clinical practice guidelines

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

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incidence

The crude incidence of gallbladder and extrahepatic biliary cancer (ICD-10: C23–C24) in the European Union is ∼3.2 and ∼5.4/100 000 per year for males and females, respectively. Age-adjusted mortality is 1.4 and 1.9/100 000 for males and females, respectively. The incidence of intrahepatic cholangiocarcinoma (ICD-10: C22.1) is increasing and may be estimated as ∼0.9–1.3 and 0.4–0.7/100 000 for males and females, respectively, as 10–15% of primary liver cancer (ICD-10: C22). In high-risk areas in Europe (south Italy), the incidence is estimated to be up to ∼4.9–7.4 and ∼2.9–4.3/100 000 for males and females, respectively, and worldwide, e.g. in northeast Thailand, up to 96/100 000.

diagnosis

Diagnosis should be made on the basis of radiological investigations [magnetic resonance imaging (MRI) and computed tomography (CT) are both useful] and pathomorphological assessment according to the World Health Organization classification from a biopsy, fine needle aspiration or biliary brush cytology. A final pathological diagnosis has to be obtained before any chemotherapy, radiotherapy or other non-surgical oncological therapy, but is not critical for planning surgery in patients with characteristic findings of resectable biliary cancer.

staging

Staging consists of complete history and physical examination, blood counts, liver function tests, chest X-ray, imaging of the abdomen by sonography and CT scan or MRI, endoscopic retrograde or percutaneous transhepatic cholangiography and possibly endoscopic ultrasonography, cholangioscopy and laparoscopy. Upper and lower endoscopy has to be performed in patients with an isolated intrahepatic mass. The staging is to be given according to the TNM 2010 system seperately for gallbladder cancer (Table 1), intrahepatic cholangiocarcinoma (Table 2a), perihilar cholangiocarcinoma (Table 2b) and distal cholangiocarcinoma (Table 2c). Hilar cholangiocarcinoma (Klatskin's tumor) is clinically staged depending on the involvement of the hepatic ducts according to the Bismuth–Corlette classification, which is presented in Table 3.

treatment after incidental finding of gallbladder cancer on pathological review

A radical reresection (after a complete staging including laparoscopy demonstrating resectability) is highly recommended for patients with incidental gallbladder carcinoma stage T1b (tumor invades muscle layer) or greater. Patients with T1a tumors (tumor invades lamina propria) do not benefit further from re-resection if the gallbladder was removed intact, and should be observed only [III, B].

treatment after incidental finding of gallbladder cancer at surgery

After incidental finding of gallbladder cancer at surgery, staging has to be performed intraoperatively, and extended cholecystecomy including *en bloc* hepatic resection and lymphadenectomy with or without bile duct excision has to be considered depending on resectability and the expertise of the surgeon.

treatment of resectable tumors

Complete surgical resection is the only potentially curative treatment available. Resection of gallbladder cancer consists of extended cholecystecomy including *en bloc* hepatic resection and lymphadenectomy (porta hepatis, gastrohepatic ligament, retroduodenal) with or without bile duct excision. Major hepatectomy including caudate lobectomy such as

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Table 1. TNM staging of gallbladder cancer

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma *in situ*		
T1	Tumor invades lamina propria or muscular layer		
T1a	Tumor invades lamina propria		
T1b	Tumor invades muscular layer		
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver		
T3	Tumor 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	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery and/or portal vein		
N2	Metastases to periaortic, pericaval, superior mesenteric artery and/or celiac artery lymph nodes		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1–3	N1	M0
Stage IVA	T4	N0–1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

Table 2a. TNM staging of intrahepatic cholangiocarcinoma

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma *in situ* (intraductal tumor)		
T1	Solitary tumor without vascular invasion		
T2a	Solitary tumor with vascular invasion		
T2b	Multiple tumors, with or without vascular invasion		
T3	Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion		
T4	Tumor with periductal invasion		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis present		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis present		
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	Any T	N1	M0
Stage IVB	Any T	Any N	M1

extended right lobe resection with portal vein resection increases resectability and radicality for stage 3 and 4 hilar cholangiocarcinomas and has been associated with higher 5-year survival rates [III, B]. Preoperative transarterial or portal vein embolization increases the remnant liver volume in patients with estimated postresection volumes of <25% and appears to reduce postoperative liver dysfunction. An indication of biliary drainage should be systematically discussed with specialized surgeons before surgery.

Even in patients undergoing aggressive surgery, 5-year survival rates are 5–10% for gallbladder cancer and 10–40% for cholangiocarcinoma.

adjuvant (and additive) therapy

Additive fluorouracil-based chemotherapy has been associated with a small survival benefit after non-curative resection of gallbladder cancer [II, B]. Postoperative treatment after non-curative resection of cholangiocarcinoma remains controversial, and both supportive care and palliative chemotherapy and/or radiotherapy may be taken into consideration.

As both gallbladder and biliary tract neoplasms present a high incidence of local failure after surgical resection, reaching 52%, a locoregional adjuvant treatment may be considered. Several retrospective reports on adjuvant and recently also on neoadjuvant (chemo)radiotherapy suggest survival benefit in both gallbladder and biliary duct cancer, and postoperative chemoirradiation may be considered as an option. Fluorouracil was mostly used for chemoradiotherapy in biliary cancers. Recently concomitant gemcitabine with or without oxaliplatin has shown feasibility with radiotherapy in this disease.

treatment of unresectable tumors

Palliation of jaundice can be accomplished by endoscopic or percutaneous stenting of the biliary tree or by operative biliary–enteric bypass. Urgent biliary drainage and broad-

Table 2b. TNM staging of perihilar cholangiocarcinoma

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma *in situ*		
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue		
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue		
T2b	Tumor invades adjacent hepatic parenchyma		
T3	Tumor invades unilateral branches of the portal vein or hepatic artery		
T4	Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery and portal vein)		
N2	Metastasis to periaortic, pericaval, superior mesenteric artery and/or celiac artery lymph nodes		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a–b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1–3	N1	M0
Stage IVA	T4	N0–1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

Table 2c. TNM staging of distal cholangiocarcinoma

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma *in situ*		
T1	Tumor confined to the bile duct histologically		
T2	Tumor invades beyond the wall of the bile duct		
T3	Tumor invades the gallbladder, pancreas, duodenum or other adjacent organs without involvement of the celiac axis, or the superior mesenteric artery		
T4	Tumor involves the celiac axis, or the superior mesenteric artery		
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 grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Table 3. The Bismuth–Corlette classification scheme of biliary structures cancer

Type I	Tumor involves the common hepatic duct
Type II	Tumor involves the bifurcation of the common hepatic duct
Type IIIa	Tumor involves the right hepatic duct
Type IIIb	Tumor involves the left hepatic duct
Type IV	Tumor involves both the right and left hepatic ducts

spectrum antibiotics are crucial in patients with cholangitis due to obstructive jaundice.

Palliative chemotherapy added to both quantity and quality of life in advanced biliary cancer in a single phase III study [II, B], but the survival benefit for chemotherapy in general is not yet clearly established. Resently, results of a multicenter, randomized phase III trial, the UK ABC-02 trial evaluating gemcitabine with or without cisplatin in patients with advanced or metastatic biliary tract cancer, demonstrated a clear survival advantage (hazard ratio 0.68, $P = 0.002$) for the combination of gemcitabine with cisplatin without added clinically significant toxicity, setting a new standard of care in this disease [I, A]. In a case where cisplatin is not applicable, oxaliplatin might be an option for combination with gemcitabine, as several phase II trials demonstrated antitumor

activity and good tolerability of gemcitabine with oxaliplatin in biliary cancers. In the past, lacking randomized controlled trials and an accepted standard, 5-fluorouracil or gemcitabine was routinely used. Monotherapy with these agents should be considered in a case where gemcitabine combined with either cisplatin or oxaliplatin is not applicable. Limiting toxicity of cisplatin may be renal or neuronal toxicity, myelosuppression or ototoxicity, whereas sensory neuropathy may be limiting for oxaliplatin.

The biologicals erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, and bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, have shown clinical activity in biliary cancer in a phase II trial. Due to infrequent grade 3 and 4 adverse effects in patients with this disease, the combination of bevacizumab and erlotinib may be a therapeutic alternative to cytostatic chemotherapy.

Concurrent chemoirradiation is an additional therapeutic option. After years of fluorouracil-based chemoradiotherapy, gemcitabine and oxaliplatin have demonstrated feasibility as concomitant chemotherapy (see adjuvant/additive therapy). High radiation doses delivered by use of brachytherapy boost using iridium-192 may improve local control of disease. Recently, intensity-modulated radiotherapy (IMRT) was shown to allow safe dose escalation to much higher doses compared with 3D-conformal radiotherapy and in this the way for future trials to test the effect of radiotherapy in this disease, as recently shown in a retrospective comparative trial. Neoadjuvant therapy is not a routine option in biliary cancers. However, if restaging in patients with locally advanced disease shows potentially resectable tumors, resection should be considered.

Liver transplantation is indicated under strict research protocols at selected centers, for patients with early stage cholangiocarcinoma and anatomically unresectable lesions, but this approach is experimental and should not be offered outside the scope of clinical trials. Data on photodynamic therapy are slightly more advanced. In cholangiocarcinoma, photodynamic therapy after decompression of the biliary tree has been proved to provide survival benefit in two small randomized trials [II, B]. In patients with a large visible mass on radiographic studies, the effect of photodynamic therapy may be limited and combination with chemotherapy may be considered, although appropriate trials are lacking.

response evaluation

Response evaluation is recommended 3 months after photodynamic therapy by means of cholangiography during routine stent exchange and after two or three cycles (8–12 weeks) of chemotherapy by clinical evaluation, subjective symptom evaluation, blood tests and repeating the initially abnormal radiological or ultrasound examinations. In a phase II trial of palliative chemotherapy in patients with advanced biliary cancer, decreases in SUV(max) on [^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET) scans after 8 weeks of treatment were associated with disease control and increases in progression-free and overall survival.

follow-up

There is no evidence that regular follow-up after initial therapy may influence the outcome. Follow-up visits after complete resection should be restricted to history and physical examination considering symptoms, nutrition and psychosocial problems.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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