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Biliary cancer: ESMO Clinical Recommendation 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. 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) incidence is estimated 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 and CT are both useful) and pathomorphological assessment according to the World Health Organization classification from a biopsy, fine needle aspiration or biliary brush cytology. Final pathologic diagnosis has to be obtained before any chemotherapy, 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 computed tomography scan or magnetic resonance, 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 2002 system separately for gallbladder cancer, extrahepatic bile duct tumors, and liver cancer including intrahepatic bile duct cancer. TNM classification for gallbladder and bile duct tumors is presented in Tables 1 and 2. TNM classification for liver cholangiocarcinoma is the same as for hepatocellular liver cancer. 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 pathologic review

A radical re-resection (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 further benefit 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 cholecystectomy including en bloc hepatic resection and lymphadenectomy with or without bile duct excision has to be considered depending on resectability and 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 cholecystectomy 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 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 transartial or portal vein embolisation increases the remnant liver volume in

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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 muscle layer
T1a: Tumor invades lamina propria
T1b: Tumor invades the muscle layer
T2: Tumor invades the perimuscular connective tissue; no extension beyond the serosa or into the liver
T3: Tumor perforates the serosa (visceral peritoneum) or directly invades one adjacent organ, or both (extension 2 cm or less into the liver)
T4: Tumor extends more than 2 cm into the liver, and/or into two or more adjacent organs (stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts, any involvement of the liver)
Regional lymph nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in cystic duct, pericholedochal, and/or hilar lymph nodes (i.e. in the hepatoduodenal ligament)
N2: Metastasis in peripancreatic (head only), periduodenal, periportal, celiac, and/or superior mesenteric lymph nodes
Distant metastasis (M)
MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

Table 2. TNM Staging of biliary canal cancer

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 liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left)
T4: Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall
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)
MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

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

patients with estimated postresection volumes of <25% and appears to reduce postoperative liver dysfunction. 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.

Additive fluorouracil-based chemotherapy has been associated with a small survival benefit after noncurative resection of gallbladder cancer [II, B]. Postoperative treatment after noncurative 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 should be considered. Several retrospective reports on adjuvant radiotherapy suggest survival benefit both in gallbladder and biliary duct cancer and postoperative chemoirradiation could be considered as an option.

treatment of unresectable tumors

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 proven to induce survival benefit in two small randomised trials [II, B]. In patients with a large mass visible on radiographic studies the effect of photodynamic therapy may be limited and combination with chemotherapy may be considered although appropriate trials are lacking. 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. Lacking randomised controlled trials and an accepted standard, 5-fluorouracil or gemcitabine are routinely used. Based on the results of a pooled analysis of predominantly phase II trials, gemcitabine combined with platinum compounds could also be an acceptable chemotherapy modality, since this combination offered the highest rates of objective response and tumor control in advanced biliary cancer [III, B]. Concurrent chemoirradiation is an additional therapeutic option and high radiation doses delivered by use of brachytherapy boost may improve local control of disease. 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-spectrum antibiotics are crucial in patients with cholangitis due to obstructive jaundice.

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 radiologic or ultrasound examinations.

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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