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Increased multimodality treatment options has improved survival for Hepatocellular carcinoma but poor survival for biliary tract cancers remains unchanged

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ABSTRACT

Background: Primary hepatobiliary cancer incidence in the UK is rising and survival rates are low. Surgery is the main curative option for these cancers, but multimodality therapies are expanding. The aim of our original study was to determine trends in survival, over an 8-year period, of patients treated for primary hepatobiliary cancers at our tertiary referral Centre.

Method: Patients treated for the most common types of primary hepatobiliary cancers, namely Hepatocellular carcinoma (HCC), Cholangiocarcinoma and Gallbladder cancer between January 2009 and December 2016 were retrospectively analysed from a prospective database linked to UK Hospital Episode Statistics data.

Results: A total of 1536 patients with primary hepatobiliary cancers were assessed and treatment plans formulated at our supra-regional specialist Hepatobiliary MDT. The primary hepatobiliary cancers treated were HCC (n = 836), Cholangiocarcinoma (n = 516), and Gallbladder cancer (n = 184). Survival for all the 3 cancers was significantly better with curative treatment. Overall median survival times were 350, 180, and 150 days respectively for HCC, Cholangiocarcinoma and Gallbladder cancer. Excluding best supportive care patients, the respective survival figures were 900, 600, and 400 days. Survival for HCC patients improved over time and was significantly increased in the final 3 years of the study ($p \leq 0.011$ for all). Cholangiocarcinoma and Gallbladder cancer survivals were poor and did not change significantly over time.

Conclusion: HCC outcome has improved in association with expanded multimodal therapies. Survivals for cholangiocarcinoma and gallbladder cancer remain poor in parallel with limited expansion of multimodal therapies highlighting an unmet therapeutic need for biliary tract cancers.

Introduction

Death rates are increasing for primary hepatobiliary cancers, namely Hepatocellular carcinoma (HCC), Cholangiocarcinoma and Gallbladder cancer [1]. Epidemiological data published a decade ago suggested increasing age-standardised incidence rates of primary hepatobiliary cancers in England [2], but more recent age-

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standardised incidence rates are stable [3].

HCC remains the leading cause of cancer death worldwide [1]. Hepatitis C is the most frequent risk factor for HCC in the Western world, but chronic hepatitis B infection is the main risk factor in East Asia and sub-Saharan Africa where incidence rates of HCC are the highest [4]. Biliary tract cancers, namely cholangiocarcinoma and gallbladder cancer, are less common in the West than HCC. The worldwide incidence of cholangiocarcinoma is highest in Asian countries such as Thailand where liver fluke infection is endemic [5]. Gallbladder cancer incidence is highest in Chilean females, the main risk factor being gallstones [5].

In line with national guidance, all patients referred to our Hepatobiliary Unit with primary hepatobiliary cancers are reviewed at our weekly tertiary supra-regional multidisciplinary team (MDT) meeting and the outcome communicated back to the patient by the doctor or specialist nurse responsible for their care. The MDT is comprised of several specialists who collectively have the full range of expertise needed to effectively manage and treat every aspect of primary liver cancer. The MDT facilitates patient access to established and new multimodality therapies by consultation with all the involved care-providing specialists who themselves maintain awareness of cutting-edge therapies in their fields including oncology clinical trial drugs and a range of interventional procedures. These emerging treatments have led to updates of some treatment algorithms for the primary hepatobiliary cancers. The more established use of technologies such as teleconferencing and emailing via secure servers has helped minimize inter-provider communication errors and ensure timely treatment via our MDT. Considering these changes over time, we report an original study aimed at determining if the overall survival of patients with primary hepatobiliary cancers has altered over an 8-year period.

Methods

Using Somerset Cancer Register we identified 1536 patients who had treatment recommended by our HPB MDT for primary hepatobiliary cancers between January 2009 and December 2016. They were analysed retrospectively from a prospective database linked to UK Hospital Episode Statistics data. Cases were assessed at our tertiary supra-regional MDT meeting and management plans created. To avoid confusion as some patients received multiple treatment options at different times, year of treatment was defined as the year in which first treatment of any intent was initiated. Distal cholangiocarcinomas were excluded from the analysis as these are managed as pancreatobiliary rather than hepatobiliary cancers, hence not within the remit of our study.

Statistical analysis

Patient demographics and management details were obtained from the primary hepatobiliary cancer database or case records. Overall survival was analysed by Kaplan-Meier method, with comparisons between groups performed using the log-rank test. A multivariate landmark analysis by Cox regression was subsequently performed to evaluate the impact of age and gender after controlling for year of treatment. All analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL), STATA version 10.0 (release 2007; STATA, College Station, TX).

Results

A total of 1536 with primary liver cancer were managed via our tertiary referral Centre's HPB MDT during the 8-year period from 2009 through 2016. The median age at the time of treatment was 71 years (IQR 17–98) and there were 942 males (61.3%). The tumours included 836 Hepatocellular carcinomas (54.4%), 516 Cholangiocarcinomas (33.6%), and 184 Gallbladder cancers (12.0%). At the end of the 8-year study period, 1240 (80.7%) patients had died and 296 (19.3%) remained alive. Patient demographics are summarised in separate tables for each cancer type (Tables 1–3).

Hepatocellular carcinoma

Curative-intent treatment options were liver transplantation (n = 19), liver resection (n = 68), and ablation (n = 142). Non-curative options were transarterial chemoembolization (n = 148) and sorafenib (n = 78). The numbers of patients treated with curative and non-curative intent progressively increased from 2013 onwards and reached statistical significance ($p < 0.01$). There were similar numbers of patients treated with best supportive care in all the study years. Overall HCC resection rate was 30%.

Kaplan-Meier analysis showed median overall survival for curatively-treated HCC patients was 6.0 (4.9 - n/a*) years, 1.4 (1.1–1.7) years for non-curative treatment, and 2.1 (2.0–2.8) months for best supportive care. Compared to curative treatment as a baseline, hazard ratios (95% confidence interval) for patients receiving non-curative and best supportive therapies were significantly ($p < 0.001$) higher at 3.17 (2.46–4.09) and 9.70 (7.61–12.36)

Table 1
Demographics of patients with Hepatocellular carcinoma.

Hepatocellular carcinoma		Treatment intent		
		Curative (N = 229)	Non-Curative (N = 226)	Best Supportive (N = 381)
Gender, n (%)	Female	59 (25.8%)	41 (18.1%)	103 (27.0%)
	Male	170 (74.2%)	185 (81.9%)	278 (73.0%)
Year of treatment, n (%)	2009	8 (3.5%)	16 (7.1%)	30 (7.9%)
	2010	26 (11.4%)	20 (8.8%)	38 (10.0%)
	2011	24 (10.5%)	19 (8.4%)	51 (13.4%)
	2012	20 (8.7%)	26 (11.5%)	54 (14.2%)
	2013	38 (16.6%)	38 (16.8%)	68 (17.8%)
	2014	39 (17.0%)	45 (19.9%)	50 (13.1%)
	2015	39 (17.0%)	30 (13.3%)	56 (14.7%)
	2016	35 (15.3%)	32 (14.2%)	34 (8.9%)
Number Alive or Dead, n (%)	Alive	137 (60.0%)	43 (19.0%)	14 (3.7%)
	Dead	92 (40.2%)	183 (80.1%)	367 (96.3%)
Age (years)	Mean	67.7	68.1	72.3
	SD	9.9	9.5	11.5
	Median	68.5	68.1	73.0
	Min	42	36	37
	Max	91	88	99

Table 2
Demographics of patients with Cholangiocarcinoma.

Cholangiocarcinoma		Treatment intent		
		Curative (N = 77)	Non-Curative (N = 128)	Best Supportive (N = 311)
Gender, n (%)	Female	43 (55.8%)	51 (40.0%)	158 (50.8%)
	Male	34 (44.2%)	77 (60.0%)	153 (49.2%)
Year of treatment, n (%)	2009	3 (3.9%)	2 (1.6%)	25 (8.0%)
	2010	11 (14.3%)	14 (10.9%)	24 (7.7%)
	2011	9 (11.7%)	8 (6.3%)	36 (11.6%)
	2012	9 (11.7%)	14 (10.9%)	47 (15.1%)
	2013	7 (9.1%)	20 (15.6%)	65 (20.9%)
	2014	7 (9.1%)	26 (20.3%)	34 (10.9%)
	2015	15 (19.5%)	29 (22.7%)	55 (17.7%)
	2016	16 (20.8%)	15 (11.7%)	25 (8.0%)
Number Alive or Dead, n (%)	Alive	38 (49.4%)	24 (18.8%)	5 (1.6%)
	Dead	39 (50.6%)	104 (81.2%)	306 (98.4%)
Age (years)	Mean	66.1	71.2	75.3
	SD	11.0	11.3	10.1
	Median	68.0	72.8	76.0
	Min	35	17	17
	Max	88	95	97

Table 3
Demographics of patients with Gallbladder cancer.

Gallbladder cancer		Treatment intent		
		Curative (N = 82)	Non-Curative (N = 20)	Best Supportive (N = 82)
Gender, n (%)	Female	64 (78.0%)	14 (70.0%)	62 (75.6%)
	Male	18 (22.0%)	6 (30.0%)	20 (24.4%)
Year of treatment, n (%)	2009	7 (8.5%)	1 (5.0%)	10 (12.2%)
	2010	8 (9.8%)	1 (5.0%)	10 (12.2%)
	2011	9 (11.0%)	2 (10.0%)	5 (6.1%)
	2012	14 (17.1%)	2 (10.0%)	13 (15.9%)
	2013	20 (24.4%)	7 (35.0%)	15 (18.3%)
	2014	12 (14.6%)	3 (15.0%)	5 (6.1%)
	2015	7 (8.5%)	0 (0.0%)	8 (9.8%)
	2016	5 (6.1%)	4 (20.0%)	16 (19.5%)
Number Alive or Dead, n (%)	Alive	22 (26.8%)	1 (5.0%)	0 (0.0%)
	Dead	60 (73.2%)	19 (95.0%)	82 (100%)
Age (years)	Mean	71.6	69.8	76.6
	SD	10.2	11.2	9.6
	Median	72.0	72.5	79.0
	Min	48	48	54
	Max	91	92	95

respectively. (* indicates that the upper limit of confidence interval could not be calculated as it does not fall below 0.5).(Fig. 1)

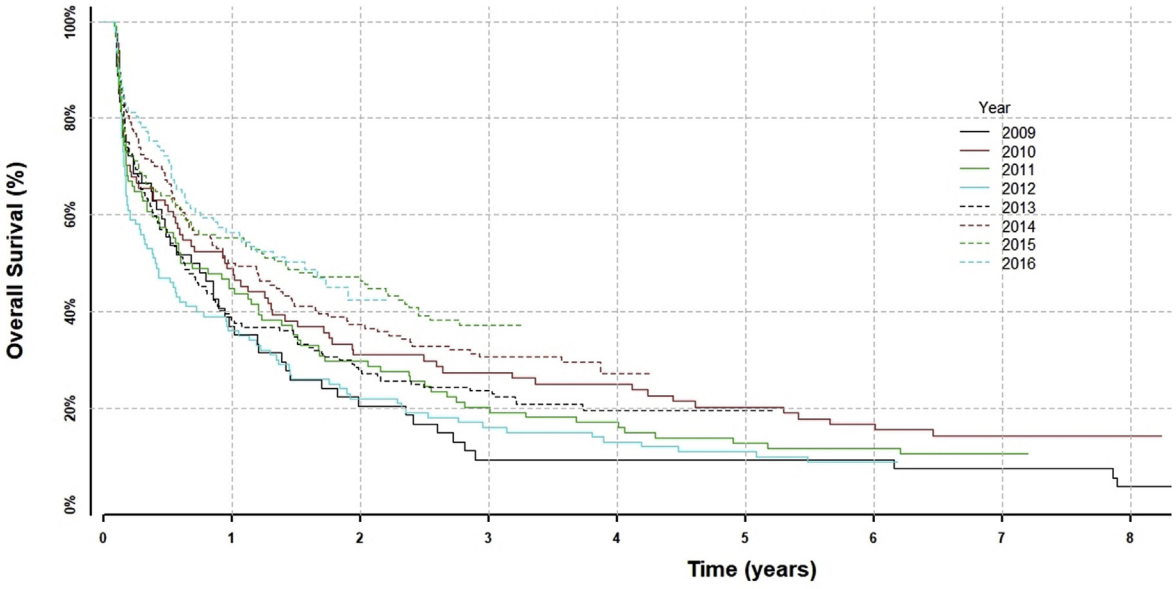
The median overall survival for the entire cohort of HCC patients, regardless of treatment, was approximately 350 days. However, if we excluded those managed by best supportive care, the median overall survival was 900 days. There was a statistically significant difference (Log Rank Test, $p < 0.001$) between the survival of patients who had treatment in different years, with univariate analysis showing the treatment years 2014–2016 had significantly better survival than the baseline year of 2009. Multivariate analysis showed no effect of age and gender on survival.

To elucidate if a particular treatment modality accounted for the improved survival, we then compared median overall survival for HCC patients by the specific treatments, rather than just treatment intent. The best median overall survival was achieved with liver transplantation, significantly greater than other curative treatment options. Liver resection and ablation were not significantly different. It was not possible to fully calculate median overall survival and confidence intervals for any of the curative options as some or all the required variables did not fall below 0.5 estimated survival in Kaplan-Meier analysis. For non-curative options, survival with TACE of 1.8 (1.5–2.4) years was significantly better ($p < 0.001$) than for Sorafenib; 0.6 (0.5–0.9) years.

Cholangiocarcinoma

Curative intent treatment was bile duct/liver resection (n = 77). Seventy-five off the 77 resected cholangiocarcinomas were hilar, and a total of 393 of the starting cohort of 524 cholangiocarcinoma patients referred to our MDT with had hilar lesions. Non-curative intent treatments were chemotherapy (n = 107), ablation (n = 4), chemoradiotherapy (n = 15), and selective internal radiation therapy (n = 1). Five patients received chemotherapy (CXT) as part of clinical trials (4 in ABC [Advanced Biliary Cancer]-03 and 1 in ABC-06). Photostent treatment was used in 2 patients as part of the Photostent-02 trial. The numbers of patients treated with non-curative intent increased significantly ($p < 0.05$) in 2014 and 2015 but this was not sustained in 2016. The numbers of patients treated with curative intent increased significantly ($p < 0.05$) in 2015 and 2016. Similar numbers of patients were treated with best supportive care in all the study years apart from 2013 to 2015 when numbers peaked in parallel with the largest numbers of cholangiocarcinoma patients treated in single study years. The resection rate for cholangiocarcinoma was 15%, and that for the hilar anatomical subtype alone was 19%.

Kaplan-Meier analysis showed the median overall survival for curatively-treated Cholangiocarcinoma patients was 4.2 (2.6 - n/a*)



Numbers at risk

2009	54	20	11	5	5	5	5	4	2
2010	84	41	26	23	21	17	14	12	3
2011	94	42	28	19	16	12	11	6	0
2012	100	36	22	16	13	11	2	0	0
2013	144	55	40	34	28	5	0	0	0
2014	134	67	50	41	7	0	0	0	0
2015	125	69	59	12	0	0	0	0	0
2016	101	57	13	0	0	0	0	0	0

Fig. 1. Hepatocellular carcinoma median overall survival by year of treatment. The Kaplan-Meier graph compares median overall survival for HCC patients by year of treatment. Median overall survival was 350 days with inclusion of best supportive care patients, and 900 days if excluded. The treatment years 2014–2016 had significantly better survival than the baseline year of 2009.

years, 1.4 (1.3–1.8) years for non-curative treatment, and 2.6 (2.2–3.3) months for best supportive care. Compared to curative treatment as a baseline, hazard ratios (95% confidence interval) for patients receiving non-curative and best supportive therapies were significantly ($p < 0.001$) higher at 2.23 (1.53–3.24) and 8.10 (5.70–11.50) respectively. *upper limit of confidence interval not calculated as does not fall below 0.5.(Fig. 2)

The median overall survival for the entire cohort of cholangiocarcinoma patients, regardless of treatment, was approximately 180 days. The corresponding figure on exclusion of patients managed by best supportive care was 600 days. There was no significant difference (Log Rank Test, $p = 0.093$) between the survival of patients who had treatment in different years of the study. Multivariate analysis showed advancing age significantly reduced survival (HR 1.02, 95% CI 1.01–1.03, $p = 0.001$) but gender had no effect.

Gallbladder cancer

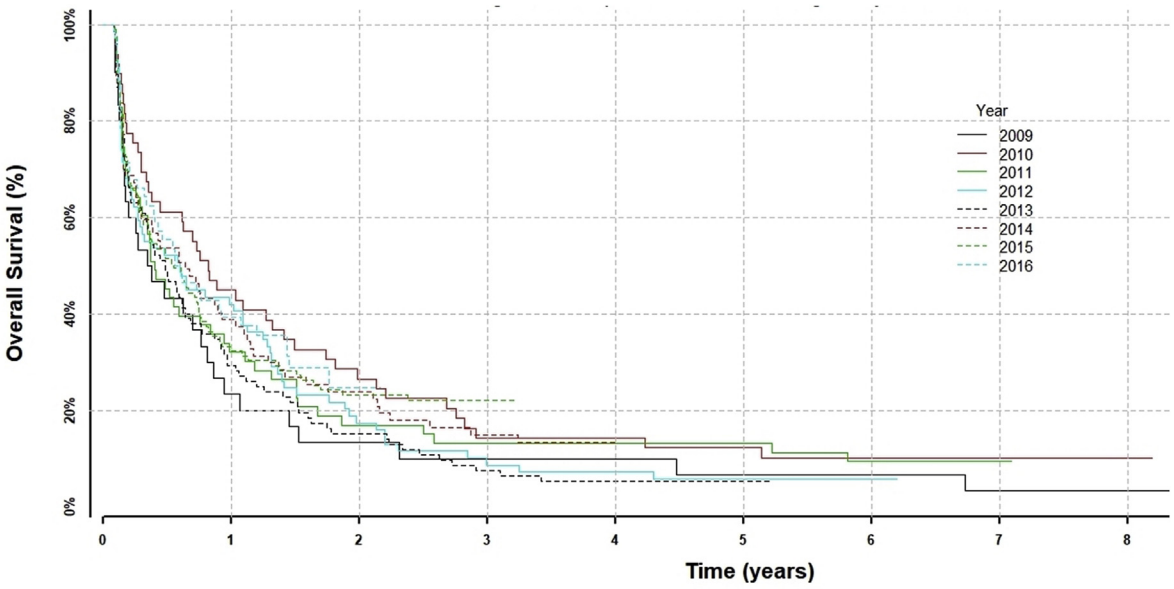
Curative intent treatment was surgical resection ($n = 82$), of which some received adjuvant chemotherapy ($n = 23$). Non-curative intent treatment was chemotherapy ($n = 20$). Patients were enrolled in chemotherapy clinical trials, namely ABC-03 ($n = 2$) and BILCAP ($n = 2$). The numbers of patients treated with curative, non-curative, or best supportive intent did not differ across study years apart from 2013 to 2015 when the highest number of patients were treated with curative intent or by best supportive care (all $p > 0.1$) in parallel but with the largest numbers of Gallbladder cancer patients treated in single study years. The resection rate for gallbladder cancer was 45%, this figure including patients who underwent simple cholecystectomy and those who additionally underwent liver resection.

Kaplan-Meier analysis showed the median overall survival if curative treatment was 0.9 (0.7–2.0) years, 0.6 (0.3–1.1) years if non-curative treatment, and 2.3 (1.8–2.6) months if best supportive care. Compared to curative treatment as a baseline, hazard ratios (95% confidence interval) for patients receiving non-curative and best supportive therapies were significantly ($p \leq 0.008$) higher at 2.20 (1.23–3.92) and 6.16 (4.08–9.29) respectively.(Fig. 3)

The median overall survival was for the entire cohort of Gallbladder cancer patients, regardless of treatment, was approximately 150 days. Excluding those managed by best supportive care, the median overall survival was 400 days. Survival did not differ (Log Rank Test, $p = 0.383$) between the in different treatment years of the study. Multivariate analysis showed age and gender had no effect on survival.

Discussion

To our knowledge, this is the first paper evaluating time trends in management of primary liver and biliary cancers. The joint expertise of our supra-regional primary Hepatobiliary cancer MDT is key to improvements seen in HCC survival. Surgery remains the most effective curative option for all primary hepatobiliary cancers,



Numbers at risk

2009	30	7	4	3	3	2	2	1	1
2010	49	22	13	7	7	6	5	5	2
2011	53	17	9	7	7	7	5	1	0
2012	69	29	12	6	5	4	2	0	0
2013	92	27	14	7	5	1	0	0	0
2014	67	26	16	10	1	0	0	0	0
2015	99	32	23	9	0	0	0	0	0
2016	56	22	3	0	0	0	0	0	0

Fig. 2. Cholangiocarcinoma median overall survival by year of treatment. The Kaplan-Meier graph compares median overall survival for Cholangiocarcinoma patients by year of treatment. Median overall survival was 180 days with inclusion of best supportive care patients, and 600 days if excluded. There was no significant difference ($p = 0.093$) between the survival of patients who had treatment in different years.

but most patients are not surgical candidates at the time of diagnosis. The Hepatobiliary MDT is crucial to ensuring other treatment modalities are considered, including clinical trials whenever possible and best supportive care where appropriate. This quality assurance process optimizes patient care on both curative and palliative pathways.

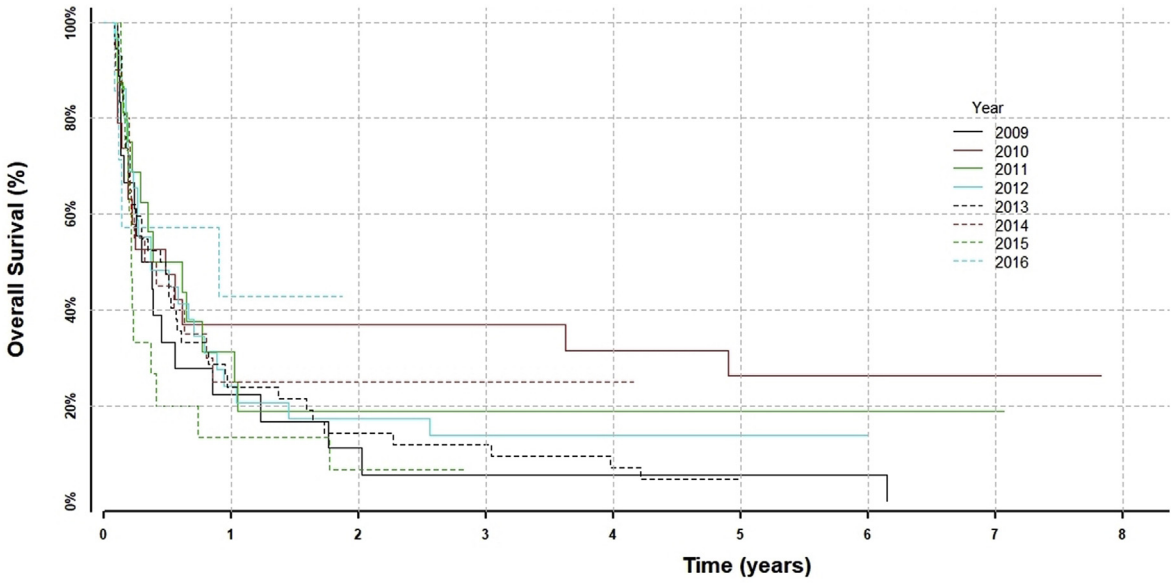
During data analysis, we considered the possibility that the relatively larger number of patients who underwent best supportive care for each cancer type may have affected the overall survival results obtained. Re-analysis excluding all the best supportive care patients yielded the same results for survival trends over time, thus further validating our findings.

HCC screening has undoubtedly helped early detection of tumours allowing prompt commencement of treatment which positively impacts on patients' survival. NICE (UK) recommends adults with cirrhosis are offered 6-monthly surveillance for HCC, using ultrasonography with or without measurement of serum alpha-fetoprotein (AFP). The largest RCT on HCC screening was conducted in China, included 18,816 HBV patients who had AFP and ultrasound assessment every 6 months, and showed a 37% reduction in mortality attributed to better detection of subclinical HCC amenable to effective treatment [6].

The treatment algorithm we used for our HCC patients was based on the Barcelona Clinic Liver Cancer (BCLC) staging system, which is validated and most commonly used for HCC. We considered curative treatments for BCLC stages O and A, palliative treatments for BCLC stages B and C, and symptomatic treatment for BCLC stage D. Our median overall survival figures of 6 years for BCLC 0/A, 1.5 years for BCLC B/C, and 2 months for BCLC D agree with published data [7] showing respective median survivals of >5yrs, >1yr and 3 months.

Survival for HCC with curative intent treatment was clearly greater than with non-curative. Of the non-curative options, TACE was the most used primary treatment modality in 151 patients. TACE was additionally used in 30 other patients who received other treatment modalities recognised to have a greater impact on survival, hence TACE was not considered their primary treatment modality. Survival with TACE was significantly better than with Sorafenib.

Liver resection is the first line treatment option for patients with solitary HCC tumours and well-preserved liver function [4]. As in most UK centres, our patients with HCC were listed for transplantation based on the expanded Milan criteria [8]. We believe liver transplantation delivered the best results for HCC patients because it simultaneously eliminates the tumour and the underlying at-risk diseased liver. There is certainly an element of better tumour biology that explains the better results with liver transplantation as small tumours $\leq$3 cm, as selected for liver transplantation, are considered relatively benign and independently predict better prognosis in HCC. Surgery is achieved in 46.5% of screened patients and 7.8% of unscreened patients [6]. A series of 333 HCC patients from a high-volume European centre reported surgical resection with curative intent in 35% [9]. The authors also performed meta-analysis of 6108 HCC cases in the worldwide



Numbers at risk

2009	18	4	2	1	1	1	1	0	0
2010	19	7	7	7	6	5	5	5	0
2011	16	5	3	3	3	3	3	1	0
2012	29	7	5	4	4	4	0	0	0
2013	42	10	6	5	3	0	0	0	0
2014	20	5	5	5	1	0	0	0	0
2015	15	2	1	0	0	0	0	0	0
2016	7	3	0	0	0	0	0	0	0

Fig. 3. Gallbladder cancer median overall survival by year of treatment. The Kaplan-Meier graph compares median overall survival for Gallbladder cancer patients by year of treatment. Median overall survival was 150 days with inclusion of best supportive care patients, and 400 days if excluded. There was no significant difference ($p = 0.383$) between the survival of patients who had treatment in different years.

literature which showed resectability rate of 30%, with higher rates in Eastern compared to Western series [9]. This resection rate quoted in the literature is comparable to our HCC resectability rate of 30%. Ablation was the most commonly used curative treatment modality. We used ablation for treating patients with early-stage HCC <2 cm [10]. The survival with liver resection compared favourably to ablation, despite patients with ablation having disease with better prognosis (<2 cm).

Local ablation is considered the standard of care for patients with early stage tumours (BCLC 0-A), with comparable outcomes to surgery for very small tumours, and was used in 65% of our HCC patients treated with curative intent.

Transarterial chemoembolization (TACE) and Sorafenib were the most commonly used non-curative treatment modalities. TACE and Sorafenib were respectively used in 65% and 34% of patients treated with non-curative intent, as similarly reported by other centres [9]. TACE is the standard of care for patients with intermediate stage hepatocellular carcinoma. TACE is recommended for patients with BCLC stage B, multinodular asymptomatic tumours without vascular invasion or extra-hepatic spread. Drug-eluting beads are as effective but possibly have less side effects than cTACE which uses an emulsion with lipidol rather than drug eluting beads [11]. TACE is discouraged in patients with decompensated liver disease. Of note, most patients in our centre who received TACE did so as part of TACE trials.

NICE (UK) recommend Sorafenib, a multikinase inhibitor, for treating advanced HCC in patients with Child-Pugh grade A liver impairment, with advanced tumours (BCLC stage C), or those tumours progressing despite loco-regional therapies. There is no second-line treatment for patients who fail sorafenib and systemic chemotherapy is not recommended for HCC patients. Selective internal radiation therapy (SIRT) shows promise but is not recommended as standard therapy since there are uncertainties about its effectiveness compared with other treatments.

Overall, HCC outcomes have been improved by newer treatments, screening and better measures to manage the underlying liver disease.

Biliary tract cancers, defined as cancers which develop in the gallbladder and bile ducts, carry poor prognoses as most patients have advanced disease at presentation and despite surgery, there is frequent disease recurrence. Surgery is the only effective curative option for cholangiocarcinoma, yielding 5-year survival rates of approximately 40% [12]. Our current resection rate for hilar cholangiocarcinomas of 19% is a modest, yet important advance on our previous figure of 16.5% published 4 years ago [12]. Most series agree that resection rates for cholangiocarcinoma are low but there is heterogeneity in resectability rates, a range of 10–40% of presenting patients being reported by a recent review [13]. This variation in resectability rates depends partly depends on patient factors including the anatomical location of cholangiocarcinoma, patients' attitudes towards undergoing major surgical resection, and the general fitness of the local elderly population as they are predominantly affected by cholangiocarcinoma. There are also institutional factors such as differences in clinical management

decision-making between local MDTs and the availability of specialist surgical expertise to undertake complex liver resections. We observed more cholangiocarcinoma resections in 2015/2016 and feel the reasons are multifactorial. Firstly, it is likely that improved awareness coupled with our referral network that had become increasingly efficient over the 8-year study period meant there was an increasing number of patients being assessed for cholangiocarcinoma treatment. Another factor is the increased experience of our Centre over the study period which allowed more aggressive surgical approaches, sometimes accompanied by portal vein embolization.

To mitigate the high recurrence rate and poor 5-year survival of as low as 20% for hilar cholangiocarcinoma, some centres use neoadjuvant chemoradiotherapy in conjunction with liver transplantation yielding 5-year survival rates of up to 70% but these are highly selected patients [14]. None of the hilar cholangiocarcinoma patients in our series received this treatment regimen.

Advanced biliary tract cancers do however respond to chemotherapy and the palliative regimen has been standardised in the Advanced Biliary Cancer (ABC)-02 trial which showed cisplatin plus gemcitabine significantly improved survival compared to gemcitabine monotherapy, without substantial additional toxicity [15]. There were 4 cholangiocarcinoma patients enrolled in clinical trials in our cohort.

Approximately half of patients with inoperable cholangiocarcinoma die because of local tumour progression causing bile duct obstruction complicated by cholangitis and biliary sepsis. Palliative management of these patients, aimed at reducing obstructive cholestasis and its sequelae, is heavily supported by our Unit's proactive ERCP service which offers an emergency service for timely intervention in these frail patients [16]. Patients also received advanced endoscopic therapy for malignant biliary strictures via ERCP-directed photodynamic therapy or radiofrequency ablation. Photodynamic therapy has been delivered as part of the Photostent-02 trial comparing the combination of systemic chemotherapy and photodynamic therapy to photodynamic therapy alone in unresectable hilar cholangiocarcinoma. Some patients with advanced inoperable cholangiocarcinomas also received Amphinex-induced photochemical internalisation of Gemcitabine as part of the photochemical internalisation (PCI) trial. These palliative ERCP-directed therapies have crucially offered a survival advantage to patients with inoperable hilar cholangiocarcinoma [17].

SIRT was used for 1 cholangiocarcinoma patient in our cohort and there was good tumour response. Unfortunately, the funding for SIRT to treat intrahepatic cholangiocarcinoma which was previously provided through NHS England's Commissioning through Evaluation, a programme enabling a limited number of patients gain access to treatments that are not funded by the NHS but show significant future promise, ceased in March 2017. Withdrawal of funding occurred despite Biliary Cancer Guidelines from the European Society of Medical Oncology (ESMO) recommending use of SIRT, based on response rates of 28% in treated patients, and 10% rate of downstaging to resectable disease [5].

Finally, our resectability rate for gallbladder cancer compares favourably with other published series [18]. Regarding surgery performed, 68 out of the total cohort of 82 patients received only an initial operative treatment while the remaining 14 patients underwent re-operative surgery to achieve clear resection margins. At original surgery, 66 out of 68 patients had simple cholecystectomy while 2 patients had radical cholecystectomy. There were 5 gallbladder cancer patients enrolled in clinical trials of chemotherapy.

So how can our study findings be applied to clinical practice to improve the outcomes of patients with primary hepatobiliary cancers? It appears improved survival in HCC has been realised in parallel with established surveillance of at-risk-groups and development of effective multimodal therapies, in addition to successful recruitment of large numbers of patients into therapeutic clinical trials of new therapies. Unfortunately, there is no evidence-based surveillance policy for Cholangiocarcinoma, even in patients with primary sclerosing cholangitis where the risk is increased several-fold. Biliary tract cancers as whole lack an evidence-based approach for surveillance and this includes Gallbladder cancers. This combined with limited therapeutic modalities is likely to account for the sustained poor outcomes seen with biliary tract cancers. We thus propose that further investment to develop multimodal therapies and effective surveillance strategies in biliary tract cancers will provide HPB MDTs with the armamentarium to improve survival as has been demonstrated for HCC.

Conclusion

The outcomes for resection for HCC as well as Cholangiocarcinoma and Gallbladder cancer in our institution are consistent with those quoted in the international literature [9,13,18]. Our experience shows HCC survival has improved over time and we speculate this has been driven by screening, multimodality therapy and the large number of patients recruited into trials. Existing multimodality treatment options for biliary tract cancers are of limited therapeutic value as survival has not improved over time, thus making these cancers an area of unmet need.

Declarations of interest

None.

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