b | Any N | M0 |
| | Any T | N3 | M0 |
| Stage IVB | Any T | Any N | M1 |

AJCC, American Joint Committee on Cancer; M, metastasis; N, node; T, tumour; UICC, Union for International Cancer Control
Brierley JD et al (eds). TNM Classification of Malignant Tumours, 8th edition. John Wiley & Sons, Inc.; 2016. Reprinted with permission

- Nutritional status and history of weight loss should be assessed according to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [Cederholm T et al. Clin Nutr 2017;36(1):49-64]
  - Nutritional support should be provided according to ESPEN guidelines [Bischoff SC et al. Clin Nutr 2020;39(1):5-22]
- Reduced physical fitness is associated with worse outcomes; therefore, a supervised exercise programme can be recommended
- Geriatric screening and assessment can help to identify patients who need additional support and/or are at increased risk of treatment-associated side-effects

## TREATMENT

### Management of local and locoregional oesophageal cancer

- Multidisciplinary assessment and planning are mandatory before any treatment
- Treatment should be determined in collaboration with the patient, based on histological subtype, clinical TNM stage, tumour location and the patient's predicted treatment tolerance

- Treatment for malnutrition may be needed before curative-intent therapy
  - Enteral feeding is occasionally necessary, either via feeding jejunostomy or nasogastric tube
- Endoscopic stenting should be avoided in patients undergoing treatment with curative intent as this may worsen prognosis
- Management options are shown in the figure opposite

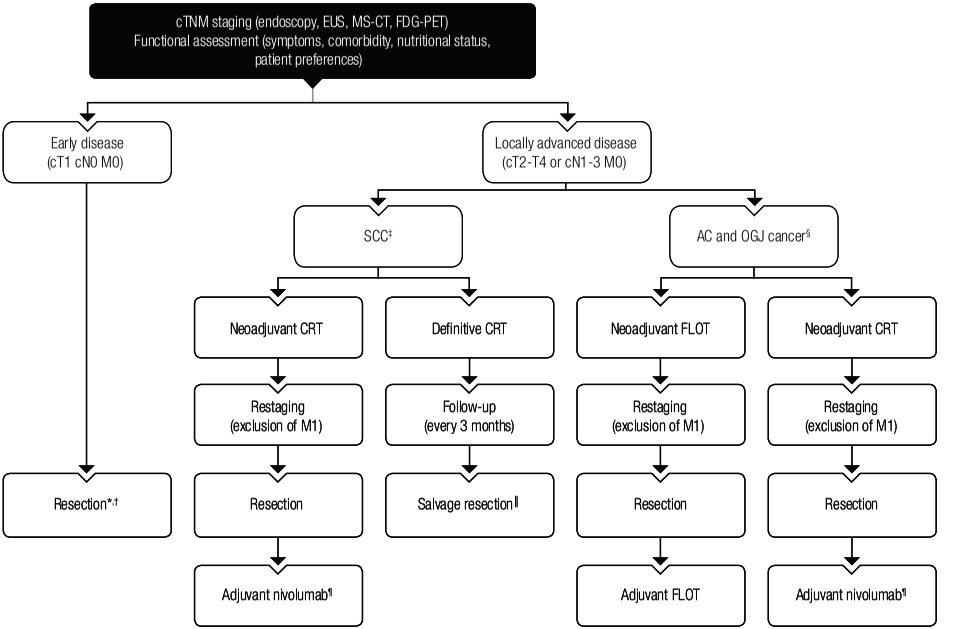
*Early oesophageal cancer (cT1 N0 M0)*

- For lesions with intraepithelial high-grade dysplasia and most T1 tumours, endoscopic *en bloc* resection via endoscopic mucosal resection or endoscopic submucosal dissection is preferred
- In both SCC and AC, further surgery with appropriate lymphadenectomy should be offered to patients with involved deep endoscopic resection margins or significant risk factors for lymph node metastases
  - Chemoradiotherapy (CRT) could be considered for stage IA SCC with organ preservation

*Locally advanced resectable oesophageal cancer*

- Surgery is still the backbone of curative-intent treatment for locally advanced resectable oesophageal SCC and AC
  - The procedure of choice in fit patients is radical transthoracic oesophagectomy with *en bloc* two-field lymphadenectomy
  - In experienced centres, minimally-invasive oesophagectomy is the preferred surgical approach
- Locally advanced oesophageal SCC should be treated with CRT followed by surgery
  - Definitive CRT with surveillance and salvage oesophagectomy (when needed for local tumour control) is also a recommended option, even in upfront resectable cases of oesophageal SCC
  - Definitive CRT is recommended for cervically localised tumours where surgery would entail a laryngectomy
- Locally advanced AC of the oesophagus and OGJ should be treated with preoperative CRT or pre-/perioperative chemotherapy (ChT) followed by surgery
  - The recommended neoadjuvant CRT should be based on the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) regimen [weekly carboplatin–paclitaxel combined with radiotherapy (RT) to a dose of 41.4 Gy in 23 fractions]
  - The recommended perioperative ChT regimen is 5-fluorouracil (5-FU)–leucovorin (LV)–oxaliplatin–docetaxel (FLOT)

## MANAGEMENT OF LOCAL/LOCOREGIONAL RESECTABLE OESOPHAGEAL AND OGJ CANCER



*Criteria for endoscopic instead of surgical resection are specified in the text

†For patients unable or unwilling to undergo surgery, combined CRT is superior to RT alone

‡Evidence suggests that neoadjuvant CRT followed by surgery and definitive CRT are equally effective in terms of OS. Oesophageal surgery should be carried out in experienced (high-volume) centres only. For patients unwilling to undergo oesophageal surgery or who are medically unfit for major surgery, definitive CRT should be preferred

§Sufficient evidence supports the use of perioperative ChT as well as neoadjuvant CRT. Several ongoing studies in Europe are comparing both modalities and inclusion of patients in one of these studies is encouraged

‖Optional in cases of incomplete response to CRT or local relapse and should only be carried out in selected patients at experienced centres

¶With residual vital tumour in the resection specimen

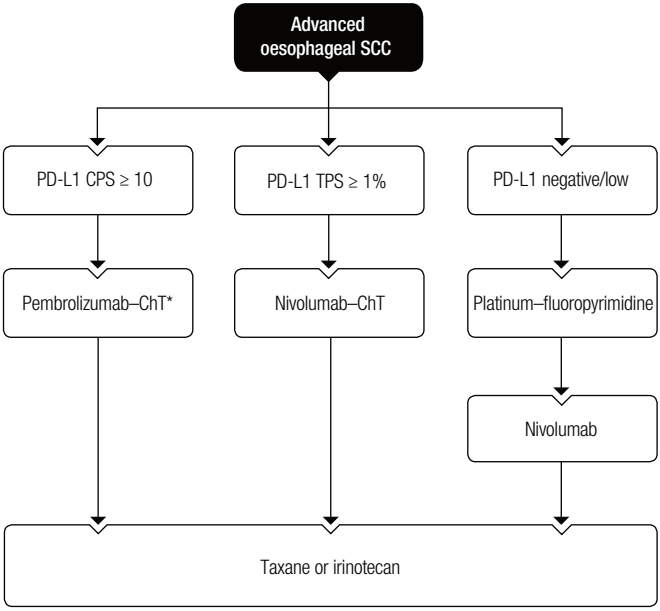
AC, adenocarcinoma; ChT, chemotherapy; CRT, chemoradiotherapy; cTNM, clinical tumour–node–metastasis; EUS, endoscopic ultrasound; FDG-PET, [$^{18}$F]2-fluoro-2-deoxy-D-glucose-positron emission tomography; FLOT, 5-fluorouracil–leucovorin–oxaliplatin–docetaxel; MS-CT, multislice-computed tomography; OGJ, oesophagogastric junction; OS, overall survival; RT, radiotherapy; SCC, squamous cell carcinoma

- Even after a complete response to preoperative CRT or ChT, patients with resectable oesophageal AC should undergo surgery, as data for a watch-and-wait strategy are limited
- Adjuvant nivolumab is recommended for patients with SCC or AC of the oesophagus (including OGJ cancer) who have undergone neoadjuvant CRT and show evidence of residual pathological disease in the resection specimen
- Definitive CRT is recommended for patients with unresectable, locally advanced SCC and those who are unable to undergo surgery
  - The traditional standard regimen for definitive CRT is four cycles of cisplatin–5-FU (or capecitabine) combined with RT (50.4 Gy in 28 fractions or 50 Gy in 25 fractions)
  - Alternatively, six cycles of 5-FU–LV–oxaliplatin can be considered. Weekly carboplatin–paclitaxel (as in the CROSS regimen) is also commonly used due to its favourable toxicity profile
  - As a minimum requirement, RT should be delivered using 3D conformal RT, but intensity modulated RT or volumetric arc therapy are preferred to minimise the radiation dose to critical normal tissues
  - There is limited evidence to support the use of RT doses > 50.4 Gy for the definitive treatment of oesophageal cancer

### Management of advanced and metastatic oesophageal cancer

- Treatment of advanced AC of the oesophagus and OGJ should be according to the ESMO CPG for gastric cancer (https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/gastric-cancer)
- Management options for advanced oesophageal SCC are shown in the figure opposite

**MANAGEMENT OF ADVANCED OESOPHAGEAL SCC**




*EMA approval is for tumours with PD-L1 CPS ≥ 10, FDA approval is irrespective of PD-L1 expression

ChT, chemotherapy; CPS, combined positive score; EMA, European Medicines Agency; FDA, Food and Drug Administration; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma; TPS, tumour proportion score

### *First-line treatment of advanced oesophageal SCC*

- ChT with platinum–fluoropyrimidine is recommended as a standard first-line treatment for advanced oesophageal SCC
  - Dose-reduced oxaliplatin–capecitabine is an alternative option for patients who are unsuitable for full-dose ChT
- Pembrolizumab–ChT is recommended, with the greatest benefit observed in patients with a PD-L1 CPS ≥ 10
- Nivolumab–ChT is recommended in patients with tumours expressing PD-L1 with a TPS ≥ 1%

- Nivolumab–ipilimumab is also an option but several factors should be considered, including:
  - Nivolumab–ipilimumab is associated with a lower radiological response rate compared with ChT alone or nivolumab–ChT
  - There is an increased risk of early progression and death in patients not treated with ChT

*Second and subsequent lines of treatment for advanced oesophageal SCC*

- Nivolumab monotherapy is recommended for oesophageal SCC previously treated with platinum–fluoropyrimidine
- Where approved, pembrolizumab may be an option for previously treated patients with SCC who have not received first-line ICI therapy and have a PD-L1 CPS ≥ 10
- ChT with a taxane or irinotecan can be considered in fit patients who have previously received platinum–fluoropyrimidine and/or nivolumab or pembrolizumab

*Supportive care and nutrition*

- Supportive care is critical for the wellbeing of patients with advanced oesophageal cancer and should include early palliative care referral and nutritional support
- Supportive care should follow the recommendations provided in the ESMO CPG for gastric cancer (https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/gastric-cancer)

## FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

- Surveillance strategies after successful therapy for oesophageal and OGJ cancers remain controversial
  - Although ~90% of relapses occur within the first 2 years after completion of local therapy, potentially treatable relapses have been reported > 5 years after local therapy
  - Metachronous malignancies should also be considered in long-term survivors
- There is no evidence that regular follow-up after initial therapy has an impact on survival except in patients who may be candidates for an endoscopic reintervention or early salvage surgery after endoscopic resection or definitive CRT
- Follow-up visits should focus on symptoms, nutrition and psychosocial support
  - Patients can develop a variety of needs and problems associated with loss of the oesophagus, other treatment sequelae or psychosocial needs
  - The expertise of a dietician, radiologist, gastroenterologist, psychologist and social worker are often needed during follow-up
- In case of a complete response to definitive CRT, a 3-month follow-up based on endoscopy, biopsies and a CT scan may be recommended to detect early recurrence

# GASTRIC CANCER

## GENETIC PREDISPOSITION, SCREENING AND PREVENTION

- Gastric cancer demonstrates familial aggregation in ~10% of cases
- Referral to a geneticist is recommended if a familial cancer syndrome is suspected
- Associated syndromes are shown in the table below

## GENE MUTATIONS ASSOCIATED WITH INHERITED PREDISPOSITION TO GASTRIC CANCER

| GENE MUTATION | ASSOCIATED SYNDROME |
|---|---|
| *APC* | FAP |
| *APC* promoter 1B | GAPPS |
| *CDH1, CTNNA1* | HDGC |
| *MLH1, MSH2, MSH6, PMS2* | Lynch syndrome |
| *SMAD4, BMPR1A* | Juvenile polyposis syndrome |
| *STK11* | Peutz–Jegher syndrome |
| *TP53* | Li–Fraumeni syndrome |

***APC***, adenomatous polyposis coli; ***BMPR1A***, bone morphogenetic protein receptor type 1A; ***CDH1***, cadherin 1; ***CTNNA1***, catenin $\alpha$1; FAP, familial adenomatous polyposis; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; HDGC, hereditary diffuse gastric cancer; ***MLH1***, MutL homologue 1; ***MSH2***, MutS homologue 2; ***MSH6***, MutS homologue 6; ***PMS2***, PMS1 homologue 2 mismatch repair system component; ***SMAD4***, mothers against decapentaplegic homologue 4; ***STK11***, serine/threonine kinase 11; ***TP53***, tumour suppressor protein p53

Rustgi SD et al. Gastrointest Endosc Clin N Am 2021;31(3):467-87. Reprinted with permission

- European and United Kingdom guidelines recommend that patients with intestinal metaplasia (IM) as well as a family history of gastric cancer, incomplete-type IM or persistent *Helicobacter pylori*-associated gastritis, should undergo endoscopic surveillance with guided biopsies every 3 years
- Population-based endoscopic screening of asymptomatic individuals is only recommended in regions with a very high incidence of gastric cancer

## DIAGNOSIS

- Gastric cancer is frequently asymptomatic in the early stages, while advanced disease commonly presents with dysphagia, asthenia, indigestion, vomiting, weight loss, early satiety and/or iron deficiency anaemia
- Endoscopic examination and forceps biopsy are the gold standard method for diagnosing gastric cancer
  - 5-8 endoscopic biopsies should be collected to guarantee adequate tumour representation

### Pathology

- Histological diagnosis should be reported according to World Health Organization (WHO) 2019 criteria
- The majority of gastric cancers (90%) are adenocarcinomas (ACs), which are subdivided histologically by the WHO classification into five subtypes: Tubular, papillary, poorly cohesive (including signet ring cell and other subtypes), mucinous and mixed ACs

### Molecular biology

- Gastric cancer can be stratified into four molecularly distinct subtypes: Epstein–Barr virus (EBV)-positive, microsatellite instability-high (MSI-H), genomically stable and chromosomal instability
- Human epidermal growth factor receptor 2 (HER2), programmed death-ligand 1 (PD-L1) and MSI/mismatch repair (MMR) are validated predictive biomarkers for drug therapy
- Other molecular markers, such as fibroblast growth factor receptor 2 *(FGFR2)* gene amplification/overexpression, MET proto-oncogene receptor tyrosine kinase *(MET)* gene amplification, claudin-18.2 overexpression and EBV are being investigated

## STAGING AND RISK ASSESSMENT

- Initial staging and risk assessment should include physical examination, complete and differential blood count, liver and renal function tests, endoscopy and contrast-enhanced computed tomography (CT) scan of the thorax, abdomen ± pelvis, as shown in the table on the next page

## DIAGNOSTIC AND STAGING INVESTIGATIONS IN GASTRIC CANCER

| PROCEDURE | PURPOSE |
|---|---|
| CBC | Assess for iron deficiency anaemia |
| Renal and liver function | Assess renal and liver function to determine appropriate therapeutic options |
| Endoscopy and biopsy | Obtain tissue for diagnosis, histological classification and molecular biomarkers, e.g. HER2 status |
| Contrast-enhanced CT of thorax + abdomen ± pelvis | Staging of tumour – to detect local/distant lymphadenopathy and metastatic disease or ascites |
| EUS | Accurate assessment of T and N stage in potentially operable tumours<br>Determine the proximal and distal extent of tumour |
| Laparoscopy + washings | Exclude occult metastatic disease involving peritoneum/diaphragm |
| PET, if available | May improve detection of occult metastatic disease in some cases. Often negative in diffuse-type gastric cancer |
| Assessment of nutritional status | May detect relevant dietary and nutritional deficiencies in both localised and advanced disease settings |

**CBC, complete blood count; CT, computed tomography; EUS, endoscopic ultrasound; HER2, human epidermal growth factor receptor 2; N, node; PET, positron emission tomography; T, tumour**

- The sensitivity of CT for lymph node staging is variable and global consensus is lacking on specific diagnostic criteria
  - Endoscopic ultrasound is more sensitive than CT for node staging
- [$^{18}$F]2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)-CT is not routinely recommended due to low tracer uptake in mucinous or diffuse tumours

- Diagnostic laparoscopy and peritoneal washings for cytology are recommended for patients with resectable gastric cancer who are also candidates for perioperative chemotherapy (ChT), to exclude radiologically and macroscopically occult peritoneal metastatic disease
  - Patients with positive lavage cytology are uncertain candidates for curatively-intended resection
- Patients should be tested for dihydropyrimidine dehydrogenase deficiency before starting treatment with 5-fluorouracil (5-FU), capecitabine or tegafur
- The tumour–node–metastasis (TNM) stage should be recorded according to the eighth edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging manual, as shown in the tables on the next pages

## TNM STAGING OF GASTRIC CANCER ACCORDING TO THE AJCC/UICC EIGHTH EDITION

| PRIMARY TUMOUR (T) | | REGIONAL LYMPH NODES (N) | | DISTANT METASTASIS (M) | |
|---|---|---|---|---|---|
| TX | Primary tumour cannot be assessed | NX | Regional lymph node(s) cannot be assessed | M0 | No distant metastasis |
| T0 | No evidence of primary tumour | N0 | No regional lymph node metastasis | M1 | Distant metastasis[§] |
| Tis | Carcinoma *in situ*: Intraepithelial tumour without invasion of the lamina propria, high grade dysplasia | N1 | Metastasis in 1-2 regional lymph nodes | | |
| T1 | Tumour invades lamina propria, muscularis mucosae or submucosa | N2 | Metastasis in 3-6 regional lymph nodes | | |
| T1a | Tumour invades lamina propria or muscularis mucosae | N3 | Metastasis in ≥ 7 regional lymph nodes | | |
| T1b | Tumour invades submucosa | N3a | Metastasis in 7-15 regional lymph nodes | | |
| T2 | Tumour invades muscularis propria | N3b | Metastasis in ≥ 16 regional lymph nodes | | |
| T3 | Tumour invades subserosa | | | | |
| T4 | Tumour perforates serosa (visceral peritoneum) or invades adjacent structures*,†,‡ | | | | |
| T4a | Tumour perforates serosa | | | | |
| T4b | Tumour invades adjacent structures*,† | | | | |

*The adjacent structures of the stomach are the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine and retroperitoneum

†Intramural extension to the duodenum or oesophagus is classified by the depth of greatest invasion in any of these sites including stomach

‡Tumour that extends into gastrocolic or gastrohepatic ligaments or into greater or lesser omentum, without perforation of visceral peritoneum, is T3

§Distant metastasis includes peritoneal seeding, positive peritoneal cytology and omental tumour not part of continuous extension

AJCC, American Joint Committee on Cancer; M, metastasis; N, node; T, tumour; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control

Amin MB et al (eds). AJCC Cancer Staging Manual. Eighth edition. Springer; 2017. Reprinted with permission

Brierley JD et al (eds). UICC TNM Classification of Malignant Tumours, 8th edition. Wiley-Blackwell; 2017. Reprinted with permission

## ANATOMIC STAGE/PROGNOSTIC GROUPS FOR GASTRIC CANCER ACCORDING TO THE AJCC/UICC EIGHTH EDITION

| STAGE GROUPING | T STAGE | N STAGE | M STAGE |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1 | N0 | M0 |
| Stage IB | T2 | N0 | M0 |
| | T1 | N1 | M0 |
| Stage IIA | T3 | N0 | M0 |
| | T2 | N1 | M0 |
| | T1 | N2 | M0 |
| Stage IIB | T4a | N0 | M0 |
| | T3 | N1 | M0 |
| | T2 | N2 | M0 |
| | T1 | N3a | M0 |
| Stage IIIA | T4b | N0 | M0 |
| | T4a | N1-2 | M0 |
| | T3 | N2 | M0 |
| | T2 | N3a | M0 |
| Stage IIIB | T4b | N1-2 | M0 |
| | T3-4a | N3a | M0 |
| | T1-2 | N3b | M0 |
| Stage IIIC | T4b | N3a-3b | M0 |
| | T3-4a | N3b | M0 |
| Stage IV | Any T | Any N | M1 |

AJCC, American Joint Committee on Cancer; M, metastasis; N, node; T, tumour; UICC, Union for International Cancer Control
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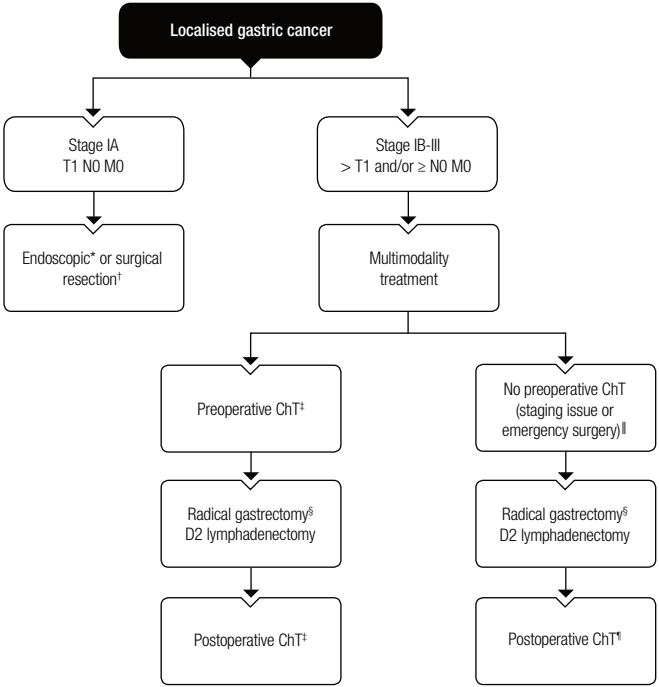
Brierley JD et al (eds). UICC TNM Classification of Malignant Tumours, 8th edition. Wiley-Blackwell; 2017. Reprinted with permission

## TREATMENT

### Management of local and locoregional gastric cancer

- Multidisciplinary treatment planning is mandatory before any therapy decisions are made
- Treatment options for localised gastric cancer are shown in the figure opposite

## MANAGEMENT OF LOCALISED GASTRIC CANCER




*Endoscopic resection indicated if (1) confined to mucosa, (2) well-differentiated grade 1-2, (3) ≤ 2 cm, (4) non-ulcerated. Endoscopic resection to be considered if no more than two expanded criteria are met according to Pimentel-Nunes P et al. Endoscopy 2015;47(9):829-54

†Lymph node dissection for T1 tumours may be confined to perigastric lymph nodes and include local N2 nodes (D1+ lymphadenectomy, with variation in nodal groups dissected according to site of cancer)

‡A triplet ChT regimen including a fluoropyrimidine, a platinum compound and docetaxel should be given when possible, for a duration of 2-3 months pre- and postoperatively

§Subtotal gastrectomy may be carried out if a macroscopic proximal margin of ≥ 3 cm can be achieved. For cancers of the poorly cohesive/diffuse subtype, a margin of ≥ 5 cm is advocated

‖For patients with stage ≥ IB gastric cancer who have undergone surgery without administration of preoperative ChT; however, a perioperative approach is preferred

¶A doublet ChT for a total duration of 6 months containing a fluoropyrimidine plus oxaliplatin or docetaxel is recommended; for patients with an R1 resection, adjuvant RT or ChT might be considered as an individual recommendation but is not standard; for patients with MSI-H gastric cancers who have undergone surgery, adjuvant ChT cannot be recommended

ChT, chemotherapy; M, metastasis; MSI-H, microsatellite instability-high; N, node; R1, microscopic tumour at the margin; RT, radiotherapy; T, tumour

*Resection*

- Endoscopic or surgical resection alone is appropriate for selected very early tumours (stage IA)
  - Endoscopic resection of early gastric cancer should be carried out *en bloc* and allow for a complete histological evaluation of the lateral and basal resection margins
- For stage IB-III gastric cancer, perioperative therapy and radical gastrectomy is recommended
  - A proximal margin of ≥ 3 cm is recommended for tumours with an expansive growth pattern (including intestinal histotypes) and ≥ 5 cm is recommended for tumours with an infiltrative growth pattern (including poorly cohesive/diffuse histotypes)
  - Subtotal gastrectomy can be considered when a satisfactory proximal resection margin can be obtained
  - Patients should undergo D2 resection of lymph nodes at a specialised high-volume surgical centre with appropriate surgical expertise and postoperative care

*Perioperative ChT*

- For stage IB-III tumours, perioperative (pre- and postoperative) therapy is recommended so that patients can benefit from systemic treatment even if the post-operative component of treatment cannot be delivered
- A triplet fluoropyrimidine–platinum–docetaxel regimen should be given when possible
  - Perioperative use of 5-FU–leucovorin (LV)–oxaliplatin–docetaxel (FLOT) is standard of care for patients who are able to tolerate a triplet cytotoxic drug regimen
- For patients unfit for triplet ChT, fluoropyrimidine–cisplatin or fluoropyrimidine–oxaliplatin is recommended
- It is currently unclear whether a different ChT regimen should be used after a poor response to neoadjuvant ChT
- The potential benefit of additional preoperative radiotherapy (RT) to perioperative ChT is currently undefined

*Adjuvant treatment*

- Adjuvant ChT is recommended in patients with stage ≥ IB gastric cancer who have undergone surgery without administration of preoperative ChT
- For patients who have undergone surgery with no residual tumour at the margin (R0), postoperative RT has no added benefit and should not be given
- For patients undergoing peri- or postoperative ChT, the addition of postoperative RT has no added benefit and should not be given
- Adjuvant chemoradiotherapy (CRT) can be considered in patients who have not received preoperative ChT and have not undergone an appropriate D2 lymphadenectomy

- Adjuvant RT or CRT might be considered in patients who have undergone surgery with microscopic residual tumour at the margin (R1), but is not standard
- For patients with MSI-H gastric cancer who have undergone curative surgery, adjuvant ChT cannot be recommended as there is no evidence of added benefit in this population
- If a response is required to downstage an MSI-H tumour before surgery, neoadjuvant FLOT is recommended

### Management of advanced/metastatic gastric cancer

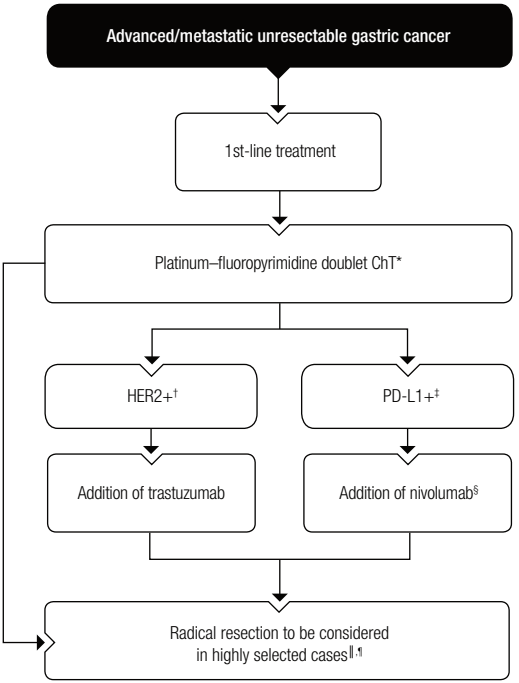
#### *First-line treatment*

- First-line treatment options for advanced and metastatic gastric cancer are shown in the figure on the next page
- First-line ChT with a platinum and fluoropyrimidine is recommended
  - Oxaliplatin is preferred, especially for older patients
  - Tegafur–gimeracil–oteracil (S-1) is commonly used in Asian patients
- Taxane-based triplet ChT is not recommended as a standard first-line approach due to higher levels of toxicity and uncertain survival benefit over recommended doublet regimens
- Irinotecan–5-FU is an alternative option for patients who do not tolerate platinum compounds
- Trastuzumab–ChT is recommended in patients with HER2-positive tumours [HER2 immunohistochemistry (IHC) score 3+ or HER2 IHC 2+ and fluorescence *in situ* hybridisation (FISH)-positive]
- Nivolumab–ChT is recommended for advanced, untreated gastric, oesophagogastric junction (OGJ) and oesophageal cancer with a PD-L1 combined positive score (CPS) of $\geq 5$
- Pembrolizumab is an option for patients with AC of the oesophagus and OGJ expressing PD-L1 with a CPS of $\geq 10$

#### *Second-line treatment*

- Second-line treatment options for advanced and metastatic gastric cancer are shown in the figure on page 49

## FIRST-LINE TREATMENT OF ADVANCED/METASTATIC UNRESECTABLE GASTRIC CANCER




*Recommended platinum compounds are oxaliplatin or cisplatin. Oxaliplatin is preferred, especially for older patients. Recommended fluoropyrimidines are IV 5-FU, oral capecitabine or oral S-1. Irinotecan–5-FU can be considered an alternative option for patients who do not tolerate platinum compounds

†HER2 IHC score 3+ or IHC score 2+/FISH-positive

‡PD-L1 status should be reported according to the CPS

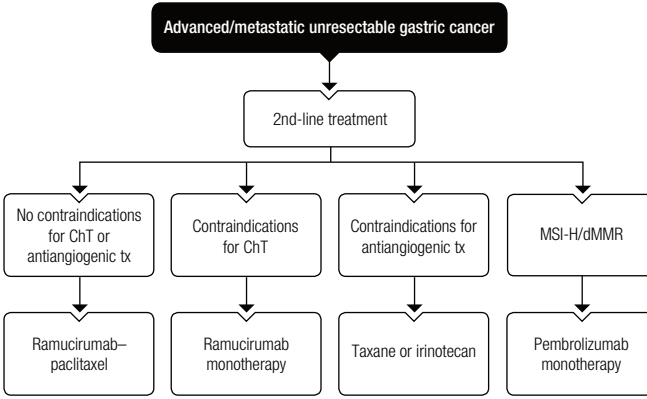
§Nivolumab–ChT is recommended for advanced, untreated gastric cancer with a PD-L1 CPS score ≥ 5 (FDA approved without PD-L1 CPS restriction, EMA approved for PD-L1 CPS ≥ 5)

‖Gastrectomy is not recommended in metastatic gastric cancer unless required for palliation of symptoms

¶Resection of metastases cannot be recommended in general, but might be considered in highly selected cases with oligometastatic disease and response to ChT

5-FU, 5-fluorouracil; ChT, chemotherapy; CPS, combined positive score; EMA, European Medicines Agency; FDA, Food and Drug Administration; FISH, fluorescence *in situ* hybridisation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; PD-L1, programmed death-ligand 1; S1, tegafur–gimeracil–oteracil

## SECOND-LINE TREATMENT OF ADVANCED/METASTATIC UNRESECTABLE GASTRIC CANCER



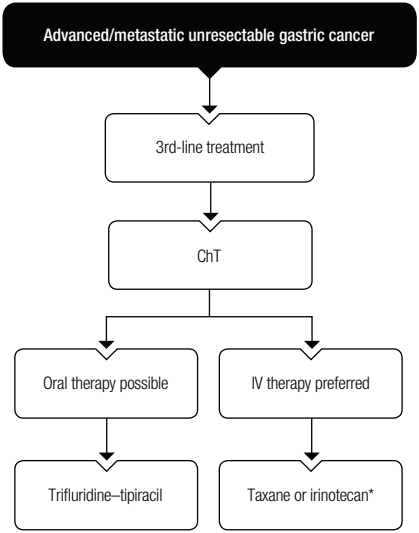

**ChT, chemotherapy; dMMR, mismatch repair deficient; MSI-H, microsatellite instability-high; tx, treatment**

- Ramucirumab–paclitaxel is recommended for the second-line treatment of gastric cancer
  - Ramucirumab monotherapy is also an option if there are contraindications for ChT
- Where ramucirumab is not available, paclitaxel, docetaxel or irinotecan monotherapy are recommended
  - 5-FU–LV–irinotecan is also used, but there are limited data to support this regimen
- Second-line trastuzumab combinations are not recommended in HER2-positive advanced gastric cancer that has progressed on first-line trastuzumab
  - Trastuzumab deruxtecan has demonstrated a survival benefit in HER2-positive pretreated gastric cancer and may be considered
- Where available, pembrolizumab is recommended for second-line treatment of patients with MSI-H/MMR deficient gastric cancer

*Third-line treatment*

- Third-line treatment options for advanced and metastatic gastric cancer are shown in the figure on the next page

## THIRD-LINE TREATMENT OF ADVANCED/METASTATIC UNRESECTABLE GASTRIC CANCER




*If not given previously for advanced/metastatic disease
ChT, chemotherapy; IV, intravenous

- Trifluridine–tipiracil is recommended for patients previously treated with two lines of therapy
- Alternative third-line treatments include a taxane or irinotecan

*Surgery for metastatic gastric cancer*

- Gastrectomy does not improve survival and is not recommended in metastatic disease unless required for palliation of symptoms
- Resection of metastases cannot be recommended in general, but might be considered in highly selected cases with oligometastatic disease and a response to ChT

*Supportive care and nutrition*

- Supportive care for patients with gastric cancer is critical and should include an early palliative care referral and nutritional support

- Dysphagia due to proximal gastric tumours may be relieved by RT or stent placement
  - Single-dose brachytherapy may be preferred over metal stent placement (even after external RT) as it provides better long-term relief of dysphagia with fewer complications
  - Stenting is recommended in patients with severe dysphagia, especially those with a short life expectancy, since the effect on swallowing is immediate
  - Options for patients who are not suitable for RT or stent placement include enteral feeding using nasojejunal or nasogastric tubes, or placement of percutaneous feeding tubes
- Distal gastric outlet obstruction may be treated by pyloric stenting or bypass surgery

**FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP**

- Regular follow-up is recommended for the investigation and treatment of symptoms, psychological support and early detection of recurrence
- Follow-up should be tailored to the individual patient and stage of disease
- Dietary support is recommended with attention to vitamin and mineral deficiencies
- In advanced disease, regular follow-up is recommended to detect symptoms of disease progression before significant clinical deterioration
  - Further investigations are needed if disease progression is suspected
  - CT of the thorax and abdomen should be carried out every 6-12 weeks in patients who are candidates for further cancer-specific therapies

# BILIARY TRACT CANCER

## DIAGNOSIS

- Biliary tract cancers (BTCs) arise from the gallbladder or cystic duct [gallbladder carcinoma (GBC)] or the biliary tree [cholangiocarcinoma (CCA)]
- BTCs should be classified according to the International Classification of Diseases Eleventh revision criteria
- CCA is subclassified as:
  - Intrahepatic CCA (iCCA) arising from bile ductules proximal to the second-order bile ducts
  - Perihilar CCA (pCCA) arising in the right and/or left hepatic duct and/or at their junction
  - Distal CCA (dCCA) arising from the epithelium distal to the insertion of the cystic duct
- The recommended diagnostic and staging investigations for BTC are shown in the table below

### DIAGNOSTIC AND STAGING INVESTIGATIONS IN BILIARY TRACT CANCER

| PROCEDURE | PURPOSE |
|---|---|
| Blood tests | Assess liver function and the presence of underlying liver or biliary tract disease (e.g. HBV, HCV, NAFLD, NASH, IBS, PSC or PBC) |
| ERCP/PTC ± biopsy (or cholangioscopy) | Assessment/treatment of biliary obstruction<br>Obtain tissue for diagnosis, histological classification and NGS |
| EUS ± biopsy | Accurate assessment of: Locoregional extension of p/dCCA and GBC; biliary obstruction; hepatic, vascular and lymph node invasion; metastases<br>Obtain tissue for diagnosis, histological classification and NGS |
| MRI, including MRCP | Accurate assessment of local extension of p/dCCA, including biliary tract and vascular anatomy and identification of hepatic metastases |
| CT of thorax + abdomen ± pelvis | Staging of tumour – to detect local/distant lymphadenopathy and metastatic disease |
| PET/CT, if available | May allow identification of nodal metastases, distant metastases and disease recurrence |

**CT, computed tomography; dCCA, distal cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; GBC, gallbladder carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; IBS, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NGS, next-generation sequencing; PBC, primary biliary cholangitis; pCCA, perihilar cholangiocarcinoma; PET, positron emission tomography; PSC, primary sclerosing cholangitis; PTC, percutaneous transhepatic cholangiography**

### Pathology

- Pathological diagnosis should be confirmed via core biopsy before any non-surgical treatment
- Surgery may be undertaken to obtain a pathological diagnosis in patients with localised tumours amenable to curative surgery
  - Non-tumour liver tissue should also be evaluated for underlying liver disease
- In patients with d/pCCA without extraductal metastasis, percutaneous transhepatic cholangiography (PTC)- or endoscopic retrograde cholangiopancreatography (ERCP)-guided biopsies should be carried out to obtain adequate tissue for diagnostic pathology and molecular profiling
- Endoscopic ultrasonography-guided fine-needle aspiration (FNA) may be an option to obtain biopsies of enlarged regional nodes and to obtain a tumour biopsy if ERCP-guided biopsies are negative or inconclusive
- Cases of tumour seeding along the FNA needle track have been reported; therefore, decisions to undertake primary tumour biopsy via any transperitoneal approach in patients with potentially resectable tumours should be made in a multidisciplinary setting

### Molecular diagnostics

- For patients with advanced disease who are suitable for systemic treatment, molecular analysis is recommended either before or during first-line therapy
- Parallel sequencing of several genes using focused next-generation sequencing is preferred over single gene testing
- The gene panel should include the respective coding DNA regions (target regions) of isocitrate dehydrogenase 1 *(IDH1)* and *IDH2*, human epidermal growth factor receptor 2 *(HER2)*, v-raf murine sarcoma viral oncogene homologue B1 *(BRAF)*, fibroblast growth factor receptor 2 *(FGFR2)*, *BRCA1/2*, partner and localiser of *BRCA2 (PALB2)* and Kirsten rat sarcoma virus *(KRAS)* to test for mutations
  - The rapidly evolving landscape of drug targets and predictive biomarkers may soon necessitate larger panels
- For tissue-based testing, gene fusions involving *FGFR2* and neurotrophic tyrosine receptor kinase *(NTRK)* genes should be interrogated at the RNA level
  - Microsatellite instability (MSI) status should also be assessed
- Elevated serum carbohydrate antigen 19-9 (CA 19-9) is associated with poorer prognosis and can be useful for assessing response to treatment

## STAGING AND RISK ASSESSMENT

- Risk assessment should consider performance status (PS), medical history, comorbidities and liver function

- Imaging is essential for positive and differential diagnosis, assessment of extension and treatment planning
- The level of biliary obstruction, hepatic, vascular and lymph node invasion and presence of metastases must be assessed
- If possible, staging should be carried out before placement of a biliary stent
- Magnetic resonance imaging (MRI) is the reference examination for local extension of d/pCCA and for identification of hepatic metastases
  - Hepatic MRI sequences must be combined with contrast-enhanced and cholangiography sequences (i.e. magnetic resonance cholangiopancreatography)
- Thoraco-abdomino-pelvic computed tomography (CT) is the reference examination for lymph node and metastatic extension
- [$^{18}$F]2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) is not recommended for primary diagnosis, but may help to identify nodal metastases, distant metastases and disease recurrence
- Staging is carried out according to the Union for International Cancer Control (UICC) tumour–node–metastasis (TNM) eighth edition staging manual and is specific for every subtype of BTC, as shown in the tables on the next pages

## STAGING OF CCA AND GBC ACCORDING TO THE UICC TNM EIGHTH EDITION

| CCA | | | | | | GBC | |
|---|---|---|---|---|---|---|---|
| iCCA | | pCCA | | dCCA | | | |
| PRIMARY TUMOUR (T) | | PRIMARY TUMOUR (T) | | PRIMARY TUMOUR (T) | | PRIMARY TUMOUR (T) | |
| TX | Primary tumour cannot be assessed | TX | Primary tumour cannot be assessed | TX | Primary tumour cannot be assessed | TX | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour | T0 | No evidence of primary tumour | T0 | No evidence of primary tumour | T0 | No evidence of primary tumour |
| Tis | Carcinoma *in situ* (intraductal tumour) | Tis | Carcinoma i*n situ* | Tis | Carcinoma *in situ* | Tis | Carcinoma *in situ* |
| T1a | Solitary tumour ≤ 5 cm in greatest dimension without vascular invasion | T1 | Tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue | T1 | Tumour invades the bile duct wall to a depth of < 5 mm | T1 | Tumour invades the lamina propria or muscular layer |
| T1b | Solitary tumour > 5 cm in greatest dimension without vascular invasion | T2a | Tumour invades beyond the wall of the bile duct to surrounding adipose tissue | T2 | Tumour invades the bile duct wall to a depth of 5-12 mm | T1a | Tumour invades the lamina propria |
| T2 | Solitary tumour with intrahepatic vascular invasion or multiple tumours, with or without vascular invasion | T2b | Tumour invades the adjacent hepatic parenchyma | T3 | Tumour invades the bile duct wall to a depth of > 12 mm | T1b | Tumour invades the muscular layer |
| T3 | Tumour perforating the visceral peritoneum | T3 | Tumour invades unilateral branches of the portal vein or hepatic artery | T4 | Tumour involves the coeliac axis, the superior mesenteric artery and/or the common hepatic artery | T2 | Tumour invades perimuscular connective tissue; no extension beyond the serosa or into the liver |

## STAGING OF CCA AND GBC ACCORDING TO THE UICC TNM EIGHTH EDITION (CONT'D)

| CCA | | | | | | GBC | |
|---|---|---|---|---|---|---|---|
| iCCA | | pCCA | | dCCA | | | |
| PRIMARY TUMOUR (T) | | PRIMARY TUMOUR (T) | | PRIMARY TUMOUR (T) | | PRIMARY TUMOUR (T) | |
| T4 | Tumour involving local extrahepatic structures by direct hepatic invasion | T4 | Tumour invades the main portal vein or its branches bilaterally or the common hepatic artery or unilateral second order biliary radicals with contralateral portal vein or hepatic artery involvement | | | T2a | Tumour invades perimuscular connective tissue on the peritoneal side with no extension to the serosa |
| | | | | | | T2b | Tumour invades perimuscular connective tissue on the hepatic side with no extension into the liver |
| | | | | | | T3 | Tumour perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum or extrahepatic bile ducts |
| | | | | | | T4 | Tumour invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures |

| REGIONAL LYMPH NODES (N) | | REGIONAL LYMPH NODES (N) | | REGIONAL LYMPH NODES (N) | | REGIONAL LYMPH NODES (N) | |
|---|---|---|---|---|---|---|---|
| NX | Regional lymph nodes cannot be assessed | NX | Regional lymph nodes cannot be assessed | NX | Regional lymph nodes cannot be assessed | NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis | N0 | No regional lymph node metastasis | N0 | No regional lymph node metastasis | N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis | N1 | Metastases to 1-3 regional lymph nodes | N1 | Metastases to 1-3 regional lymph nodes | N1 | Metastases to 1-3 regional lymph nodes |
| | | N2 | Metastasis to ≥ 4 regional lymph nodes | N2 | Metastasis to ≥ 4 regional lymph nodes | N2 | Metastasis to ≥ 4 regional lymph nodes |
| **DISTANT METASTASIS (M)** | | **DISTANT METASTASIS (M)** | | **DISTANT METASTASIS (M)** | | **DISTANT METASTASIS (M)** | |
| M0 | No distant metastasis | M0 | No distant metastasis | M0 | No distant metastasis | M0 | No distant metastasis |
| M1 | Distant metastasis | M1 | Distant metastasis | M1 | Distant metastasis | M1 | Distant metastasis |

CCA, cholangiocarcinoma; dCCA, distal cholangiocarcinoma; GBC, gallbladder carcinoma; iCCA, intrahepatic cholangiocarcinoma; M, metastasis; N, node; pCCA, perihilar cholangiocarcinoma; T, tumour; Tis, carcinoma *in situ*; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control

Brierley JD et al (eds). TNM Classification of Malignant Tumours, 8th edition. John Wiley & Sons, Inc.; 2017. Reprinted with permission

## ANATOMIC STAGE/PROGNOSTIC GROUPS FOR CCA AND GBC ACCORDING TO THE UICC EIGHTH EDITION

| | CCA | | | | | | | | | GBC | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | iCCA | | | pCCA | | | dCCA | | | | | |
| Stage 0 | | | | Tis | N0 | M0 | Tis | N0 | M0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 | T1 | N0 | M0 | T1 | N0 | M0 | | | |
| Stage IA | T1a | N0 | M0 | | | | | | | T1a | N0 | M0 |
| Stage IB | T1b | N0 | M0 | | | | | | | T1b | N0 | M0 |
| Stage II | T2 | N0 | M0 | T2a<br>T2b | N0<br>N0 | M0<br>M0 | | | | | | |
| Stage IIA | | | | | | | T1<br>T2 | N1<br>N0 | M0<br>M0 | T2a | N0 | M0 |
| Stage IIB | | | | | | | T2<br>T3<br>T3 | N1<br>N0<br>N1 | M0<br>M0<br>M0 | T2b | N0 | M0 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stage IIIA | T3 | N0 | M0 | T3 | N0 | M0 | T1<br>T2<br>T3 | N2<br>N2<br>N2 | M0<br>M0<br>M0 | T3 | N0 | M0 |
| Stage IIIB | T4<br>Any T | N0<br>N1 | M0 | T4 | N0 | M0 | T4 | Any N | M0 | T1<br>T2<br>T3 | N1<br>N1<br>N1 | M0<br>M0<br>M0 |
| Stage IIIC | | | | Any T | N1 | M0 | | | | | | |
| Stage IV | Any T | Any N | M1 | | | | Any T | Any N | M1 | | | |
| Stage IVA | | | | Any T | N2 | M0 | | | | T4<br>T4 | N0<br>N1 | M0<br>M0 |
| Stage IVB | | | | Any T | Any N | M1 | | | | Any T<br>Any T | N2<br>Any N | M0<br>M1 |

CCA, cholangiocarcinoma; dCCA, distal cholangiocarcinoma; GBC, gallbladder carcinoma; iCCA, intrahepatic cholangiocarcinoma; M, metastasis; N, node; pCCA, perihilar cholangiocarcinoma; T, tumour; Tis, carcinoma *in situ*; UICC, Union for International Cancer Control

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- pCCAs are further subclassified according to the Bismuth–Corlette classification to describe their anatomical location, as shown in the table below

**BISMUTH–CORLETTE CLASSIFICATION OF pCCA**

| | |
|---|---|
| **Type I** | Tumour involves the common hepatic duct |
| **Type II** | Tumour involves the bifurcation of the common hepatic duct |
| **Type IIIa** | Tumour involves the right hepatic duct |
| **Type IIIb** | Tumour involves the left hepatic duct |
| **Type IV** | Tumour involves both the right and left hepatic ducts |

pCCA, perihilar cholangiocarcinoma

Bismuth H, Corlette MB. Surg Gynecol Obstet 1975;140(2):170-8. Reprinted with permission

## TREATMENT

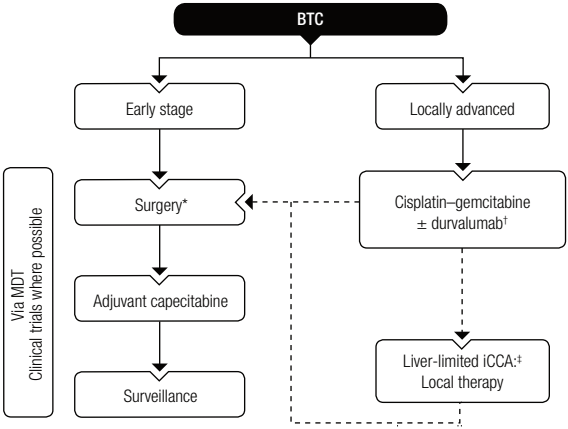
### Management of local and locoregional biliary tract cancer

- The therapeutic strategy varies for each type of BTC depending on its site of origin
- Management of local and locoregional BTCs is shown in the figure on the next page

*Surgery*

- Radical surgery including lymphadenectomy is currently the only curative-intent treatment for BTC
  - The exact nature and extent of surgery depends on the tumour subtype/location and should be agreed at a specialist hepatobiliary multidisciplinary tumour board
- Surgery involving hepatic resection should consider the future liver remnant and may require portal vein embolisation or double vein embolisation
  - Right portal vein embolisation is often needed to induce hypertrophy of the future liver remnant
- Radiological imaging should be carried out before ERCP or PTC in patients with jaundice as the inserted drains/stents can obscure diagnosis and assessment of the extent of disease
- Consideration of non-tumour related factors (e.g. PS, comorbidities) is important, as resection carries a significant risk of mortality
- Liver transplantation for locally advanced unresectable pCCA has been explored using a multidisciplinary approach, but this is not considered a standard treatment and participation in clinical trials should be encouraged
- dCCA requires removal of the pancreatic head, usually via a partial duodeno-pancreatectomy with extended bile duct resection up to the hilum

## MANAGEMENT OF LOCAL AND LOCOREGIONAL BILIARY TRACT CANCER




Dashed lines indicate optional treatment for consideration

*Special considerations: (1) consider the need for preoperative drainage; (2) avoid percutaneous biopsy in resectable d/pCCA; (3) assess future liver remnant; (4) neoadjuvant approach (selected cases); (5) completion surgery for incidental GBC stage ≥ T1b

†Salvage surgery or local therapies should be considered in responding patients with initially inoperable disease

‡Reconsider surgery in the event of an adequate response to treatment

BTC, biliary tract cancer; dCCA, distal cholangiocarcinoma; EMA, European Medicines Agency; FDA, Food and Drug Administration; GBC, gallbladder carcinoma; iCCA, intrahepatic cholangiocarcinoma; MDT, multidisciplinary team; pCCA, perihilar cholangiocarcinoma

- In case of incidentally-diagnosed GBC (post-cholecystectomy), reoperation with radical intent should be offered to sufficiently fit patients with stage ≥ T1b disease, provided there is no metastatic spread
  - Resection of some or all of segment IVb/V of the liver is carried out together with a lymphadenectomy of the hepatoduodenal ligament
  - Resection of the port sites may also be considered if the gallbladder was not removed with a bag or if the gallbladder was perforated
  - Curative-intent resection of tumours at the infundibulum requires resection of the bile duct, the duodenal bulb and, potentially, the pancreatic head

### *Adjuvant therapy*

- Adjuvant chemotherapy (ChT) with capecitabine should be considered for patients with CCA or GBC

- Radiotherapy (RT) after completion of adjuvant capecitabine might be considered in selected patients who have undergone resection of GBC or d/pCCA with microscopic residual tumour at the margin (R1)

*Management of patients with non-metastatic biliary tract cancer not suitable for surgery*

- The management of patients with locally advanced disease differs depending on the site of origin
- Local ablation should be considered for patients with iCCA ≤ 3 cm who have contraindications to surgery
- External beam RT or chemoradiotherapy to the primary tumour as definitive treatment should not be used outside of clinical trials for locally advanced CCA
  - Stereotactic body RT can be considered for patients with iCCA in case of contraindication to surgery for liver-limited disease
- Intra-arterial therapies, including hepatic arterial infusion of ChT, transarterial chemoembolisation and selective internal RT in combination with ChT, can be considered to improve response and disease control in patients with liver-limited iCCA
- Photodynamic therapy and intraductal radiofrequency ablation are considered investigational and should not be used outside of clinical trials for pCCA
- Following response to locoregional or systemic treatment of locally advanced tumours, patients should be reassessed by the multidisciplinary team to discuss surgery

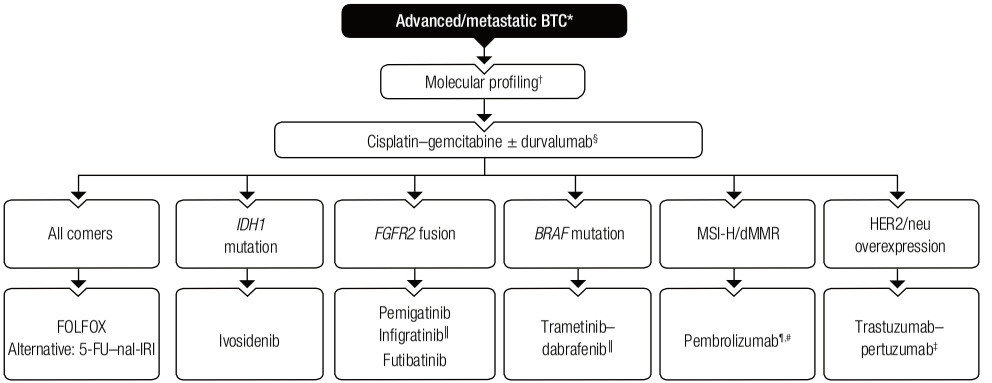
**Management of advanced and metastatic biliary tract cancer**

- Management options for advanced and metastatic BTC are shown in the figure opposite

*First-line treatment*

- Cisplatin–gemcitabine is recommended as standard of care for patients with a PS of 0-1
  - Oxaliplatin may be substituted for cisplatin when there are concerns about renal function
  - Gemcitabine monotherapy may be preferred in patients with a PS of 2 or other factors of fragility
  - There is currently insufficient evidence to recommend continuous treatment beyond 6 months; decisions should be based upon individual patient toxicity, tolerability and tumour response
- Durvalumab–cisplatin–gemcitabine should be considered in the first-line setting

## MANAGEMENT OF ADVANCED AND METASTATIC BILIARY TRACT CANCER




*Clinical trial recommended when available

†Molecular profiling gene panel should include *FGFR2*, *IDH1*, *HER2* and *BRAF* to test for hotspot mutations, but may also include genes such as *NTRK* and *c-MET*

‡Not EMA approved; not FDA approved

§Cisplatin–gemcitabine–durvalumab is recommended for first-line treatment. Gemcitabine monotherapy is an option in patients with a compromised PS or significant debility who are at risk of toxicity from platinum-based ChT

‖FDA approved; not EMA approved

¶Anti-PD-1 therapy is recommended for patients with MSI-H/dMMR tumours who have not been treated with first-line immunotherapy

#EMA approved for MSI-H/dMMR BTC; FDA approved for all MSI-H/dMMR solid tumours

5-FU, 5-fluorouracil; *BRAF*, v-raf murine sarcoma viral oncogene homologue B1; BTC, biliary tract cancer; ChT, chemotherapy; *c-MET*, mesenchymal to epithelial transition proto-oncogene; dMMR, mismatch repair deficient; EMA, European Medicines Agency; FDA, Food and Drug Administration; *FGFR2*, fibroblast growth factor receptor 2; FOLFOX, 5-fluorouracil–leucovorin–oxaliplatin; HER2, human epidermal growth factor receptor 2; *IDH1*, isocitrate dehydrogenase 1; MSI-H, microsatellite instability-high; nal-IRI, nanoliposomal irinotecan; *NTRK*, neurotrophic tyrosine receptor kinase; PD-1, programmed cell death protein 1; PS, performance status

*Second- and later-line treatment*

- 5-fluorouracil (5-FU)–leucovorin–oxaliplatin (FOLFOX) is the standard of care following cisplatin–gemcitabine
- 5-FU–nanoliposomal irinotecan can be considered as an alternative option for patients with contraindications to FOLFOX
- Evidence for irinotecan-based therapies is limited
- Molecular analysis should be carried out before or during first-line therapy to evaluate options for second and later lines of treatment as early as possible in patients with advanced disease. Following progression on or intolerance to ≥ 1 prior treatment, the following are treatment options:
  - The IDH1 inhibitor ivosidenib is recommended for the treatment of patients with *IDH1* mutations
  - Fibroblast growth factor receptor (FGFR) inhibitors (e.g. pemigatinib, infigratinib) are recommended in patients with *FGFR2* fusions
  - HER2-directed therapy (e.g. pertuzumab–trastuzumab) can be considered in patients with *HER2* amplification
  - *BRAF*-directed therapy (e.g. trametinib–dabrafenib) can be considered in patients with *BRAF V600E* mutations
  - Pembrolizumab is recommended in patients with microsatellite instability-high (MSI-H) tumours
  - NTRK inhibitors (e.g. larotrectinib, entrectinib) are recommended in patients with *NTRK* fusions
- Patients with *BRCA1/2* or *PALB2* mutations responding to platinum-based therapy can be considered for treatment with poly (ADP-ribose) polymerase (PARP) inhibitors
- During systemic and locoregional therapy for advanced disease, assessments should be scheduled every 8-12 weeks
  - In addition to imaging, CA 19-9 or carcinoembryonic antigen levels may be used to monitor the course of the disease if they are known to be secreted

*Supportive care*

- Supportive care for patients receiving systemic therapies for advanced, recurrent or metastatic disease should include active identification and management of obstructive complications
- Biliary drainage and subsequent treatment should be carried out in the case of biliary obstruction
  - When endoscopic access is not possible, percutaneous transhepatic drainage is recommended
  - In patients with a life expectancy of > 3 months, a metal stent is preferred

- Some patients require repeat stenting; this should be considered when planning stent placement
- Sepsis secondary to biliary obstruction is common and should be treated promptly
- Patients should be advised of the likely duration of stent patency and of the signs and symptoms indicative of biliary obstruction or infection

## FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

### Follow-up and long-term implications

- There is no universal follow-up schedule after potentially curative treatment for BTC
- Surveillance may consist of 3-6-monthly visits during the first 2 years and 6-12-monthly visits for up to 5 years or as clinically indicated
  - Regular visits can be extended thereafter and prolonged to yearly visits after 5 years of follow-up
  - A combination of clinical examination, laboratory investigations, tumour markers and CT scan of the thorax, abdomen and pelvis may be appropriate
- Patients with postoperative biliary obstruction require specialised multidisciplinary evaluation to determine the location of the obstruction, the optimal approach to drainage and assess for recurrence

### Survivorship

- There is an emerging cohort of BTC survivors due to the success of new therapeutic strategies
- Rehabilitation to counteract impairments related to the cancer and its treatments might help to maximise quality of life
- Long-term survivors should be followed up using a targeted and personalised multidisciplinary approach
- For younger patients, specific aspects should be considered and monitored, including the impact of treatment on fertility, psychological wellbeing and the development of secondary tumours

# PANCREATIC CANCER

## SCREENING

- Familial pancreatic cancer (PC), defined as at least two first-degree relatives with PC, accounts for only 4-10% of all cases of PC
- Genes and related syndromes that are linked to an increased risk of PC are shown in the table below

## GENES AND RELATED SYNDROMES ASSOCIATED WITH INCREASED RISK OF PC

| GENE | RELATED PREDISPOSING SYNDROME |
|---|---|
| *ATM* | Familial breast cancer |
| *BRCA1*<br>*BRCA2* | Hereditary breast and ovarian cancer |
| *CDKN2A* | FAMMM syndrome |
| Mismatch repair genes:<br>*MLH1, MSH2*<br>*MSH6, PMS2* | Lynch syndrome |
| *PALB2* | Familial breast cancer |
| *PRSS1*<br>*SPINK1* | Hereditary pancreatitis |
| *STK11* | Peutz–Jegher syndrome |
| *TP53* | Li–Fraumeni syndrome |
| *APC*<br>*MUTYH* | Familial adenomatous polyposis |

***APC*, adenomatous polyposis coli; *ATM*, ataxia telangiectasia mutated; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; FAMMM, familial atypical multiple mole melanoma; *MLH1*, mutL homologue 1; *MSH2*, mutS homologue 2; *MSH6*, mutS homologue 6; *MUTYH*, mutY DNA glycosylase; *PALB2*, partner and localiser of BRCA2; PC, pancreatic cancer; *PMS2*, PMS1 homologue 2 mismatch repair system component; *PRSS1*, serine protease 1; *SPINK1*, serine peptidase inhibitor Kazal type 1; *STK11*, serine/threonine kinase 11; *TP53*, tumour suppressor protein p53 gene**

- Variants in *BRCA2* are the most common genetic abnormalities in familial PC
- Individuals from families at risk should receive genetic counselling and be considered for enrolment in investigational screening registries
- Surveillance to detect early PC is recommended in high-risk individuals
  - This usually begins at 50 years of age (or 10 years earlier than the age of the youngest affected relative)
  - Annual endoscopic ultrasound (EUS) and/or pancreatic magnetic resonance imaging (MRI) are preferred for surveillance

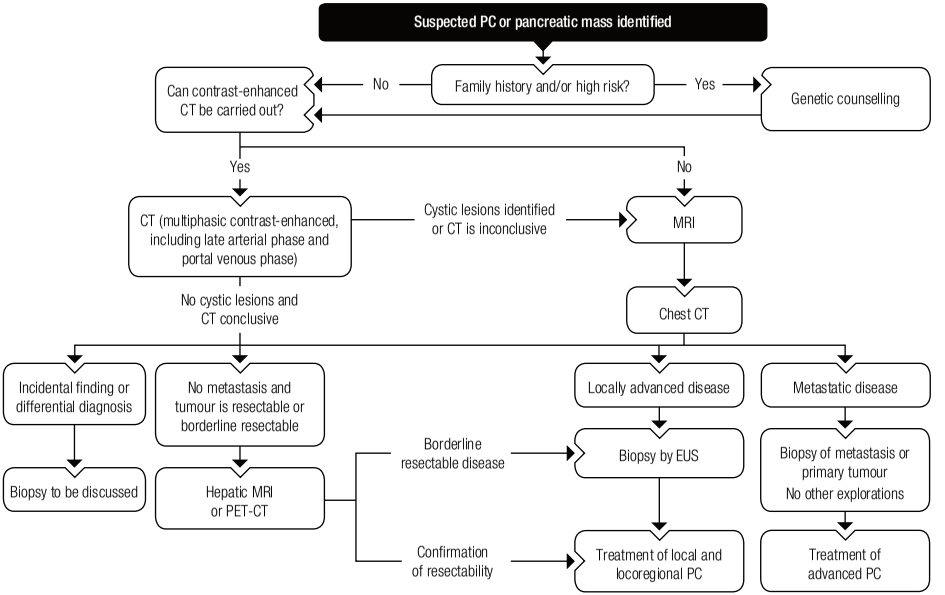
- Not smoking, limiting alcohol intake and reaching and maintaining a healthy weight are highly recommended to reduce the risk of developing PC

## DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

### Diagnosis

- Common presenting symptoms of PC include jaundice, abdominal pain, weight loss, steatorrhoea and new onset or worsening of pre-existing diabetes
- A suggested diagnostic work-up of suspected PC is shown in the figure on the next page
- The aim of imaging is to assess tumour location and size, peripancreatic venous and arterial vascular involvement, locoregional involvement and metastatic extent (liver, lymph nodes, peritoneum and lung)
- Multiphasic contrast-enhanced thoracic-abdominal and pelvic computed tomography (CT), including late arterial phase and portal venous phase, should be the first-line imaging modality for suspected PC
- In case of jaundice due to an obstructive head PC, imaging should be carried out before biliary drainage or stenting
- Imaging should be carried out in the 4 weeks preceding start of treatment
- Abdominal MRI may be used when CT is inconclusive or when contrast-enhanced CT is contraindicated; staging must include chest CT
- MRI sequences should include T2-, fat suppressed T1- and diffusion-weighted sequences and magnetic resonance cholangiopancreatography (two dimensional and/or three dimensional), followed by multiphasic contrast-enhanced sequences
- Comprehensive analysis of imaging findings should be incorporated in standardised reporting templates
- Positron emission tomography (PET)-CT is not recommended for diagnosis of primary tumours but may be useful for staging localised tumours and in cases where the presence of distant metastasis is uncertain [doubtful imaging or high carbohydrate antigen 19-9 (CA 19-9) levels]
- Hepatic MRI is recommended prior to surgery to confirm the absence of small liver metastases
- Biopsy is not routinely advised if surgical resection is planned; however, cytology or biopsy proof of PC should be obtained before initiation of chemotherapy (ChT), preferably via EUS guidance
- All patients with localised disease should have their imaging reviewed at a multidisciplinary tumour board (MDTB), which should include experts in pancreas imaging, pancreas surgery and oncology

## DIAGNOSTIC WORK-UP OF SUSPECTED PC




CT, computed tomography; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; PC, pancreatic cancer; PET, positron emission tomography

### Pathology

- The most common type of PC (~80%) is ductal adenocarcinoma
- Other variants of PC, such as adenosquamous carcinoma and undifferentiated carcinomas with osteoclast-like giant cells, are associated with a poorer prognosis
- Acinar PCs have a slightly better prognosis than ductal adenocarcinoma
- The most frequent precursor lesions for PC are pancreatic intraepithelial neoplasia, followed by intraductal papillary mucinous neoplasia and mucinous cystic neoplasia

### Molecular biology

- Mutational activation of oncogenes, predominantly Kirsten rat sarcoma virus *(KRAS)*, is observed in > 90% of PC cases
- Other common genetic mutations in PC include inactivation of tumour suppressor genes and genome maintenance genes that control DNA damage repair, and alterations in genes involved in the homologous recombination repair pathway (e.g. *BRCA1/2)*
  - *KRAS* and *BRCA* testing are generally recommended
- If a *KRAS* wild type (WT) tumour is identified with next-generation sequencing, additional profiling can be carried out to look for rare, potentially actionable findings
  - Microsatellite instability (MSI) status and neurotrophic tyrosine receptor kinase *(NTRK)* fusion status should be assessed in patients with *KRAS*-WT metastatic PC
  - If multigene sequencing is not carried out, MSI and *NTRK* fusions can be detected using standard methods
- CA 19-9 can be used as a marker to measure disease burden and potentially guide treatment decisions

## STAGING AND RISK ASSESSMENT

- The prognosis of PC is primarily determined by tumour-related factors captured in the Union for International Cancer Control (UICC) tumour–node–metastasis (TNM) eighth edition, as shown in the tables on the next page
- Resectability can be assessed using both anatomical National Comprehensive Cancer Network (NCCN) criteria and biological and conditional features following the International Association of Pancreatology consensus
- Another major factor determining the prognosis of patients with resected tumours is the feasibility to receive and complete adjuvant treatment
- In advanced disease, impaired general condition [Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥ 2], age > 65 years, albumin < 35 g/L, presence of synchronous metastases, presence of liver metastases, number of metastatic sites and high serum CA 19-9 are negatively associated with survival

## STAGING OF PC ACCORDING TO THE UICC TNM EIGHTH EDITION

| PRIMARY TUMOUR (T) | |
|---|---|
| TX | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour |
| Tis | Carcinoma *in situ** |
| T1 | Tumour ≤ 2 cm in greatest dimension |
| T1a | Tumour ≤ 0.5 cm in greatest dimension |
| T1b | Tumour > 0.5 cm and ≤ 1 cm in greatest dimension |
| T1c | Tumour > 1 cm but ≤ 2 cm in greatest dimension |
| T2 | Tumour > 2 cm but ≤ 4 cm in greatest dimension |
| T3 | Tumour > 4 cm in greatest dimension |
| T4 | Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery |
| **REGIONAL LYMPH NODES (N)** | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastases in 1-3 regional lymph node(s) |
| N2 | Metastases in ≥ 4 regional lymph nodes |
| **DISTANT METASTASIS (M)** | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

***Tis also includes the 'PanIN-III' classification**

**M, metastasis; N, node; PanIN, pancreatic intraepithelial neoplasia; PC, pancreatic cancer; T, tumour; Tis, carcinoma *in situ*; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control**

**Brierley J et al. TNM classification of malignant tumours, Eighth edition. John Wiley & Sons, Inc., Chichester, West Sussex, UK Reprinted with permission from John Wiley & Sons, Ltd**

## STAGE GROUPING FOR PC ACCORDING TO THE UICC TNM EIGHTH EDITION

| STAGE GROUPING | T STAGE | N STAGE | M STAGE |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1 | N0 | M0 |
| Stage IB | T2 | N0 | M0 |
| Stage IIA | T3 | N0 | M0 |
| Stage IIB | T1, T2, T3 | N1 | M0 |
| Stage III | T1, T2, T3 | N2 | M0 |
| | T4 | Any N | M0 |
| Stage IV | Any T | Any N | M1 |

**M, metastasis; N, node; PC, pancreatic cancer; T, tumour; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control**

**Brierley J et al. TNM classification of malignant tumours, Eighth edition. John Wiley & Sons, Inc., Chichester, West Sussex, UK Reprinted with permission from John Wiley & Sons, Ltd**

## TREATMENT

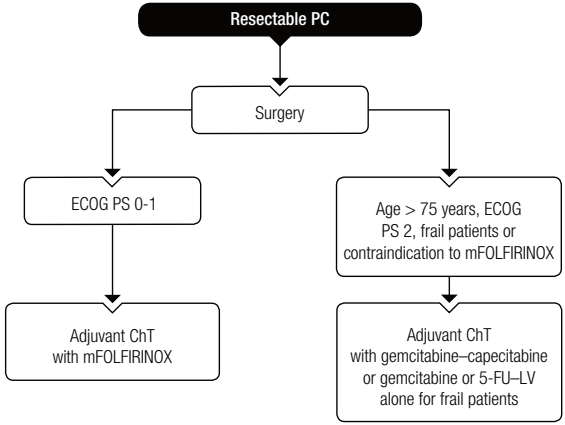
- After staging and discussion in an MDTB, PC should be categorised as resectable, borderline resectable, locally advanced or advanced/metastatic
  - A treatment decision must be taken in accordance with these findings, accounting for factors such as nutritional status, PS and comorbidities
- Discussion in an MDTB in expert centres is required to define a recommended treatment strategy for patients with PC
  - The multidisciplinary team should include radiologists, surgeons, medical oncologists, gastroenterologists, radiation oncologists and supportive and palliative care specialists
- Most patients present with locally advanced or metastatic PC
- Surgical excision is feasible in only 10-20% of patients

### Management of local and locoregional pancreatic cancer

*Treatment of resectable PC*

- Treatment options for resectable PC are shown in the figure below

**MANAGEMENT OF RESECTABLE PC**



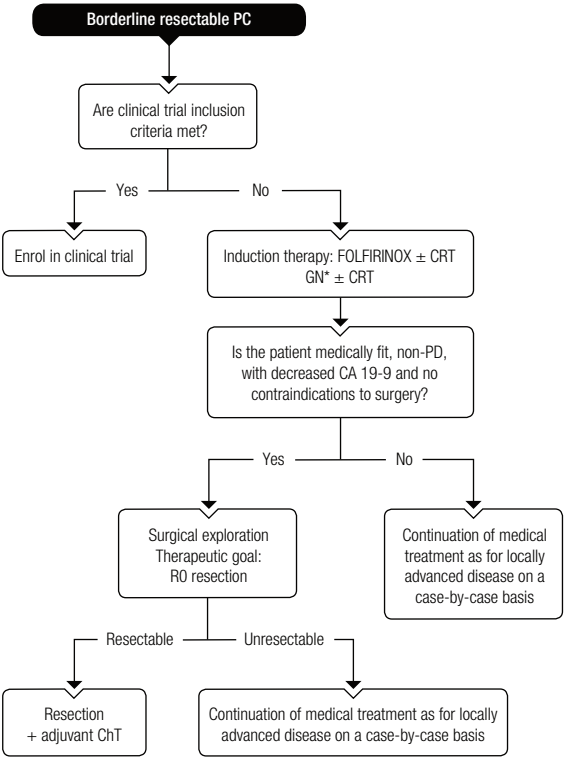

**5-FU, 5-fluorouracil; ChT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; LV, leucovorin; mFOLFIRINOX, modified leucovorin–5-fluorouracil–irinotecan–oxaliplatin; PC, pancreatic cancer; PS, performance status**

- Surgical resection is the only potentially curative treatment for PC
  - Following radiological evaluation, only patients with a high probability of surgical resection with no residual tumour at the margin (R0; defined as no cancer cells within 1 mm of all resection margins) are good candidates for upfront surgery
- The location and size of the tumour determine the type of surgery
  - Patients with tumours in the head of the pancreas are treated with pancreatoduodenectomy (Whipple procedure)
  - For patients with tumours in the body or tail of the pancreas, distal pancreatectomy, including resection of the body and tail of the pancreas and spleen, is usually undertaken
- Frozen section analysis of pancreatic neck transection and common bile duct transection margins is suggested
- Tumour clearance should be defined for all margins identified by the surgeon
- Standard lymphadenectomy should involve the removal of ≥ 16 lymph nodes to allow adequate pathological staging
  - The number of lymph nodes examined and lymph node ratio (number of involved lymph nodes as a proportion of the number of lymph nodes examined) should be reported in the pathological analysis
- Patients undergoing surgery should receive perioperative thromboprophylaxis with either unfractionated heparin or low-molecular-weight heparin, unless contraindicated
- Endoscopic drainage is recommended if bilirubin levels are > 250 µmol/L in patients with cholangitis, when neoadjuvant treatment is planned or when surgery will be delayed for > 2 weeks
- Neoadjuvant therapy is only recommended for resectable PC in the context of clinical trials due to limited Phase III evidence
  - A decision regarding resectability status following neoadjuvant therapy should be made at an MDTB based on imaging findings, serum CA 19-9, PS and clinical response
- Six months of adjuvant ChT is strongly recommended following resection
  - Adjuvant modified leucovorin (LV)–5-fluorouracil (5-FU)–irinotecan–oxaliplatin (mFOLFIRINOX) is recommended for patients with resected PC and ECOG PS 0-1
  - Adjuvant gemcitabine–capecitabine is an alternative option for patients who are not candidates for mFOLFIRINOX (age > 75 years, ECOG PS 2 or contraindication to mFOLFIRINOX)
  - Adjuvant gemcitabine or 5-FU–LV should be limited to frail patients
- Adjuvant chemoradiotherapy (CRT) is not recommended and should not be given to patients following surgery outside the setting of a clinical trial

*Treatment of borderline resectable PC*

- Treatment options for borderline resectable PC are shown in the figure below

**MANAGEMENT OF BORDERLINE RESECTABLE PC**




***Not EMA or FDA approved as induction therapy**

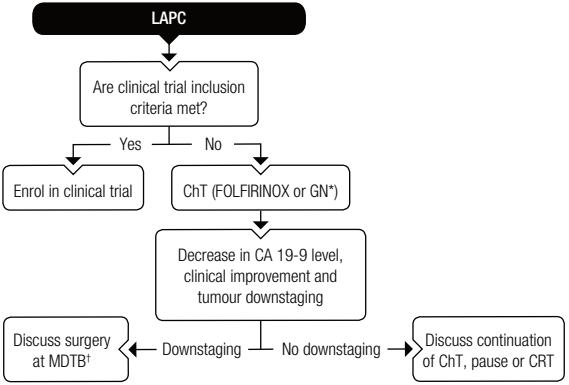
**CA 19-9, carbohydrate antigen 19-9; ChT, chemotherapy; CRT, chemoradiotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; FOLFIRINOX, leucovorin–5-fluorouracil–irinotecan–oxaliplatin; GN, gemcitabine–nab-paclitaxel; PC, pancreatic cancer; PD, progressive disease; R0, no residual tumour at the margin**

- Patients with borderline resectable disease have a high probability of surgical resection with microscopic residual tumour at the margin (R1) and should be considered for induction treatment
- Patients should be included in clinical trials whenever possible
- If inclusion in a clinical trial is not feasible, induction therapy is recommended over initial surgery
- A period of induction ChT [LV–5-FU–irinotecan–oxaliplatin (FOLFIRINOX) or gemcitabine–nab-paclitaxel (GN)], followed by CRT on a case-by-case basis and subsequent surgery is suggested, although GN is not European Medicines Agency (EMA) or Food and Drug Administration (FDA) approved in this setting
  - Gemcitabine combined with oxaliplatin or capecitabine may be considered when FOLFIRINOX or GN are not feasible
  - CRT with capecitabine may be considered after induction ChT
- Following induction, medically fit patients without disease progression and with a decrease in CA 19-9 should undergo surgical exploration, unless contraindicated

*Treatment for locally advanced PC*

- Treatment options for locally advanced PC (LAPC) are shown in the figure below

**MANAGEMENT OF LAPC**




*Not EMA or FDA approved for locally advanced disease

†To be discussed if significant decrease in CA 19-9 level, clinical improvement and tumour downstaging

CA 19-9, carbohydrate antigen 19-9; ChT, chemotherapy; CRT, chemoradiotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; FOLFIRINOX, leucovorin–5-fluorouracil–irinotecan–oxaliplatin; GN, gemcitabine–nab-paclitaxel; LAPC, locally advanced pancreatic cancer; MDTB, multidisciplinary tumour board

- All patients with LAPC should be evaluated for resectability every 2-3 months at the local MDTB
- Patients should be included in clinical trials whenever possible
- A conversion surgery strategy utilising the standard of care of up to 6 months of combination ChT [FOLFIRINOX or GN (not EMA or FDA approved for locally advanced PC)] can be considered
- Surgical exploration for resection could be discussed if there is a significant decrease in CA 19-9 level, clinical improvement and tumour downstaging
- In experienced centres, arterial resections can be considered as a possibility after induction therapy on a case-by-case basis in selected patients

**Management of advanced pancreatic cancer**

- Treatment options for advanced PC are shown in the figure on the next page

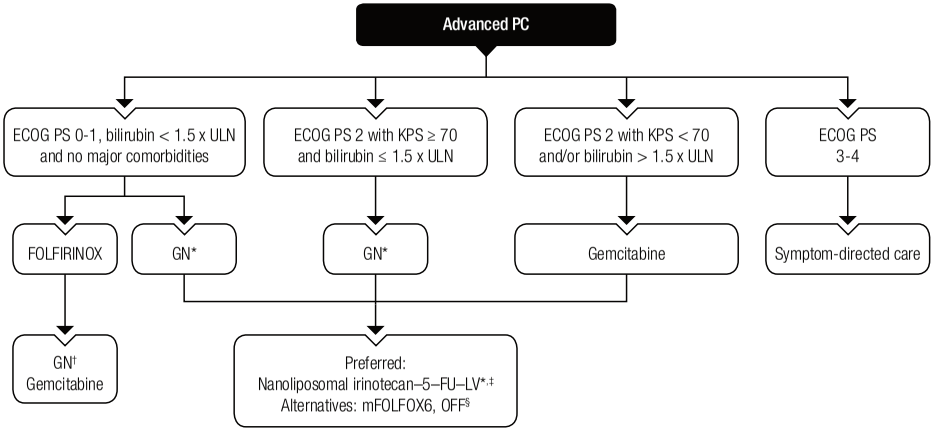
*First-line treatment*

- Options to treat patients with metastatic PC are dependent on PS
  - FOLFIRINOX or GN should be considered for patients with ECOG PS 0-1 and bilirubin level < 1.5 times the upper limit of normal (x ULN)
  - GN can also be considered for patients with ECOG PS 2, Karnofsky PS (KPS) ≥ 70 and bilirubin level ≤ 1.5 x ULN
  - Gemcitabine monotherapy should be considered for patients with ECOG PS 2, KPS < 70 and/or bilirubin level > 1.5 x ULN
  - Symptom-directed care should be considered for patients with ECOG PS 3-4 as the risks of ChT likely outweigh any benefit
- Efficacy should be evaluated every 8-12 weeks and should be based on clinical status, CA 19-9 trajectory and imaging
- Patients with *BRCA* mutations should receive platinum-based ChT

*Second-line treatment*

- After FOLFIRINOX treatment, GN or gemcitabine alone may be offered to patients with ECOG PS 0-1 and a favourable comorbidity profile (GN is not EMA or FDA approved as second-line therapy)
- After gemcitabine-based treatment, nanoliposomal irinotecan–5-FU–LV (EMA and FDA approved in metastatic PC, not advanced PC) can be considered in patients with, or who have recovered to, ECOG PS 0-1
- Oxaliplatin-based second-line treatment [oxaliplatin–5-FU–LV (OFF) or modified LV–5-FU–oxaliplatin (mFOLFOX6)] remains controversial but may be considered in patients with ECOG PS 0-2 if not given previously

## MANAGEMENT OF ADVANCED PC




*EMA and FDA approved in metastatic PC only (not advanced PC)

†Not EMA or FDA approved as second-line therapy

‡Only in patients with, or who have recovered to, ECOG PS 0-1

§If not given previously

5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; FOLFIRINOX, leucovorin–5-fluorouracil–irinotecan–oxaliplatin; GN, gemcitabine–nab-paclitaxel; KPS, Karnofsky performance status; LV, leucovorin; mFOLFOX6, modified leucovorin–5-fluorouracil–oxaliplatin; OFF, oxaliplatin–5-fluorouracil–leucovorin; PC, pancreatic cancer; PS, performance status; ULN, upper limit of normal

- Symptom-directed care is recommended in patients with ECOG PS 3-4 as the risks of ChT likely outweigh any benefit

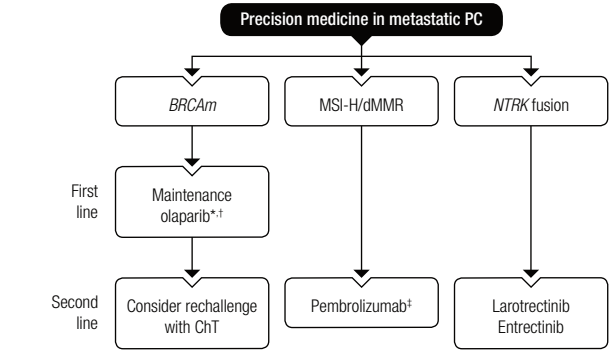
*Third-line treatment*

- Most patients are considered unsuitable for third-line treatment due to poor nutritional status and/or PS
  - In such cases, no standard regimen can be recommended and best supportive care is the appropriate treatment choice
- In patients with a good PS, inclusion in a clinical trial is the first option when available

*Precision medicine*

- Options for the use of precision medicine in metastatic PC are shown in the figure below

**PRECISION MEDICINE IN METASTATIC PC**




***For patients whose disease is stable or responsive to platinum-based ChT**

**†EMA and FDA approved in patients with metastatic PC and *gBRCA* mutations**

**‡FDA approved; not EMA approved as a dMMR/MSI-H tumour-agnostic indication but for specific tumour types (excludes PC)**

***BRCAm*, *BRCA* mutated; ChT, chemotherapy; dMMR, mismatch repair deficient; EMA, European Medicines Agency; FDA, Food and Drug Administration; g*BRCA*, germline *BRCA*; MSI-H, microsatellite instability high; *NTRK*, neurotrophic tyrosine receptor kinase; PC, pancreatic cancer**

- *BRCA* genetic testing should be offered to patients with metastatic PC to determine eligibility for platinum-based treatment and subsequent maintenance with olaparib
- Olaparib maintenance treatment is an option for patients with metastatic PC and a g*BRCA1/2* variant whose disease is stable or responsive to platinum-based ChT

- Pembrolizumab can be proposed for patients with microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) PC [FDA approved; not EMA approved as a dMMR/MSI-H tumour-agnostic indication but for specific tumour types (excludes PC)]
- Larotrectinib or entrectinib are recommended in patients with an *NTRK* fusion

## FOLLOW-UP, SUPPORTIVE CARE, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

### Follow-up

- Regular follow-up is suggested for patients with resected PC, although there is insufficient evidence of an impact on overall survival
  - Patients within active surveillance programmes may be more likely to have recurrences detected at an asymptomatic stage and to receive treatment

### Supportive and palliative care

- Exercise is recommended as an effective therapy for patients to manage fatigue and psychological distress, mitigate muscle loss and decline in physical function and maintain quality of life
- Primary thromboprophylaxis should be considered in patients with advanced PC receiving ChT
- Endoscopic placement of a fully-covered, self-expandable metallic biliary stent is suggested in the event of biliary obstruction
- Duodenal obstruction can be preferentially managed by endoscopic placement of an expandable metal stent instead of digestive bypass
- Pancreatic enzyme replacement therapy can help manage the symptoms of exocrine insufficiency, such as weight loss, abdominal discomfort or steatorrhoea
- Effective pain control is strongly recommended and should involve a pain control specialist when required
  - Coeliac plexus block via EUS guidance should be used for persistent pain only if the PS is adequate

# GLOSSARY

5-FU, 5-fluorouracil
AC, adenocarcinoma
AFP, α-fetoprotein
AJCC, American Joint Committee on Cancer
ALBI, albumin–bilirubin
*ARID1A*, AT-rich interactive domain-containing protein 1A
*ARID2*, AT-rich interactive domain-containing protein 2
BCLC, Barcelona Clinic Liver Cancer
*BRAF, v-raf* murine sarcoma viral oncogene homologue B1
BTC, biliary tract cancer
CA 19-9, carbohydrate antigen 19-9
CAPS, Cancer of the Pancreas Screening
CCA, cholangiocarcinoma
CD34, cluster of differentiation 34
*CDH1*, cadherin 1
*CDKN2A*, cyclin-dependent kinase inhibitor 2A
ChT, chemotherapy
CK19, cytokeratin 19
CPG, Clinical Practice Guideline
CPS, combined positive score
CROSS, Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study
CRT, chemoradiotherapy
CT, computed tomography
*CTNNB1*, catenin β1
dCCA, distal cholangiocarcinoma
DEB, doxorubicin-eluting bead
DGC, diffuse gastric cancer
dMMR, mismatch repair deficient
EASL, European Association for the Study of the Liver
EBRT, external beam radiotherapy
EBV, Epstein–Barr virus
ECOG, Eastern Cooperative Oncology Group
EMA, European Medicines Agency
ERCP, endoscopic retrograde cholangiopancreatography
ESMO, European Society for Medical Oncology
ESPEN, European Society for Clinical Nutrition and Metabolism
EUS, endoscopic ultrasound
EZH2, enhancer of zeste homologue 2
FAP, familial adenomatous polyposis
FDA, Food and Drug Administration
FDG, [$^{18}$F]2-fluoro-2-deoxy-D-glucose
FDR, first-degree relative

# GLOSSARY (CONT'D)

FGFR, fibroblast growth factor receptor
*FGFR2*, fibroblast growth factor receptor 2
FIGC, familial intestinal gastric cancer
FISH, fluorescence *in situ* hybridisation
FLOT, 5-fluorouracil–leucovorin–oxaliplatin–docetaxel
FNA, fine-needle aspiration
FOLFOX, 5-fluorouracil–leucovorin–oxaliplatin
FOLFIRINOX, leucovorin–5-fluorouracil–irinotecan–oxaliplatin
GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach
GBC, gallbladder carcinoma
g*BRCA*, germline *BRCA*
GI, gastrointestinal
GN, gemcitabine–nab-paclitaxel
HBV, hepatitis B virus
HCC, hepatocellular carcinoma
HCV, hepatitis C virus
HER2, human epidermal growth factor receptor 2
HP, hereditary pancreatitis
HSP70, heat shock protein 70
iCCA, intrahepatic cholangiocarcinoma
ICI, immune checkpoint inhibitor
*IDH1*, isocitrate dehydrogenase 1
*IDH2*, isocitrate dehydrogenase 2
IGCLC, International Gastric Cancer Linkage Consortium
IHC, immunohistochemistry
IM, intestinal metaplasia
KPS, Karnofsky performance status
*KRAS*, Kirsten rat sarcoma virus
LAPC, locally advanced pancreatic cancer
LBC, lobular breast cancer
LR, liver resection
LS, Lynch syndrome
LV, leucovorin
MDTB, multidisciplinary tumour board
*MET*, MET proto-oncogene receptor tyrosine kinase
mFOLFIRINOX, modified 5-fluorouracil–irinotecan–leucovorin–oxaliplatin
mFOLFOX6, modified 5-fluorouracil–leucovorin–oxaliplatin
MMR, mismatch repair
mRECIST, modified Response Evaluation Criteria in Solid Tumours
MRI, magnetic resonance imaging
MSI, microsatellite instability
MSI-H, microsatellite instability-high

MWA, microwave ablation
N, node
NCCN, National Comprehensive Cancer Network
*NTRK*, neurotrophic tyrosine receptor kinase
OFF, oxaliplatin–5-fluorouracil–leucovorin
OGJ, oesophagogastric junction
OLT, orthotopic liver transplantation
OS, overall survival
*PALB2*, partner and localiser of *BRCA2*
PARP, poly (ADP-ribose) polymerase
PC, pancreatic cancer
pCCA, perihilar cholangiocarcinoma
PD-L1, programmed death-ligand 1
PET, positron emission tomography
PFS, progression-free survival
PJS, Peutz–Jegher syndrome
PS, performance status
PTC, percutaneous transhepatic cholangiography
PV, portal vein
R0, no residual tumour at the margin
R1, microscopic residual tumour at the margin
RECIST, Response Evaluation Criteria In Solid Tumours
RFA, radiofrequency ablation
RT, radiotherapy
S-1, tegafur–gimeracil–oteracil
SBRT, stereotactic body radiotherapy
SCC, squamous cell carcinoma
SIRT, selective internal radiotherapy
T, tumour
TACE, transarterial chemoembolisation
*TERT*, telomerase reverse transcriptase
TNM, tumour–node–metastasis
*TP53*, tumour suppressor protein p53
TPS, tumour proportion score
UCSF, University of California San Francisco
UICC, Union for International Cancer Control
ULN, upper limit of normal
WHO, World Health Organization
WT, wild type

# NOTES

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Access the full ESMO Clinical Practice Guidelines

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