

REVIEW ARTICLE

Guidelines for palliative surgery of cholangiocarcinomaH. WITZIGMANN¹, H. LANG² & H. LAUER¹¹*Department of General and Visceral Surgery, Hospital Dresden-Friedrichstadt, Dresden, Germany and* ²*Department of General and Visceral Surgery, University of Mainz, Germany***Abstract**

The aims of the guidelines are to help assess the evidence for palliation surgery in patients with cholangiocarcinoma (CCA). The guidelines are classified in accordance with the location of the primary lesion, i.e. intrahepatic, hilar, and distal. They are based on comprehensive literature surveys, including results from randomized controlled trials, systematic reviews and meta-analysis, and cohort, prospective, and retrospective studies. Intrahepatic CCA: resection of lymph-node-positive tumors and R1/R2 resections have not been shown to provide survival benefit: Evidence levels: 2b, 4; Recommendation grade C. Hilar CCA: R1 resection is justified as a very efficient palliation: Evidence levels 2b, 4; Recommendations grade B. Non-surgical biliary stenting is the first choice of palliative biliary drainage: Evidence levels 2b; Recommendation grade B. Distal CCA: Resection of lymph-node-positive tumors and R1/R2 resections should be performed: Evidence level 4; Recommendation grade C. Non-surgical stenting is regarded as the first choice of palliation for patients with short life expectancy. For patients with longer projected survival, surgical bypass should be considered: Evidence levels 1a, 2b, 4; Recommendation grade B. Palliative resections have a relevant beneficial impact on the outcome of patients with distal and hilar CCA. Non-surgical stenting is the first choice of palliative biliary drainage for patients with hilar CCA and for those with distal CCA and short life expectancy. For patients with distal CCA and longer projected survival, surgical bypass should be considered.

Key Words: *Distal cholangiocarcinoma, guidelines, hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma*

Introduction

Each location of cholangiocarcinoma (CCA) arising from the distal extrahepatic duct (DCC), the hilar bifurcation (HCC), or from the intrahepatic ducts (ICCs) represents an individual tumor entity with a different natural history, clinical presentation, and prognosis. The following guidelines aim to assess the evidence of palliative surgery in the case of patients with CCA.

Patients and methods

The guidelines are classified according to the location of the primary lesion: intrahepatic, hilar, and distal. They are based on comprehensive literature surveys, including results from randomized controlled trials, systematic reviews and meta-analyses, and cohort, prospective, and retrospective studies. Series with <10 treated patients were excluded. Evidence levels and categories for recommendations were assessed in

accordance with the Centre for Evidence-Based Medicine in Oxford, UK (available at: <http://www.cebm.net>) [1].

Intrahepatic cholangiocarcinoma

There are only a few data with a small number of patients on the role of non-curative resection for intrahepatic CCA [2–8]. In only one study with few patients ($n \leq 10$ patients each group) was a significant survival benefit seen after palliative resection compared to no resection [2], and in three reports no survival benefit was seen after non-curative resection [6–8].

Jaundice proved to be an independent negative prognostic factor in the study by Weimann et al. [9], and no patient with a total bilirubin over 1.2 mg/dl was found to be resectable in the series by Roayaie et al. [2]. Long-term survival was reported in only a few patients after resection of lymph node positive

tumors [10–12]. It is unproved whether R0 resection of intrahepatic CCA with lymph node metastases, even in the regional site, provides relevant survival benefit. Two recent series recommend extended liver resection with complex vascular and biliary reconstruction [7] or hepatopancreatoduodenectomy [13] for patients with advanced intrahepatic CCA, if a potentially curative resection is possible. A recent study by Lang et al. [12] shows that there might be some survival benefit after R1 resection of solitary intrahepatic CCA compared to R1 resection of multifocal tumors.

Recommendation

Resection of lymph-node-positive tumors and R1 and R2 resections have not been shown to provide survival benefit and should be performed only in highly selected patients. An aggressive surgical approach is justified to achieve complete tumor removal.

Hilar cholangiocarcinoma

The median survival time of patients with non-resectable hilar CCA is approximately 3 months without intervention [14] and 4–10 months with biliary drainage [12,14–21].

Palliative resection

In a study by Seyama et al. [22], no difference in survival was seen between R0 resection with a margin <5 mm and R1 resection. Table I indicates that, in most reports, resection with a histological positive margin offers survival benefit compared to palliative treatment [15,16,18,23,24]. The studies by Jarnagin

et al. [25] and Zhang et al. [26] reveal longer survival after palliative resection compared to no resection without statistical significance. In a non-randomized study of 35 patients with hilar CCA, Baton et al. found that R1 hepatic resection with no other risk factor can offer long-term survival [27].

Long-term survival has been reported in a few patients with regional and distant (pM1) lymph node metastases [15,16,23–25,28–30]. In the study by Kitagawa et al., the most important study regarding the role of lymphadenectomy in hilar CCA, a 5-year survival rate of 14.7% for patients with regional lymph node metastases and of 12.3% for those with positive para-aortic nodes was reported [29].

On the basis of these data, and despite the lack of prospective randomized trials, R1 resection is an efficient palliation, and regional lymph node involvement is no contraindication for resection.

Biliary drainage

The palliative surgical options for biliary drainage include segment III (SgIII) cholangiojejunostomy, right sectoral duct bypass, and transtumoral tube placement. The commonly performed operative biliary drainage procedure for hilar CCA is the SgIII cholangiojejunostomy. Studies concerning SgIII cholangiojejunostomy reveal a surgical complication rate ranging between 17% and 55% and a surgical mortality from 0% to 17.6% [16,31–35]. The reported survival times after SgIII cholangiojejunostomy for hilar CCA range between a median survival of 6.3 months and a mean survival of 18.5 months [15,31–35]. Relief of jaundice was achieved in at least 70%.

Table I. Hilar cholangiocarcinoma: survival after palliative resection versus no resection.

Study	Evidence level	Survival (months)		p
		Palliative resection (n)	No resection (n)	
Pichlmayr et al., 1996 [16] retrospective	2 b	R1 resection (n=27) Median: 12.7 mo	Exploratory laparotomy (n=99) 5.6 mo	<0.0005
Kosuge et al., 1999 [23] retrospective	2 b	R1 resection (n=31)	Non-resectional surgery (n=24) Non-surgical procedure (n=18)	<0.0001 0.045
Jarnagin et al., 2001 [25] retrospective	2 b	R1 resection (n=18) Median: 21 mo	Exploratory laparotomy (n=80) 16 mo	NS
Kawasaki et al., 2003 [15] retrospective	2 b	R1 resection (n=25) Mean: 28 mo	Exploratory laparotomy (n=27) 10 mo	<0.0001
Hemming et al., 2005 [18] prospective database	2 b	R1 resection (n=11) Median: 24 mo	Surgical bypass (n=14) 12 mo	<0.05
Witzigmann et al., 2006 [24] prospective database	2 b	R1 resection (n=11) Median: 12.2 mo R2 resection (n=7) Median 12.2 mo	vs. Stenting (n=56) 6.4 mo vs. Stenting+PDT (n=68) 12 mo	<0.05 NS
Zhang et al., 2006 [26] retrospective	2 b	Palliative resection (n=61) Median: 10.2 mo	Endoscopic biliary drainage (n=21) 6.2 mo	NS

NS, not significant; PDT, photodynamic therapy.

Table II. Hilar cholangiocarcinoma: Surgical vs. non-surgical palliative biliary drainage.

Author	Evidence level	Diagnosis	Technique		Mortality		Survival (months)	
			Surgical (n)	Non-surgical (n)	Surgical	Non-surgical	Surgical	Non-surgical
Lai et al., 1992 [32] retrospective	4	HCC 21 GB-Ca 12 Others 17	Intrahepatic CJ n = 34	Endoscopically or percutaneously n = 16	17.6%	37.5% (NS)	Median: 3.03 mo	1.46 mo (NS)
Nordback et al., 1994 [36] retrospective	2 b	HCC	Transhepatic stents n = 44	Percutaneously n = 21	7%	14% (NS)	Median: 8 mo	5 mo (p = 0.06)
Pichlmayr et al., 1996 [16] retrospective	2 b	HCC	SIII-CJ n = 42	Percutaneously n = 29	17.4%	10.7% (NS)	Median: 6.3 mo	6.7 mo (NS)
Kosuge et al., 1999 [23] retrospective	2 b	HCC	— n = 24	— n = 18	—	—	No survival difference	—
Li et al., 2003 [35] retrospective	2 b	HCC	Intra-/extra hepatic CJ n = 123	Endoscopically or percutaneously n = 49	8.9%	8.2%	Mean: 9.3 mo	8.7 mo (NS)
Zhang et al., 2006 [26] retrospective	2 b	HCC	T-tube n = 24	Endoscopically n = 21	0 %	—	Median: 6.1 mo	6.25 mo (NS)

HCC, hilar cholangiocarcinoma; SIII-CJ, segment III cholangiojejunostomy; GB-Ca, gallbladder carcinoma; CJ, cholangiojejunostomy; NS, not significant.

The results of six studies comparing surgical and non-surgical biliary drainage are given in Table II [16,23,26,32,35,36]. In these retrospective series, few patients were included, different techniques were used, and 3 out of the 6 series were published more than 10 years ago. In all studies, survival time revealed no significant difference between surgical and non-surgical biliary drainage.

Recommendation

All studies are single-arm and single-institution cohort studies. The data of these reports were analyzed retrospectively or were based on prospective databases.

Palliative resection

Resection with microscopic positive margins offers significant survival benefit over non-resectional treatment. Therefore R1 resection is justified as efficient palliation. Regional lymph-node involvement should not be considered as a contraindication for resection if a complete tumor removal is possible.

Biliary drainage

Because surgical drainage procedures have been demonstrated not to be superior to non-surgical palliation with respect to procedure-related mortality and survival, non-operative biliary stenting is regarded as the first choice of palliative biliary drainage.

Surgical bypass should only be re-considered in patients with a good estimated life expectancy, where endoscopic and/or percutaneous stenting has failed. The SgIII cholangiojejunostomy is favoured.

Distal cholangiocarcinoma

Almost all considered data for these guidelines included patients with malignant distal biliary obstruction caused by pancreatic cancer, distal CCA, and other tumors. In clinical practice, palliative management of malignant distal biliary obstruction is not influenced by the underlying histological diagnosis.

Palliative resection

Only a few data are available concerning palliative resectioning. Jang et al. reported that 6 out of 49 actual 5-year survivors had either microscopic tumor disease (n = 3) or positive lymph nodes (n = 3) in the resected specimens [37]. In a study by Murakami et al., 3 out of 17 lymph-node-positive patients survived more than 5 years [38]. Lillemoe et al. showed that, for pancreatic carcinoma, patients with localized disease who underwent pancreaticoduodenectomy with evidence of gross or microscopic disease

(R1 and R2 resection) have significantly improved survival compared with similar patients who received surgical biliary bypass alone [39]. A recent series by DeOliveira et al. described a survival benefit for patients with R1/R2 resection compared to non-resectional palliation [40].

Biliary drainage

No data are available for distal CCA alone. A current systematic review and meta-analysis of endoscopic versus surgical bypass results by Moss et al. [41] in patients with malignant distal biliary obstruction revealed three prospective randomized trials published in the years 1988, 1989, and 1994 [42–44]; 64% to 86% of the participants in the surgical groups had pancreatic carcinoma. The majority of surgical interventions were cholecystojejunostomy or choledochoduodenostomy. The results are summarized in Table III. There was no difference between surgery and endoscopic plastic stents in rates of technical success, therapeutic success, survival, and quality of life. The relative risk of complications was significantly reduced in those receiving stents and relative risk of recurrent biliary obstruction is favored.

Table IV gives the results after palliative surgical biliary drainage in four other studies. In contrast to the series of van den Bosch [45] published in 1994, three newly published studies show low surgical mortality rates ranging between 0% and 4% after surgical bypass procedures [46–48]. In the study by Nieveen et al., prolonged survival was seen after surgical bypass. The Heidelberg group identified predictors of poor outcome after palliative bypass surgery, predictors that allow identification of patients likely to benefit from palliative bypass surgery [48].

Recommendation

Palliative resection

The few data support an aggressive surgical approach in the presence of regional positive lymph nodes and even when positive resection margin might result.

Biliary drainage

Considerable advances have taken place in use of the endoscopic technique and in biliary and pancreatic surgery. In recent studies, surgical mortality after palliative biliary bypass has been low. However, it is likely that results with metal stents will compare more favorably with surgery than plastic stents when it comes to recurrent biliary obstruction. At present, non-surgical stenting is regarded as the first choice of palliation for patients with short life expectancy. Patients who, at the time of laparotomy for planned tumor resection, are found to have unresectable diseases and concomitant predictors of a favorable

Table III. Malignant distal biliary obstruction: Systematic review and meta-analysis of surgical bypass versus endoscopic plastic stents [41].*

Z	Evidence level	Technical success	Therapeutic success	Complications	30-day mortality	Recurrent Biliary obstruction	survival	Quality of Life
Surgical bypass vs Plastic stent (RR)	1a	1.04 NS	1.00 NS	0.6 <i>p</i> = 0.0007 in favor of stenting	0.58 <i>p</i> = 0.07 in favor of stenting	18.6 <i>p</i> < 0.00001 in favor of surgery	NS	NS**

Including 306 patients out of 3 randomized controlled trials [42–44]; **only [42]; RR: relative risk.

Table IV. Malignant distal biliary obstruction: Outcome after palliative surgical and endoscopic biliary drainage.

Author	Evidence level	Diagnosis		Technique		Mortality		Long-term outcome		Survival (months)	
		Surgical (<i>n</i>)	Endoscopic (<i>n</i>)	Surgical	Endoscopic	Surgical	Endoscopic	Surgical	Endoscopic	Surgical	Endoscopic
van den Bosch et al., 1994 [45] retrospective	4	<i>n</i> = 44	<i>n</i> = 63	CJ: <i>n</i> = 34	Plastic stents	13.6%	12.7%[NS]	93.2%	95.2% [NS]	Median: 5.5 mo	4.7 mo
Nieveen et al., 2003 [47], prospective randomized	2b	Cancer of pancreatic head or periampullary region <i>n</i> = 13	<i>n</i> = 14	CD: <i>n</i> = 5 CCD: <i>n</i> = 5 HJ+GJ	Wallstent	0%	0%	hospital readmission 64%	64%	Median: 6.4 mo (<i>p</i> = 0.05)	3.1 mo
Kuhlmann et al., 2007 [46] retrospective	2b	<i>n</i> = 269	—	HJ+GJ: <i>n</i> = 234	—	2.6%	—	9 %-read- missions related to surgical bypass	—	Median: 7.5 mo	—
Müller et al., 2008 [48] prospective database	2b	PC: <i>n</i> = 227 DCC: <i>n</i> = 11 Others: <i>n</i> = 31 <i>n</i> = 136	—	HJ: <i>n</i> = 35 HJ+GJ: <i>n</i> = 98 HJ: <i>n</i> = 17 GJ: <i>n</i> = 21	—	4%	—	—	—	Median: 8.3 mo	—

CJ, choledochojejunostomy; CD, choledochoduodenostomy; CCD, cholecystoduodenostomy; PC, pancreatic carcinoma; DCC, distal cholangiocarcinoma; HJ, hepaticojejunostomy; GJ, gastrojejunostomy.

outcome, and also occasional patients with longer projected survival, should be considered as candidates for surgical bypass. Studies, differentiating between short- and long-term survivors, need to be performed.

Conclusion

Palliative resections have a relevant beneficial impact on the outcome of patients with distal and hilar CCA. Non-surgical stenting is the first choice of palliative biliary drainage for patients with hilar CCA and for those with distal CCA and short life expectancy. For patients with distal CCA and longer projected survival, surgical bypass should be considered.

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