Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence and epidemiology

Biliary tract cancer (BTC), comprising <1% of all human cancers and ~10%–15% of all primary liver cancers, presents mostly in the seventh decade with a small male predominance (male:female ratio of 1.2–1.5:1.0) [1]. They are subclassified as intrahepatic cholangiocarcinoma (iCCA), originating from the biliary tree within the liver, and extrahepatic cholangiocarcinoma (eCCA), outside the liver parenchyma; the latter is further subdivided into perihilar cholangiocarcinoma (pCCA or Klatskin tumour) and distal cholangiocarcinoma (dCCA) [2], with a frequency of 10%–20% iCCA, 50% pCCA and 30%–40% eCCA.

cholangiocarcinoma

In Europe, USA and Australasia, the incidence of cholangiocarcinoma (CCA) is low (0.3–3.5/100 000); in parts of the world where liver fluke infection is common (e.g. Thailand, China and Korea), rates are much higher [3]. Northeast Thailand has the highest CCA rate in the world, with an annual incidence of 90/100 000, accounting for >80% of all primary liver cancers [4].

CCA incidence and mortality rates have increased overall in the past few decades in most Western countries; specifically, iCCA rates are rising and eCCA rates falling [5], with the exception of Denmark, Norway and the Czech Republic, where iCCA rates have fallen. CCA rates in Asia overall have remained static. These trends may be explained by:

1) improved diagnostic tools and imaging;
2) misclassification (particularly of pCCA during serial updates of the International Classification of Disease [6]);
3) changing migration patterns in the West [7];
4) the increasing burden of chronic liver disease (e.g. viral hepatitis and fatty liver disease as specific risk factors for iCCA [8–10]); and
5) the potential role of environmental toxins [11, 12].

Furthermore, increased laparoscopic cholecystectomy rates over the past few decades have significantly reduced the prevalence of gallstone disease, a stronger risk factor for eCCA than iCCA [13].

gallbladder cancer

The incidence of gallbladder cancer (GBC) in Western Europe and the USA is low (1.6–2.0/100 000); however, it is a significant health problem in Chile, India and Central/Eastern Europe. In the Valdivia region of Chile, GBC incidence reaches 24.3/100 000 in females (and 8.6/100 000 in males) [14]. Gallstones are the strongest risk factor for GBC; other risk factors include porcelain gallbladder, gallbladder polyps, primary sclerosing cholangitis, chronic infection (e.g. salmonella typhi), congenital malformations and obesity.

diagnosis and pathology/molecular biology

When diagnosing a BTC, it is important to distinguish the subtype (iCCA, pCCA, dCCA or GBC) as every subtype has its own specific characteristics, requiring individual workup. Overall, however, the best diagnostic tool is magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP), contrast-enhanced and diffusion-weighted imaging [15]. Computed tomography (CT) is generally less useful.

Pathology diagnosis should be obtained before any non-surgical treatment modality (not essential in patients planned for curative surgery where radiological features are characteristic). Endoscopic retrograde cholangiopancreatography (ERCP)-guided biopsies are preferred to biliary brush cytology and should be carried out whenever possible [III, A]. Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is also useful for obtaining microbiopsies [16] [II, C] and may be
considered if ERCP-guided brush cytology or biopsies are negative or inconclusive. Cases of tumour seeding along the FNA needle track have been reported [17]; the exact level of risk is uncertain, though it appears to be low. Decisions to undertake biopsy should be made in a multidisciplinary setting, particularly in patients with potentially resectable tumours. Advances in pathology allow identification of distinct pathological subgroups based on immunohistochemistry, reflected in the updated World Health Organization (WHO) classification [18], highlighting the importance of tissue acquisition.

Serum carbohydrate antigen (CA)19-9 (with cut-off >129 U/ml) has some added value [III, C] [19]. In addition, there is an increasing understanding of different genomic profiles across BTC [20], and although currently these differences do not direct therapy, they may do so in future.

staging and risk assessment

Staging needs to take into account the patient’s performance status [using WHO or European Cooperative Oncology Group (ECOG) scores], past medical history/co-morbidities and liver function tests (LFTs). Imaging consists of MRI (for assessment of tumour [T]-stage and bile duct involvement), thorax CT (metastases (M)-stage) and EUS (lymph node (N)-stage). Whenever necessary (e.g. inconclusive MRCP), ERCP or percutaneous transhepatic cholangiography (PTC) should be carried out to improve assessment of T-stage, as this is crucial for surgical decision-making [IV, B]. Contrast CT is effective in defining the relationship between the tumour and the vasculature (portal vein and hepatic artery). The utility of positron emission tomography (PET)-CT is controversial and should only be used on a case-by-case basis.

Staging is carried out according to the TNM 2010 system and is specific for every subtype of BTC (see Table 1) [21]; pCCA may be further subclassified according to the Bismuth–Corlette classification (Table 2).

Risk assessment is different for every CCA subtype. When considering pCCA, patients suffering from primary sclerosing cholangitis (PSC) in the Western world and patients with hepatobiliary flukes or hepatolithiasis in Asian countries are at an increased risk. Guidelines for surveillance of PSC patients are available [23]. Cirrhosis and hepatotropic viruses are risk factors for iCCA, with odds ratios (ORs) of 22.92 [95% confidence interval (CI): 18.24–28.79] for cirrhosis, 4.84 (95% CI: 2.41–9.71) for hepatitis C and 5.10 (95% CI: 2.91–8.95) for hepatitis B, according to a recent meta-analysis [8]. The presence of iCCA should be considered in cirrhotic patients although the development of a hepatocellular carcinoma, for which patients are already undergoing screening, is more likely. Screening for CCA in newly defined at-risk groups (e.g. with obesity and the metabolic syndrome [8]) has not been established.

Patients with premalignant lesions predisposing to GBC warrant surveillance; the risk of malignancy is related to the size of gallbladder polyps (the most prevalent finding), which are often found incidentally. Lesions ≥20 mm should be managed as GBC after completion of staging investigations. Ultrasound surveillance is recommended for polyps measuring 6–9 mm (6-monthly for 1 year, then annually for 5 years), with resection only in enlarging polyps (to 10–20 mm in size) [24].

management of local/locoregional disease

The therapeutic strategy varies for each type of BTC depending on its site of origin. A treatment algorithm is shown in Figure 1.

intrahepatic cholangiocarcinoma

iCCAs usually arise within normal background liver parenchyma, and their radiological appearance is, most typically, of a mass-forming arterially enhancing tumour. Radical surgical removal with clear margins is the only potentially curative therapy [III, A]. There are well-known prognostic parameters that should be taken into account when assessing prognosis including the presence of lymph node involvement; this has led to the recommendation of routine lymphadenectomy at the level of the hepato-duodenal ligament during surgery [II, A] [25]. Several other factors including size and number of tumours, grade, the presence of satellite nodules, vascular and/or perineural invasion should be reported by the pathologist to guide decisions regarding adjuvant therapy, although robust evidence for its use is lacking [IV, B].

perihilar cholangiocarcinoma (Klatskin tumour)

Diagnosis of a pCCA and assessment of resectability according to the Bismuth–Corlette classification can only be determined in a considerable number of patients with surgical exploration. It is important that, for patients presenting with jaundice, initial radiological imaging is carried out before an ERCP or PTC is undertaken, as the inserted drains/stents obscure the diagnosis and assessment of the extent of disease [III, A]. The practice of biliary drainage before resection (versus immediate surgery) remains controversial and has to be decided on by the treating team taking into consideration non-tumour related factors, such as performance status and co-morbidities [II, B]. The anatomically longer left hepatic duct before segmental distribution usually implies that an extended right hemi-hepatectomy is necessary for curative intent and may require portal vein embolisation (including the segment IV branches) to induce hypertrophy of the future liver remnant (preservable segments II and III) [IV, A] [26]. Segment I, which drains into the ductal bifurcation, where the cancer lies, has to be removed in any curative procedure. Vascular resections at the hilum are possible but their invasion affects prognosis. Lymphadenectomy should be a standard addition in every CCA surgery.

Liver transplantation in locally unresectable cases has been explored in a multidisciplinary approach including a strategy consisting of neoadjuvant chemoradiotherapy followed by liver transplantation by the Mayo Clinic; however, this has not become the standard of care [III, C]. The ongoing French phase III TRANSPHIL trial compares this strategy with standard surgical resection.

distal cholangiocarcinoma

In contrast to the other forms of CCA, this type requires the removal of the pancreatic head, usually a partial duodeno-pancreatectomy (PDP) with extended bile duct resection up to the hilum. PDP is a standard procedure that includes draining lymph node dissection and reconstruction of the stomach and
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<tr>
<th>Cholangiocarcinoma</th>
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<th>Cholangiocarcinoma - distal</th>
<th>Gallbladder cancer</th>
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<td>Solitary tumour without vascular invasion</td>
<td>Tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue</td>
<td>Tumour confined to the bile duct histologically</td>
<td>Tumour invades the lamina propria or muscular layer</td>
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<td>T1a</td>
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<td>Solitary tumour with vascular invasion</td>
<td>Tumour invades beyond the wall of the bile duct to the surrounding adipose tissue</td>
<td>Tumour invades beyond the wall of the bile duct</td>
<td>Tumour invades the muscular layer</td>
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<td>T2b</td>
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<td>Multiple tumours, with or without vascular invasion</td>
<td>Tumour invades the adjacent hepatic parenchyma</td>
<td>Tumour invades the gallbladder, pancreas, duodenum or other adjacent organs without involvement of the coeliac axis, or the superior mesenteric artery</td>
<td>Tumour invades the perimuscular connective tissue; no extension beyond the serosa or into the liver</td>
<td>Tumour perforates the serosa (visceral peritoneum) and/or directly invades the liver</td>
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<td>Tumour perforating the visceral peritoneum or involving the local extrahepatic structures by direct invasion</td>
<td>Tumour invades unilateral branches of the portal vein or the hepatic artery</td>
<td>Tumour involves the coeliac axis, or the superior mesenteric artery</td>
<td>Tumour invades the perimuscular connective tissue; no extension beyond the serosa or into the liver</td>
<td>Tumour perforates the serosa (visceral peritoneum) and/or directly invades the liver</td>
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<td>Tumour with periductal invasion</td>
<td>Tumour invades the main portal vein or its branches bilaterally; or the common hepatic</td>
<td>Tumour invades the main portal vein or its branches bilaterally; or the common hepatic</td>
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artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum or extrahepatic bile ducts

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<tr>
<th>Regional lymph nodes (N)</th>
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<td>Regional lymph node metastasis present</td>
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<td>Metastasis to periaortie, pericaval, superior mesenteric artery and/or coeliac artery lymph nodes</td>
<td>Metastases to nodes along the cystic duct, common bile duct, hepatic artery and/or portal vein</td>
<td>Metastases to periaortie, pericaval, superior mesenteric artery and/or coeliac artery lymph nodes</td>
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<td>Distant metastasis</td>
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the remaining pancreas in various ways to achieve macroscopic cure. The prognosis of dCCA is better than that of adenocarcinoma of the head of the pancreas [III, A] [27].

gallbladder cancer

GBC has two typical presentations: either (a) incidentally diagnosed in the histological workup of simple cholecystectomies or (b) as a symptomatic right upper quadrant tumour at an advanced stage.

The former requires staging with appropriate imaging (MRI or CT) and detailed histopathological analysis to decide whether further resection is necessary, including T-stage, cystic duct margin, involvement of resected lymph nodes, grade, perineural and/or vascular invasion. Every T-stage above T1a and positivity of any mentioned parameters requires a reoperation where a segment IVb/V liver resection together with a ligamentary lymphadenectomy should be carried out [II, A] [28]. If the gallbladder was not removed with a bag during laparoscopic resection or the gallbladder perforated (an adverse prognostic factor), the port sites should also be resected [IV, A].

If GBC is diagnosed during imaging (for symptomatic patients) or when patients present with jaundice, evaluation of potential resectability is the key factor. Advanced T-stage (including T4 tumours) is not a contraindication for resectability provided they are located in the fundus; these tumours require major liver resection with potential resection of the transverse colon. Achieving a curative resection of an advanced tumour located at the infundibulum is much more difficult, because it requires the resection of the bile duct, the duodenal bulb and, potentially, the pancreatic head together with a major hepatectomy, especially if right-sided vessels (right hepatic artery, right portal vein) are involved [III, A].

The prognosis of a gallbladder cancer, if not diagnosed at a very early stage, is somewhat inferior to all other types of CCA.

adjuvant treatment. The high rates of local and distant recurrence following surgery justify the consideration of an adjuvant treatment. The role of adjuvant chemoradiotherapy in this setting is not well defined because of a lack of data from randomised trials. Indeed, most of the published studies are retrospective, including small numbers of patients with a mix of gallbladder and bile duct tumours. In a recent meta-analysis of published data, adjuvant chemotherapy or chemoradiotherapy appears to be associated with a survival benefit in patients with BTC with lymph node-positive disease or with microscopically involved margins (R1 resection) [29]. However, major limitations (including selection bias, heterogeneity of treatments, stage migration over time and variable data quality) preclude definitive conclusions. Moreover, a differentiation between the two modalities (chemotherapy versus chemoradiotherapy) have not been compared in this setting. When employed, the recommended dose of radiotherapy is 45 Gy in fractions of 1.8 or 2 Gy with concurrent 5-fluorouracil (5-FU) or capecitabine [IV, C]. Recently, two prospective trials have assessed a regimen combining a gemcitabine-based adjuvant chemotherapy followed by chemoradiotherapy with concurrent 5-FU [30, 31].

The results of two phase III studies that have completed accrual and are awaiting maturation of data [BilCap
(observation versus adjuvant capecitabine; UK, NCT00363584) and Prodige-12 (observation versus gemcitabine/oxaliplatin; France, NCT01313377) are awaited and are likely to define future adjuvant strategies. A further study [ACTICCA-1 (observation versus cisplatin/gemcitabine; Germany, NCT02170090)] is open and recruiting patients.

In the absence of level-1 data, the multidisciplinary team may offer adjuvant therapy (radiotherapy, chemoradiotherapy or chemotherapy alone) to patients on the best available evidence and only after a risk–benefit assessment.

### management of advanced and/or metastatic disease

#### radiation therapy

The role of radiation therapy remains unclear in the treatment of locally advanced but non-metastatic BTC. Chemoradiotherapy has been considered a possible option according to non-randomised studies with median survival rates between 9 and 14 months. The French FFCD 9902 phase III trial compared chemoradiotherapy with chemotherapy alone in this setting [32]. Patients were randomised between chemoradiotherapy (50 Gy with concurrent 5-FU and cisplatin) or chemotherapy with a combination of gemcitabine and oxaliplatin (GemOx). This trial was closed before the completion of...
### Table 3. Summary of recommendations

#### Screening
- Only at-risk populations should be considered for screening, e.g. patients with PSC (screening guidelines in PSC are available)

#### Diagnosis
- Abdominal ultrasound may be useful for the initial examination (identification of biliary obstruction)
- MRI and MRCP should be carried out before any biliary intervention; CT is less useful
- ERCP allows relief of bile duct obstruction (by stenting); brush cytology and biopsies should be carried out
- For patients deemed suitable for surgery with radical intent, a biopsy is not obligatory (brush cytology may be available). A biopsy should be restricted to selected cases (e.g. equivocal lesion) and only after discussion at a specialist hepatobiliary MDT; if so, EUS-guided biopsy is preferred and percutaneous sampling should be avoided
- For patients with advanced/inoperable disease, histological/cytological confirmation is essential; it may be obtained at EUS or metastatic lesions can be biopsied percutaneously (ultrasound or CT guided)
- FDG-PET imaging has no established role in the diagnosis of BTC
- Baseline CA19-9 should be interpreted with caution and is best used to guide treatment and follow-up; it may have a prognostic value in the absence of biliary obstruction

#### Staging
- The established staging system for biliary tract cancer is the one developed by the TNM committee of the AJCC/UICC (currently 7th Edition) with subclassifications for GBC and iCCA, pCCA and dCCA
- CT (including thorax and pelvis) allows evaluation of distant metastases and vessel involvement
- MRI plus MRCP is useful for T-staging
- EUS helps to clarify N-stage (± nodal biopsy) and adds information regarding vessel involvement
- FDG-PET scan is not routinely recommended for the staging of BTC
- Staging laparoscopy may be considered on an individual basis to exclude the presence of peritoneal metastases if it will influence the decision to proceed with major resection (e.g. locally advanced GBC)
- Pathology examination and reporting of surgically-resected specimens should follow standardised reporting tools (minimum dataset)

#### Treatment

##### Curative
- Radical surgery (with lymphadenectomy) is the only curative treatment of BTC; the exact nature and extent of surgery will depend on tumour subtype/location and should be agreed at a specialist hepatobiliary multidisciplinary tumour board
- Surgery involving hepatic resection will need to take into account the future liver remnant and may require portal vein embolisation
- For patients with incidentally diagnosed GBC (post-cholecystectomy), reoperation with radical intent should be considered for stage T1b and above (± resection of port sites)
- Adjuvant therapy (radiotherapy, chemoradiotherapy or chemotherapy alone) may be offered to patients on the understanding that the evidence base is weak and only after risk–benefit assessment; participation in clinical trials should be encouraged
- Neoadjuvant therapy and liver transplant (Mayo Clinic protocol) in early-stage hilar CCA remains investigational; participation in clinical trials should be encouraged
- Patients with initially inoperable, non-metastatic disease should be rediscussed at the multidisciplinary tumour board with a view to salvage surgery in the event of a good response to systemic and/or locoregional treatment, including participation in clinical trials

##### Palliative
- Systemic chemotherapy is the treatment of choice for patients with locally advanced or inoperable disease; combination chemotherapy for PS 0–1 patients and monotherapy for PS 2 patients
- Cisplatin/gemcitabine is the reference chemotherapy regimen for good PS (0–1) patients; oxaliplatin may be substituted for cisplatin where there is a concern about renal function
- Gemcitabine monotherapy may be considered for PS 2 patients
- There is no established second-line chemotherapy regimen; patients should be encouraged to participate in clinical trials
- There is no established evidence to support the use of targeted therapies; patients should be encouraged to participate in clinical trials
- Radiotherapy may be considered in patients with localised disease, after first-line chemotherapy; patients should be encouraged to participate in clinical trials
- Radioembolisation may be considered in patients with inoperable iCCA, usually after first-line chemotherapy; patients should be encouraged to participate in clinical trials

##### Best supportive care
- Biliary obstruction is a common occurrence in BTC; establishment of biliary drainage and subsequent stenting should be carried out
- When endoscopic stenting is not possible, percutaneous transhepatic drainage is recommended

Continued
planned inclusions, after enrolment of 34 patients. There was an advantage for GemOx, both in terms of progression-free survival (median PFS, 11 versus 5.8 months) and overall survival (OS, 20 versus 13.5 months).

Recently, intensity-modulated radiotherapy (IMRT) was shown to allow safe dose escalation [33]. Whether a dose escalation could improve the local control and survival remains unknown.

Experience is growing in the use of radioembolisation using 90Y-microspheres for patients with iCCA. Prospective, randomised data are lacking; a pooled analysis of 12 studies including 298 patients showed a median OS of 15.5 months and response rate of 28% [34]. Importantly, 77/73 (10%) patients in three selected studies were converted to resectable disease, highlighting the importance of reassessment of patients in the multidisciplinary team in the event of a good response to any treatment [IV, B].

**systemic chemotherapy**

Prospective randomised, controlled studies have shown that systemic chemotherapy extends survival in patients with advanced BTC compared with best supportive care [35, 36]. The phase III UK ABC-02 study has established the cisplatin/gemcitabine combination as a standard of care in this disease [I, A], achieving a median survival close to a year (11.7 months) for cisplatin/gemcitabine, compared with 8.1 months for gemcitabine alone (95% CI: 0.53–0.79; P<0.001) [37] with a similar benefit in the randomised phase II Japanese study [38]. A meta-analysis of these studies has shown that patients benefit from the combination independent of age (<65 versus ≥65 years), gender, primary tumour site (intra- versus extrahepatic versus gallbladder versus ampullary), stage of disease (locally advanced versus metastatic) and prior therapy (surgery or stenting); however, patients with performance status 2 may derive the least benefit from the combination [39]. In patients where there is a concern about renal function, oxaliplatin may be substituted for cisplatin [II, B]; in patients with performance status 2, gemcitabine monotherapy may be considered [I, B].

There is no established second-line systemic therapy following progression after first-line treatment although fluoropyrimidine-based therapy (either in monotherapy or in combination with other cytotoxics) is sometimes used [III, C]. A systematic review including 761 patients showed disappointing median PFS (3.2 months; 95% CI: 2.7–3.7) and response rates (7.7%; 95% CI: 4.6–10.9); the mean OS was 7.2 months (95% CI: 6.2–8.2) and no recommendation could be made about the most appropriate second-line regimen [40]. Moreover, the magnitude of benefit to patients (if any) over best supportive care is not known; results of study NCT01926236 (ABC-06) will inform this question.

**personalised medicine**

The modest gains obtained with systemic chemotherapy highlight the need for improved therapies; the epithelial growth
factor receptor (EGFR) and vascular endothelial growth factor (VEGF) axes have been studied the most. Despite a promising response rate (63%) when adding the EGFR-targeted monoclonal antibody, cetuximab, to gemcitabine and oxaliplatin in a single-arm study (leading to salvage surgery in n = 9 [30% of patients]) [41], there was no incremental benefit observed from the addition of cetuximab to GemOx in the randomised phase II BINGO study [42]; similar negative findings were observed with erlotinib or panitumumab with no clear correlation with EGFR overexpression or k-ras mutation status.

Prospective randomised phase II studies targeting VEGF have failed to show a benefit of adding sorafenib (an oral multi-tyrosine kinase inhibitor) to single-agent gemcitabine [43] or cediranib (an oral VEGFR-1, −2 and −3, PDGF and c-Kit tyrosine kinase inhibitor) to the cisplatin/gemcitabine combination [44]. There is currently no evidence to support the use of targeted therapies outside the context of a clinical trial.

A better understanding of the molecular pathology of BTC may help identify suitable targets for therapy. Molecular profiling has identified clear differences between CCA and GBC; moreover, intra- and extrahepatic CCAs have different profiles (e.g. IDH-1 and FGFR fusion rearrangements appear in iCCAs only). The significance and clinical relevance (particularly with therapeutic intent) of identifying these signatures are under evaluation.

**follow-up and long-term implications**

Follow-up after potentially curative treatment should consist of 3-monthly visits during the first 2 years after therapy including clinical examination, laboratory investigation (including LFTs and lactate dehydrogenase), tumour markers (carcinoembryonic antigen, CA19-9) and CT scan of the thorax, abdomen and pelvis [IV, A]. Regular visits can be extended to 6-monthly thereafter and prolonged to yearly visits after 5 years of follow-up.

In patients receiving treatment of advanced, recurrent or metastatic disease, best supportive care should include active identification and management of obstructive complications. These may include biliary obstruction (requiring biliary drainage and stents, as appropriate); gastric outlet obstruction (requiring duodenal stent or, occasionally, bypass surgery) and/or pancreatic duct obstruction (requiring pancreatic enzyme replacement therapy). Percutaneous transhepatic drainage is recommended if endoscopic stenting is not possible; a metal stent is preferred in patients with a life expectancy of ≥3 months. Some patients require repeat stenting on multiple occasions; anticipation for such an event is required when planning stent placement. In addition, patients should have full access to palliative care and symptom management (including pain control) throughout their treatment.

**methodology**

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development, www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 3. Levels of evidence and grades of recommendation have been applied using the system shown in Table 4. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer-review process.

**conflict of interest**

JWV has reported honoraria/consultancy for Lilly, AstraZeneca and Sirtx; research support from Lilly, AstraZeneca and NuCana. SAK has reported speakers’ fees for Bayer and BTG. FH has reported research support from Merck Serono and advisory board participation for Merck Serono, MSD and Celgene. TG has reported speakers’ bureau member of and research support from Roche, Merck-Serono, Amgen, Sanofi-Aventis and Bayer. DA has reported honoraria/consultancy for Roche, Merck-Serono, Bayer, Lilly and Servier; research support from Roche. IB has declared no potential conflicts of interest.

**references**
