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R0 but not R1/R2 resection is associated with better survival than palliative photodynamic therapy in biliary tract cancer

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Abstract

Background—There is a need for better management strategies to improve survival and quality of life in patients with biliary tract cancer (BTC).

Aim—To assess prognostic factors for survival in a large, non-selective cohort of patients with BTC.

Method—We compared outcomes in 321 patients with a final diagnosis of BTC (cholangiocarcinoma n=237, gallbladder cancer n=84) seen in a tertiary referral cancer centre between 1998–2007. Survival according to disease stage and treatment category was compared using log-rank testing. Cox regression analysis was used to determine independent prognostic factors.

Results—89 (28%) patients underwent surgical intervention with curative intent, of which 38% had R0-resections. Amongst the 321 patients, 34% were given chemo- and/or radiotherapy, 14% were palliated with photodynamic therapy (PDT) and 37% with biliary drainage procedures alone. The overall median survival was 9 months (3-year-survival 14%). R0-resective surgery conferred the most favourable outcome (3-year-survival 57%). Although patients palliated with PDT had more advanced clinical T-stages, their survival was similar to those treated with attempted curative surgery but who had positive resection margins. On multivariable analysis, treatment modality, serum CA19-9, distant metastasis and vascular involvement were independent prognostic indicators of survival.

Conclusion—In this large UK series of BTC, palliative PDT resulted in similar survival to those with curatively intended R1/R2-resections. Surgery conferred a survival advantage only in patients with R0-resection margins, emphasising the need for accurate pre-operative staging.

Keywords

biliary tract cancer; prognosis; surgical resection; photodynamic therapy

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Background

Patients with biliary tract cancer (BTC; defined as cholangiocarcinoma; intrahepatic, perihilar (Klatskin) and extrahepatic, and gallbladder cancer) tend to have advanced disease at presentation, with a median survival of approximately 6–9 months from the time of diagnosis [1]. Surgery with clear histological margins (R0 resection) offers a possibility of cure, with published five year survival rates of 24–40%[2]. Curative surgical resection, however, is only feasible in a minority of patients[3], even in the setting of radical hepatic surgery[4], including pre-operative ipsilateral portal vein embolisation to increase hepatic reserve[5] and, in highly selected cases, liver transplantation[6].

The management of patients with BTC is complex and has been changing with the advent of novel treatment options such as photodynamic therapy (PDT; a photosensitising agent, activated by light, exhibits thermal tumour destruction) and the addition of newer chemotherapy agents (e.g. gemcitabine)[7]. In general, published series have concentrated on the surgical management of cholangiocarcinoma[3,8,9,10,11], and there is a paucity of information comparing surgical and modern palliative therapies. We describe a nine year experience of consecutive patients with BTC seen in a large UK cancer centre.

Methods

We undertook a retrospective review of all patients with BTC managed at University College Hospital and Royal Free Hospital between 1998 and 2007. Patients were identified by searching a hepatobiliary database, together with cross-referencing clinic letters from the gastrointestinal and oncology departments and pathology and endoscopy records. Missing information was collected at clinic review and by telephone contact with general practitioners and patients. The census date was set at 1st July 2008 to allow at least one year follow-up in all patients.

The following parameters were evaluated: age, sex, presenting symptoms, timing of symptom onset and first attendance at our centre, as well as baseline levels of serum bilirubin and the tumour markers CA19-9 (carbohydrate-associated antigen 19-9) and CEA (carcinoembryonic antigen). Clinical T-stage (Bismuth-Corlette classification for perihilar [Klatskin] tumours), vascular involvement and, where available, tumour histological grade were also recorded, as were the number and type of diagnostic procedures and therapeutic interventions (including surgery, PDT, chemo- and/or radiotherapy, biliary drainage/ stenting). A diagnosis of BTC was confirmed by histological examination of resection or biopsy specimens, positive biliary cytology, and in some cases by multi-disciplinary team consensus and evidence of disease progression during follow-up.

Patients were classified into four groups according to the main treatment modality they received: (i) surgery with curative intent; or palliative management with (ii) PDT, (iii) chemo- and/or radiotherapy or (iv) biliary drainage only. In the case of combination therapies, subgroup analysis was performed to look for any additive effects of combined treatments.

Statistical analysis was done using SPSS software, version 14.0 (SPSS Inc., Chicago, IL). Numeric data were presented as medians with ranges or as mean values with standard errors of the mean (SEM). Inter-group comparisons were performed with the Pearson's chi-square test, Student t test or the Mann-Whitney U test as appropriate. Survival was determined from the time of diagnosis to death or last follow-up date. The Kaplan-Meier method was used for survival rate estimates, and significance between subgroups was compared with the log-rank test. Variables predicting survival independently were evaluated with the Cox proportional hazards model. A p-value of less than 0.05 was considered significant.

Results

Patient characteristics

Between July 1998 and June 2007, a total of 321 patients were diagnosed with BTC; 237 (74%) with cholangiocarcinoma and 84 (26%) with gallbladder carcinoma. Patient and tumour characteristics, including clinical stage and, for perihilar cholangiocarcinoma, Bismuth-Corlette classification, are summarised in Table 1.

Diagnosis

Ninety percent (290/321) of the patients had either histological (239/321, 74%) or cytological (51/321, 16%) confirmation of BTC. A positive tissue diagnosis had been made in the referring hospitals prior to referral in 64 (20%) cases. In 252 patients (79%), a median of one additional procedure (range 0–8; mean 1.6, SD 0.99) was performed in our hospitals and provided a tissue diagnosis in 226, corresponding to a local success rate of 226/252 (90%). In 26/321 (8%), the diagnoses were made in a multidisciplinary cancer meeting on radiological and clinical grounds and in five patients (2%) the information was missing. 84% (26/31) of the patients without tissue diagnosis for malignancy showed progressive disease over time on imaging, and there was no difference in survival between BTC patients with tissue diagnosis and those without it. The median time from symptom onset to final diagnosis was 2.0 (range 0–29) months, and from referral to our centre to final diagnosis was 0.5 (0–21) months.

Treatment

Figure 1 shows the management algorithm for the 321 patients. 89/321 (28%) patients underwent surgery with curative intent (35 with adjuvant therapies), and 12 (4%) patients had primary palliative surgery. 46/321 (14%) patients had PDT (alone in 24, combined with chemotherapy in 22), while 108 (34%) received chemotherapy and/or radiotherapy. 117/321 (37%) patients were managed with biliary drainage procedures alone, 3/321 (1%) were considered unsuitable for any intervention.

Surgical Interventions—98/112 (87%) surgical interventions took place in our institutions (11 patients underwent staging laparoscopies only). Of the 89 surgeries performed with curative intent, negative (R0) histological margins were achieved in 34 (38%; positive microscopic (R1) and positive macroscopic (R2) resection margins in 33% and 24%, respectively). In the curative-intent surgical group, there were 33 cholecystectomies (24 with gallbladder fossa resection), 27 hemi-hepatectomies, 12 pancreaticoduodenectomies, 9 common bile duct resections, two liver transplants (both in patients with primary sclerosing cholangitis who were found to have incidental cholangiocarcinoma in the explant livers) and six operations converted to palliative procedures. In the group with planned palliative surgery, the most common procedures were duodenal (n=6) and biliary bypasses (n=3), all before 2003. The 30-day mortality rate in patients undergoing surgery with curative intent was 7% (6/89); 3% (1/34) in the subgroup with R0 resections and 9% (5/55) in those with positive resection margins.

35/89 (39%) patients undergoing surgery with curative intent received additional therapies of PDT (n=3) or chemo- and/or radiotherapy (n=33; one combined with PDT). Of the 34 patients with R0 resections, 1 (3%) received neoadjuvant chemotherapy and 8 (24%) adjuvant chemotherapy.

Non-surgical interventions

Photodynamic therapy: From January 2003, PDT with porfimer sodium was offered to patients with locally advanced BTC (non-resectable disease or unfit for surgery), in the context of two prospective non-randomised phase II studies. A total of 46 patients received PDT in combination with biliary stenting (42 in the non-curative approach arm; 4 in the curative approach arm, three with tumour recurrence after curatively intended surgery). PDT was applied once in 32 patients, twice at approximately four-monthly intervals in 12 and three times in two patients.

Chemo- and/or radiotherapy: A total of 108 patients received chemo- and/or radiotherapy: 96 patients received chemotherapy, of which 20 were in combination with radiotherapy, and 12 patients received radiotherapy alone (three of them as brachytherapy). The most frequently given chemotherapy agent was gemcitabine (in 60 patients), usually in the setting of national randomised phase II (ABC-01[12]) and recently completed phase III (ABC-02[13]) studies.

Biliary drainage procedures: Fifty-three percent (117/221) of patients in the palliative group were managed by biliary drainage procedures alone, via endoscopic and/or percutaneous approaches. For the whole study population (n=321), a median of three drainage interventions (mean 3.9, range 0–14) per patient were performed. Stenting at endoscopic retrograde cholangiopancreatography successfully relieved biliary obstruction in 48% of recorded cases with a median of two (range 1–10) procedures; the remaining 52% required percutaneous biliary drainage with a median of one additional procedure (mean 1.2, range 1–6). A total of 42% of patients had self-expanding metal stents inserted, endoscopically or radiologically.

Survival analysis

Complete follow-up data were available in 293 (91%) patients, with missing data in five surgical patients and in 23 in the non-surgical group, who were excluded from the survival analysis. The overall median survival was 9 months (range 0–83, 95% confidence interval 7–11 months) with 1-, 2-, 3- and 5-year survival rates for all patients of 40%, 23%, 14% and 6%, respectively (Figure 2). There was no survival difference between patients with cholangiocarcinoma and gallbladder carcinoma (9 vs. 8 months, p=0.39).

There were significant ($p<0.001$) differences in survival between treatment groups. In patients undergoing attempted curative surgery, the median survival time was 19 (range 0–83) months, compared with 12 (1–51) months for PDT, 8 (1–49) months for chemo- and/or radiotherapy, and 3 (0–60) months for those patients who received no additional treatment other than biliary drainage procedures. The 1-year survival was 69%, 51%, 37% and 20% in the curatively intended surgery, PDT, chemo- and/or radiotherapy and biliary drainage only groups, respectively.

Figure 3 shows the survival graphs for curatively intended surgery, divided into negative (R0) and positive (R1/R2) resection margins and compared with the survival of those who had palliative PDT as the mainstay of treatment. Although PDT patients had a more advanced clinical T-stage than those undergoing surgery (93% vs. 63% T3/T4 stage, $p<0.001$; for perihilar cholangiocarcinoma trend towards higher Bismuth grades, p=0.08) and tended to be older (mean age 64 vs. 60 years, p=0.05), their survival did not differ from those treated with curatively intended surgery who had positive resection margins (PDT vs. R1, p=0.13 and PDT vs. R2, p=0.32; no survival difference between R1 and R2 resections, p=0.09). PDT treated and R1/R2 resected patients did not differ with regards to serum bilirubin (p=0.99), CA19-9 (p=0.18), CEA (p=0.64), distant metastasis (p=0.87) and

vascular involvement (p=0.83). The 1-year survival rates were 87%, 55% and 51% following curative resections (R0), non-curative resections (R1/R2) and PDT, respectively (R0 vs. R1/R2 or PDT, p<0.001 and R1/R2 vs. PDT, p=0.52). There was no early mortality in patients given PDT, whereas the 30-day mortality was 9% (5/55) following non-curative resection. PDT-treated patients had significantly better survival than those who had biliary drainage procedures alone (1-year survival 51% vs. 20%, respectively, p=0.01; T3/T4 stage in 93% vs. 85%, respectively, p=0.18), and there was a trend towards better survival compared to those who received chemo- and/or radiotherapy alone (1-year survival 51% vs. 37%, p=0.07; T3/T4 stage in 93% vs. 89%, respectively, p=0.45). There was a significant (p=0.03) difference in survival rates between the R1/R2 resection group and chemo- and/or radiotherapy alone group with 1-year survival rates of 55% and 37%, respectively. There was no difference in survival between patients who received PDT alone vs. patients who received PDT and chemo- and/or radiotherapy combined (p=0.35).

When comparing patients treated in the first 4.5 years (1998–2002; n=92) with those treated in the second 4.5 years of the study (2003–2007; n=200), there was no difference in median survival (8.3 vs. 9.0 months; p=0.63).

In the univariable analysis, the following parameters, apart from treatment category, were predictors for survival: clinical T-stage (p<0.001), distant metastases (p<0.001), serum CA19-9 (p<0.001), CEA (p<0.001) and bilirubin (p=0.002), vascular involvement (p=0.002) and tumour size (p=0.044) on imaging (Table 2).

To identify independent factor(s) related to prognosis, a stepwise multivariable Cox's proportional hazards regression analysis was carried out in patients who had definitive therapy (omitting patients with biliary drainage alone). Independent variables predicting patient survival were as follows: treatment modality (p<0.001), serum CA19-9 (p=0.001), distant metastasis (p=0.002) and vascular involvement (p=0.034) (Table 3). Restricting the analysis to patients with curatively intended surgeries, R-stage became the only independent (hazard ratio 4.12, confidence interval 1.28–13.25; p=0.017) predictor of survival.

Discussion

There are few large series or randomised controlled trials[14] comparing survival following surgical treatment with modern palliative therapies, including chemotherapy and photodynamic therapy, in patients with BTC. In this study, we describe the management of a large cohort of consecutive, non-selected patients with BTC referred to a tertiary referral centre. Palliative photodynamic therapy in BTC patients appeared to result in a survival outcome similar to curatively intended surgery but positive (R1/R2) resection margins.

A particular strength of the present study is that the diagnosis of BTC was confirmed by positive histology or cytology in 90% of cases, so that we are confident that the cohort did not include a significant number of patients with benign disease. Cytological or histological confirmation of malignancy in BTC is difficult, due in part to the small volume and desmoplastic nature of tumours, and this is reflected in recent series from the UK[9,15], Korea[16], and Germany[10], in which at most 50–70% of patients had pathological confirmation of malignancy. Recent reports suggest that up to 17% of patients undergoing surgery with curative intent for cholangiocarcinoma have benign disease, and that almost half of the benign cases have features of an autoimmune cholangiopathy, possibly IgG4-associate[17], emphasising the need for accurate diagnosis.

Surgery was performed on 32% of patients, 88% of whom underwent resections with curative intent, and 38% of this latter group had negative (R0) resection margins (11% of the total). Previous studies have reported R0 resection rates of 32–39% (13–28% of total

patients with cholangiocarcinoma)[3,8,10] with 46–56% R0 rates in highly selected, exclusively surgical cohorts[11,18]. Consistent with our own data, several studies have shown that achieving an R0 resection improves survival in comparison to R1 or R2 resection[3,19, 20, 21]; which may be explained in part by earlier diagnosis (with less advanced disease for R0 resections) and lead-time bias. The importance of achieving an R0 resection has resulted in concomitant liver resection becoming the standard of care [22] and protocols being developed to treat cholangiocarcinoma with liver transplantation[23]. In patients who underwent surgery with curative intent, R0 resection was the only independent predictor of improved survival, although well differentiated tumours[24] and negative lymph node status[11] have also been identified by other groups as predicting a better outcome.

A survival advantage of palliative resection (R1/R2) over biliary stenting alone has been reported in some studies[10,19,20,21,25], including our own, and challenged in others[3,26,27]. Comparisons of treatments tend to be hampered by dissimilar patient groups, with 'biliary stenting only' being usually reserved for patients with more advanced disease and poorer performance status, a finding also seen in our study. However, an important finding of our study was that survival for patients with curatively intended surgery but positive resection margins did not differ from those who had PDT. PDT is an emerging treatment for cholangiocarcinoma[28], which in combination with plastic biliary stenting has been shown in two small randomised studies to improve survival over stent placement alone[29,30]. The issue of whether this treatment improves survival in patients who have already had successful biliary stenting needs further study[31] and is being investigated by our group in a multi-centre randomised trial of PDT plus stenting vs. stenting alone (Photostent 2, ClinicalTrials.gov number, NCT00513539), which is currently recruiting patients. A recent analysis of a German cohort of 184 patients with hilar cholangiocarcinoma has also demonstrated no significant difference in median survival between R1/R2 resection (n=18; 12.2 months) and palliative PDT plus stenting (n=68; 12.0 months)[10]. As attempted surgical resection is associated with high morbidity and mortality rates of up to 10%[32], palliative PDT may be a good alternative for patients at high risk of non-curative resections. In order to select such patients for PDT, improvements in the accuracy of current preoperative staging are needed[33]; for example MRI/MRCP can under-stage the disease in up to 20% of cases[34]. Positron-emission tomography (PET, incl. PET-CT) has been shown to be highly sensitive for detecting metastatic deposits[35], but has relatively low specificity. Whether new diagnostic tools like intraductal cholangioscopy will improve diagnostic accuracy remains to be established.

Endoscopic stenting alone relieved malignant biliary obstruction in 48% of patients in our study. The published range of effective endoscopic biliary drainage in BTC is very wide (21–97%)[9,15,16,36,37], depending on stricture location, endoprothesis used and different definitions of success (e.g. technical endoprosthesis insertion rate vs. successful drainage rate[38]). Self-expanding metal stents, which have a larger internal diameter than plastic stents, were used in almost half of our patients. There is little consensus, however, as to the optimum approach (endoscopic vs. percutaneous), stent type (metal vs. plastic) or stent number (unilateral vs. bilateral) that should be initially used to palliate patients with hilar cholangiocarcinoma[39], due in part to the lack of high quality randomised data in this area.

Since the cause of death in BTC after successful stenting is commonly due to recurrent biliary obstruction and intra-biliary sepsis, a key aim of palliative therapy is that of control of locally progressive disease. Thirty percent of our patients received chemotherapy and/or radiotherapy. Oncological opinion supports the use of palliative chemotherapy, but until recently there has been no agreement on regimen or proven survival benefit over biliary drainage alone[14]. However, a recent meta-analysis of 104 trials involving 2810 patients reported a beneficial effect of chemotherapy with a pooled (complete and partial) response

rate of 23%, particularly when using gemcitabine and platinum-based regimens[40]. Furthermore, results of the UK phase III ABC-02 trial of gemcitabine, alone or in combination with cisplatin in 410 patients with locally advanced or metastatic BTC, reported a median survival of 11.7 vs. 8.2 months (log rank p=0.002) with gemcitabine and cisplatin over gemcitabine alone, This is the largest ever study in advanced biliary tract cancer and demonstrated a clear advantage for gemcitabine and cisplatin without added clinically significant toxicity, setting a new international standard of care[13].

In conclusion, biliary tract cancer survival increases with successful R0 resection. PDT appears to be a promising palliative measure for non-R0 resectable disease, but needs further evaluation in conjunction with chemotherapy agents and targeted therapies in phase II/III trials. The concept of neo-adjuvant therapies to achieve higher rates of clear resection margins appears worthy of further study, although improvements in preoperative staging of BTC are also needed.

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Abbreviations used in this paper

BTC	biliary tract cancer
CT	computer tomography
MRI/MRCP	magnetic resonance imaging/magnetic resonance cholangiopancreatography
PDT	photodynamic therapy

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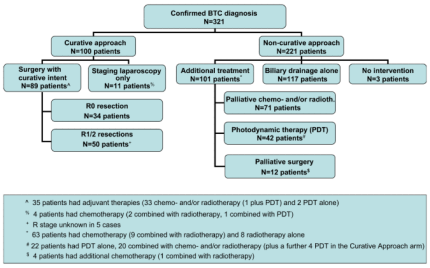

Figure 1.

Management algorithm for 321 patients with biliary tract cancer (BTC). R0, curative resection; R1, microscopic infiltration of the resection margins; R2, evidence of macroscopic residual disease.

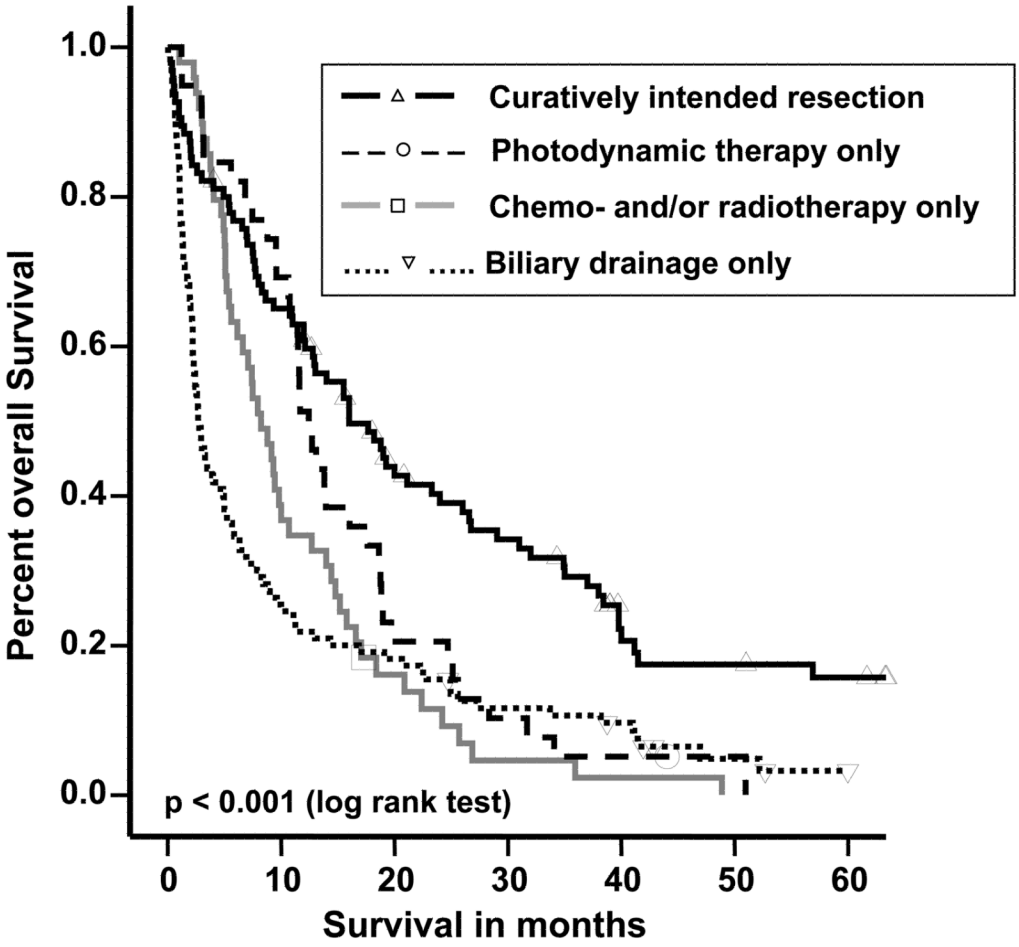

Figure 2.

Kaplan-Meier survival estimates of patients in the four treatment groups. Individual patients still alive during the follow-up period are indicated by marks on the curves. The median survival time difference between the four treatment groups was statistically significant ($p<0.001$). Comparing the treatment groups' survival times individually, the significance levels were as follows: curatively intended surgery vs. photodynamic therapy (PDT), $p=0.012$; surgery vs. chemo- and/or radiotherapy, $p<0.001$; surgery vs. biliary drainage procedure, $p<0.001$; PDT vs. chemo- and/or radiotherapy, $p=0.06$; PDT vs. biliary drainage procedure, $p=0.019$; chemo- and/or radiotherapy vs. biliary drainage procedure, $p=0.136$.

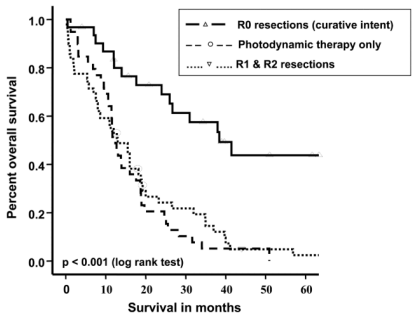

Figure 3.

Kaplan-Meier survival estimates comparing patients with curatively intended surgeries (with R0 and R1/R2 outcome) with patients receiving photodynamic therapy (PDT). Survival times differed significantly between R0 resection and PDT ($p<0.001$), as well as R0 and R1/2 resections ($p<0.001$), but there was no difference between PDT and R1/2 resections ($p=0.52$).

Table 1

Pre-treatment study group demographics and tumour characteristics

	CCA (n=237)	GBCA (n=84)
Age (years)*	63 (29–102)	74 (42–87)
Gender (female:male)	112:125 (1:1.1)	49:35 (1.4:1)
Tumour size (mm)*	35 (7–145)	30 (5–95)
Serum bilirubin (μmol/L)*	56 (4–900)	18 (3–607)
Serum CA19-9 (IU/L)*	404 (1–100,000)	180 (1–222,270)
Serum CEA (ng/ml)*	3 (1–1649)	5 (1–900)
CCA location^		
Intrahepatic (peripheral)	13 (6%)	
Perihilar (Klatskin)	189 (81%)	
Bismuth IV	90 (40%)	
Bismuth III	68 (31%)	
Bismuth II	17 (8%)	
Bismuth I	4 (2%)	
Extrahepatic (distal)	31 (13%)	
Clinical T-stage$		
T1	3 (1%)	4 (5%)
T2	36 (15%)	13 (15%)
T3	91 (38%)	23 (27%)
T4	69 (29%)	29 (35%)
Unknown	38 (16%)	15 (18%)
Distant metastasis		
Yes	50 (21%)	20 (24%)
No	140 (59%)	48 (57%)
Unknown	47 (20%)	16 (19%)

*Values are median with ranges.

^Topography data insufficient in four cases; denominator n=233.

$Assessment by means of imaging or, if available, pathological T-stage (T=tumour). CCA denotes cholangiocarcinoma, GBCA denotes gallbladder cancer, CA19-9 denotes carbohydrate-associated antigen 19-9, CEA denotes carcinoembryonic antigen.

Table 2

Univariable analysis of prognostic factors

	Survival (%)				
Parameters(n)	**1-yr**	**2-yr**	**3-yr**	**Median survival in months (95% CI)**	**p-value**
Age (years)					
<65 (147)	42	22	12	10 (7–13)	0.949
≥65 (146)	38	22	15	8 (6–10)	
Gender					
Female (142)	39	27	17	10 (7–12)	0.130
Male (151)	40	18	11	8 (6–10)	
Bilirubin (μmol/L)#					
<20 (68)	54	24	20	16 (8–24)	0.002
≥20 (134)	34	16	11	7 (5–9)	
CA19-9 (IU/L)#					
<27 (29)	64	57	42	28 (11–46)	0.000
≥27 (187)	38	18	11	8 (6–10)	
CEA (ng/ml)#					
<5 (99)	55	33	23	14 (11–18)	0.000
≥5 (61)	25	13	7	5 (3–7)	
Tumour size (mm)^					
<35 (65)	51	26	15	14 (9–19)	0.044
≥35 (71)	37	17	15	8 (5–10)	
Clinical T-stage*					
T1 (6)	100	53	53	33 (11–70)	0.000
T2 (41)	58	46	23	24 (12–36)	
T3 (109)	49	24	15	12 (9–15)	
T4 (95)	23	8	2	5 (3–8)	
Differentiation grade					
Well (29)	43	22	15	11 (6–17)	0.708
Moderate (106)	46	27	20	11 (6–15)	
Poor (29)	44	27	4	10 (5–15)	

Parameters(n)	Survival (%) 1-yr	2-yr	3-yr	Median survival in months (95% CI)	p-value
Topography (for CCA)					0.175
Intrahepatic (8)	46	46	24	26 (0–56)	
Bismuth type I (3)	67	67	0	27	
type II (16)	25	25	0	5 (0–10)	
type III (62)	47	19	9	12 (7–16)	
type IV (85)	30	14	7	7 (5–10)	
Extrahepatic (distal) (31)	48	25	21	12 (3–21)	
Treatment category					
Surgery (84)	69	46	33	19 (11–27)	0.000
Photodynamic therapy (39)	51	21	5	12 (11–14)	
Chemo- ± radiotherapy (52)	37	11	2	8 (6–10)	
Biliary stenting alone (118)	20	14	10	3 (2–3)	
Distance metastasis[^]					
No (228)	48	28	18	12 (9–14)	0.000
Yes (65)	12	2	0	3 (2–4)	
Vascular involvement[^]					
No (104)	51	29	23	13 (8–18)	0.002
Yes (71)	32	18	8	2 (4–11)	

[^] On imaging (CT or MRI).

[#] At the time of diagnosis.

[*] Clinical T-stage, unless pathological T-stage available.

CI denotes confidence interval, CA19-9 denotes carbohydrate-associated antigen 19-9, CEA denotes carcinoembryonic antigen, CCA denotes cholangiocarcinoma.

Table 3

Multivariable analysis of prognostic factors

Parameters	Hazard ratio + 95% confidence interval	p-value
Distant metastasis^	4.62 (1.78–12.02)	0.002
CA19-9# (27 IU/L cut-off)	3.22 (1.59–6.53)	0.001
Treatment modality	2.10 (1.44–3.07)	<0.001
Vascular involvement^	1.80 (1.05–3.10)	0.034
Bilirubin# (20 μmol/L cut-off)	1.31 (0.73–2.37)	0.370
CEA# (5 ng/ml cut-off)	1.29 (0.58–2.84)	0.535
Clinical T-stage*	1.09 (0.70–1.71)	0.702

^On imaging (CT or MRI).

#At the time of diagnosis.

*Clinical T-stage, unless pathological T-stage available.

CA19-9 denotes carbohydrate-associated antigen 19-9, CEA denotes carcinoembryonic antigen.