Article

Advanced intrahepatic cholangiocarcinoma: post-hoc analysis of the ABC-01, -02 and -03 clinical trials

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Abstract

Background

The incidence of intrahepatic cholangiocarcinoma (iCCA) is increasing. The aim was to provide reference survival data for patients with advanced iCCA treated with first-line cisplatin-gemcitabine chemotherapy (current standard of care).

Methods

Individual data from patients with iCCA recruited into the prospective, randomised Advanced Biliary tract Cancer (ABC)-01, -02 and -03 studies were retrieved. The prevalence and survival of liver-only iCCA was also assessed. Survival analysis was performed using univariate and multivariable Cox Regression. All statistical tests were two-sided.

Results

Of 534 patients recruited into the ABC-01, -02 and -03 studies, 109 (20.4%) had iCCA. Most patients (n=86; 78.9%) had metastatic disease at the time of recruitment; 52 patients (47.7%) had liver-only disease. Following randomisation, 66 (60.6%) iCCA patients received cisplatin/gemcitabine. The median progression-free (PFS) and overall survival (OS) was 8.4 months (95%confdence interval [CI] = 5.9-8.9) and 15.4 months (95%CI = 11.1-17.9), respectively. Of these 66 patients, 34 patients (51.5%) had liver-only disease. Following chemotherapy, 30 (45.5%) and 21 (31.8%) were progression free at 3 and 6 months from chemotherapy commencement, respectively. Median OS for patients with liver-only iCCA at diagnosis, and after 3 and 6 months of chemotherapy was 16.7 months (95% confidence interval [CI] = 8.7-20.2), 17.9 (95%CI = 11.7-20.9) and 18.9 (95%CI = 16.7-25.9) months, respectively. Multivariable analysis confirmed that iCCA had a longer OS compared to other non-iCCA BTCs (hazard ratio = 0.58, 95%CI = 0.35-0.95; p-value = 0.03); liver-only iCCA

patients also showed longer OS even though findings did not reach statistical significance (hazard ratio = 0.65, 95%CI = 0.36-1.19; p-value = 0.16).

Conclusions

Patients diagnosed with advanced iCCA have a better OS compared to other BTCs; similar trend was identified for patients diagnosed with liver-only iCCA. These findings are to be considered for future clinical trial design.

Biliary tract cancers (BTCs) include cholangiocarcinoma (intrahepatic (iCCA), hilar and distal), gallbladder and ampullary carcinoma (1). BTCs are usually diagnosed in patients aged 50 to 70 years (2) and prognosis is poor (1, 3, 4). Although considered rare(2), their incidence is increasing due to a clinically significant rise in diagnosis of iCCA (5-7).

Systemic chemotherapy is the only treatment approach that demonstrated survival benefit in randomised phase III studies for advanced BTC (8, 9). Cisplatin/gemcitabine is currently accepted as a reference first-line treatment in advanced BTC in many countries (8) based on the ABC-02 phase III clinical trial (10). These findings were confirmed in a Japanese randomised phase II study (BT22 study) (11) with no quality of life detriment in the combination arm identified (12). Other first-line chemotherapy options are under development (13-16). Role of second-line chemotherapy remains unclear (17-22), and suitable only for around 15% of patients due to rapidly-worsening performance status (19). Results of a randomised phase III study in this setting are awaited (23).

iCCA is considered a separate entity from other BTCs, due to anatomical and molecular characteristics (9). iCCAs have been identified to express specific targetable genetic aberrations such as fibroblast growth factor receptor (FGFR) fusion rearrangements (9, 24-29) and isocitrate dehydrogenase (IDH)-1 and-2 mutations (9, 30-33, 33, 34, 34-37).

Patients with iCCA are more likely to have liver-only disease. For such scenarios, liver-directed therapies (LDT) are being explored (38) and suggested by some international guidelines (39). Methods of intra-arterial therapy include hepatic-arterial-embolisation, trans-arterial-chemo-embolisation, radio-embolisation ($Yttrium^{90}$; RE) (40-45) and liver-chemosaturation (46, 47).

This post-hoc analysis aimed to provide reference survival data to inform the design, sample size calculation and feasibility of future studies exploring the role of systemic

(including targeted) therapies and LDT in advanced iCCA. Potential trial designs together with factors to consider in designing such studies are discussed.

Materials and methods

Study design

A post-hoc analysis of patient data collected as part of the prospective ABC-01 (48), -02 (10) and -03 (49) clinical trials was performed. These studies explored the role of first-line systemic chemotherapy in advanced BTCs (cisplatin/gemcitabine vs. gemcitabine [ABC-01 and ABC-02] and cisplatin/gemcitabine/cediranib vs. cisplatin/gemcitabine/placebo [ABC-03]). All patients had provided written consent for participating in the above-mentioned trials, published elsewhere (10, 48-49) . The studies were sponsored by University College of London and coordinated by the Cancer Research UK & UCL Cancer Trials Centre, which facilitated access to anonymised individual-patient data.

Patients diagnosed with iCCA were evaluable for this post-hoc analysis. Clinical data, including demographics, baseline tumour markers, complete blood count, renal/liver profile, treatment characteristics and response/survival data were retrieved. The best radiological response achieved by each patient was classified based on the version of Response Evaluation Criteria In Solid Tumours (RECIST) employed in each study: RECISTv1.0 (50) for ABC-01/-02, RECISTv1.1 (51) for ABC-03.

The primary aim of this analysis was to provide reference overall survival (OS) data of patients diagnosed with iCCA treated with first-line cisplatin/gemcitabine chemotherapy for future prospective studies. The sub-group of patients diagnosed with iCCA who were potentially eligible for LDT (defined as patients with liver-only disease) were analysed

separately. Secondary objectives included progression-free survival (PFS); description of demographic data of patients diagnosed with iCCA; and assessment of the frequency of iCCA patients with liver-only disease. Suitability for LDT at 3 and 6 months required meeting the above-mentioned criteria for LDT, and being progression-free at 3 and 6 months following chemotherapy commencement, respectively.

Statistical analysis

All eligible patients were included in the analysis. All patients diagnosed with iCCA were included for a summary of baseline characteristics. For survival analysis, only patients treated with the combination of cisplatin/gemcitabine were included (current standard of care for good-performance status patients). Since the addition of cediranib to cisplatin/gemcitabine did not result in a statistically-significant impact on survival in the ABC-03 study (49), patients receiving both cediranib and placebo were included in the survival analysis of patients treated with cisplatin/gemcitabine.

PFS and OS were measured as the time from randomisation to progression/death or death of any cause, respectively. Patients who did not experience a PFS or OS event were censored at the date of last follow-up. Calculations of PFS and OS using as a starting point 3 and 6 months from randomisation were performed to identify patients potentially suitable for LDT at 3 and 6 months, respectively. Survival analysis was performed with Kaplan-Meier method and Cox Regression (univariate and multivariable analysis including variables statistically significant in the univariate analysis (defined as p-value <0.05); Ph test was used to test for proportional-hazards assumption. For identification of prognostic factors, derived Hazard Ratio (HR), 95% confidence intervals (CI) and p-values were reported. Stata v.12 software was employed. P-values <0.05 were considered statistically significant. All statistical tests were two-sided.

Results

Study population

Data from a total of 534 patients was retrieved (86, 324, and 124 patients from the ABC-01, ABC-02, and ABC-03 studies, respectively). Although the ABC-02 clinical trial reported a total of 410 patients, 86 were patients previously recruited into the ABC-01; such patients were included only once in this study. Thus, 324 patients from ABC-02 were eligible for this post-hoc analysis. Of the whole population of eligible BTC patients, 318 (59.6%) were diagnosed with cholangiocarcinoma: 109 (20.4% of the whole population) had iCCA. By the end of follow-up, 82.9% of the whole population had died. The results are provided according to the cohorts specified in **Supplementary Figure 1**.

Whole population of patients diagnosed with BTC

Baseline characteristics are shown in **Table1**. Estimated median OS (regardless of type of chemotherapy administered; **Supplementary Figure 1/CohortA**) for the whole population of 534 patients was 10.3 months (95%CI = 8.8-11.7). When only patients receiving cisplatin/gemcitabine were included, the median PFS and OS were 7.9 months (95%CI = 6.8-8.4) and 12.2 months (95%CI = 10.7-13.6) (**Figure 1A**), respectively.

Whole iCCA population: baseline characteristics and chemotherapy treatment

The characteristics of all patients diagnosed with iCCA (109 patients; **Supplementary Figure 1/CohortB**) are summarised in **Table1**. Most of the patients with iCCA had metastatic disease (n=86; 78.9%); 52 patients (47.7%) had no extrahepatic metastases.

Of the 109 patients diagnosed with iCCA, 19, 61 and 29 patients were treated within the ABC-01, ABC-02 and ABC-03 clinical trials, respectively. Following study entry, 43 (39.5%) and 66 (60.6%) patients received gemcitabine or cisplatin/gemcitabine combination, respectively. Of the 66 patients who received cisplatin/gemcitabine chemotherapy (**Supplementary Figure 1/CohortC**), 14 also received cediranib as per the ABC-03 study protocol (49). Within these 66 patients (**Supplementary Figure 1/CohortC**), one patient (1.5%) achieved a complete radiological response. In addition, 15 (22.7%) and 26 (39.4%) patients achieved a partial response and stable disease as best response, respectively. Eleven patients (16.7%) had progression and 13 did not undergo radiological assessment. **Supplementary Table 1** summarises absolute responses achieved at each time-point explored; response rate for iCCA population was similar to the one showed for patients with non-iCCA BTC (**Supplementary Table 2**).

Estimated median OS (regardless of type of chemotherapy administered; **Supplementary Figure 1/CohortB**) for all patients diagnosed with iCCA was 12.6 months (95%CI = 8.7-15.2) respectively. When only patients receiving cisplatin/gemcitabine were included (**Table2**; **Supplementary Figure 1/CohortC**), the median PFS and OS for all patients diagnosed with iCCA were 8.4 (95%CI = 5.9-8.9) and 15.4 months (95%CI = 11.1-17.9) (**Figure 1B**), respectively. Patients diagnosed with iCCA had statistically significant longer OS when compared to other BTCs (iCCA vs. BTC [non-iCCA, reference group] univariate HR = 0.72, 95%CI = 0.53-0.98; p-value = 0.04 (**Figure 1B**); multivariable analysis for OS is shown in **Supplementary Table 3** (adjusted multivariable HR = 0.58, 95%CI 0.35-0.95; p-value = 0.03). Further detail regarding PFS and OS rates at a number of time-points is provided in **Table2** (data for additional time-points can be found in **Supplementary Table 4**). No statistically significant differences in PFS were identified between iCCA (median =

8.4, 95%CI = 5.9-8.9) and non-iCCA BTC patients (median = 7.9, 95%CI = 6.5-8.4); log rank p-value = 0.65.

Subgroup of patients with liver-only disease

Fifty-two patients diagnosed with iCCA had liver-only disease (52/109; 47.7%); **Table1** includes baseline characteristics for this patient population (**Supplementary Figure 1/CohortD**). Of the 66 patients diagnosed with iCCA receiving cisplatin/gemcitabine chemotherapy (**Supplementary Figure 1/CohortC**), 34 patients (51.5%) had liver-only disease at diagnosis (**Supplementary Figure 1/CohortE**). Of these 34 patients, 7 patients (20.6%) achieved a partial response and 17 (50%) had stable disease as best response, which accounted for a disease control rate of 70.6%. Of the remaining 10 patients, 7 (20.6%) had progression as best response and 3 had no radiological assessment of response, due to clinical progression (**Supplementary Table 1**). Response rate was similar to the one showed for patients with non-iCCA BTC (**Supplementary Table 2**).

Within these 34 patients, following chemotherapy with cisplatin/gemcitabine 30 (45.5%) and 21 (31.8%) were progression-free (liver-only disease) at 3 and 6 months, respectively. **Supplementary Figure 2** summarises the adapted consort diagram. Patients diagnosed with liver-only iCCA who were treated with cisplatin/gemcitabine had a favourable OS when compared with other BTC subgroups [iCCA (liver-only) vs. BTC (no-iCCA) (Ref) univariate HR = 0.63, 95%CI = 0.43-0.93, p-value = 0.02] (**Figure 1C**). Multivariable analysis for OS is shown in **Supplementary Table 3** and confirmed such trend despite not reaching statistical significance (adjusted multivariable HR = 0.65, 95%CI = 0.36-1.19; p-value = 0.16).

The median PFS / OS for the subgroup of patients who received cisplatin/gemcitabine diagnosed with liver-only iCCA (**Supplementary Figure 1/CohortE**) at study entry, and

following 3 and 6 months from starting chemotherapy was 8.4 months (95%CI = 5.9-10.02) / 16.7 months (95%CI = 8.7-20.2), 8.6 months (95%CI = 7.6-11.3) / 17.9 months (95%CI = 11.7-20.9) and 11.1 months (95%CI = 8.5-12.9) / 18.9 months (95%CI = 16.7-25.9), respectively (**Table2; Supplementary Table 4**). **Table2** provides further PFS and OS rate information at different time-points explored for this patient population (data for additional time-points can be found in **Supplementary Table 4**). No statistically significant differences in PFS (measured from study entry) were identified between liver-only iCCA (median = 8.4 95%CI =5.9-10.0) and non-iCCA BTC patients (median 7.9, 95%CI = 6.5-8.4; log rank p-value = 0.37).

Prognostic factors

OS was shorter in patients diagnosed with iCCA and treated with cisplatin/gemcitabine, who had a higher serum carcinoembryonic antigen (CEA) levels at baseline. This factor was independent prognostic factor on multivariable analysis adjusted for other variables statistically significant in the univariate analysis (**Table3)**.

Multivariable analysis confirmed that higher platelet count and high CEA at baseline were associated with shorter OS in the population of patients with iCCA treated with cisplatin/gemcitabine with liver-only disease (**Table3**). Although other factors were impacted on OS in the univariate analysis, none were independently prognostic in the multivariable analysis.

Discussion

There is an urgent need for additional therapies for patients with BTCs. Patients with iCCA represent a specific subgroup for whom novel targeted therapies and LDT are emerging as

promising therapeutic options. IDH and FGFR inhibitors have been tested in early phase clinical trials, and phase III studies are ongoing aimed at evaluating their efficacy (9). In addition, current evidence supporting LDT in iCCA is of limited quality (category C; as per 'Standards, Options and Recommendations' (SOR) guidelines (52)) and therefore phase III randomised studies evaluating the impact of adding LDT to current standard of care (cisplatin/gemcitabine) chemotherapy are planned in order to confirm previously-suggested benefit. This post-hoc analysis of the prospective ABC-01(48), -02(10) and -03(49) clinical trials explored the outcome of patients diagnosed with iCCA who were treated with cisplatin/gemcitabine chemotherapy in order to inform the design of such studies.

Patients diagnosed with iCCA had a prolonged OS when compared to the pooled patients with BTCs/non-iCCA, which makes them an attractive subgroup for development of further treatment approaches . Similar trend was identified when patients diagnosed with iCCA with liver-only disease (therefore suitable for LDT) were analysed. Survival may have been underestimated by the inclusion of patient with ECOG performance status 2.

Various findings support the fact that this prolonged OS is reflective of a different natural history rather than a better response to palliative chemotherapy (53). Firstly, the median PFS for cisplatin/gemcitabine-treated iCCA patients (8.4 months) was similar to the one achieved in the ABC-02 clinical trial (mixed population of BTC) [8.0 months (10)]. Secondly, this difference in survival is unlikely to be related to a stage shift, since a similar percentage of patients with metastatic disease were identified within all patient subgroups (76.8%) and within the iCCA subgroup (78.9%). Thirdly, differential molecular findings described within iCCA, such FGFR translocations and IDH mutations, have been suggested to impact survival(9). As an example, FGFR translocations [present in around 11-45% of iCCAs (9)] in iCCA have been identified as a marker for more indolent behaviour and better outcome (33, 34).

Regarding the potential role of LDT in patients with iCCA, approximately half of the patients with iCCA in the current analysis had liver-only disease and would therefore be suitable for LDT. This supports the feasibility of recruiting to future prospective studies exploring LDT in this population of patients. Potential trial designs for incorporating LDT to the treatment management of patients with iCCA are summarised in **Figure2**. Options could include the incorporation of LDT before any palliative chemotherapy (**Figure2; OptionA**), during chemotherapy (**Figure2; OptionB**) or at the end of 6 months of chemotherapy (**Figure2; OptionC**).

This study provides data on LDT-suitability (defined as presence of liver-only disease) and survival at different time-points (baseline, 3 months and 6 months), in order to explore which time-point would be more feasible to be explored. From the patient recruitment point of view, these results suggest that all three time-points would be adequate for introduction of LDT into patients' pathway; although there is a progressive drop in the number of eligible patients. OS increases progressively between these three groups, as can be expected due to an immortality bias (54). Due to the longer survival of the patient population who would be progression-free at 6 months from starting palliative chemotherapy (and therefore eligible for LDT at this point), a study incorporating LDT at this time-point would require prolonged follow-up with associated increased cost.

Few ongoing prospective studies are currently exploring the role of novel forms of LDT in iCCA, mainly focused on RE (**Table4**). A phase II single arm prospective study in Hong Kong is recruiting 30 patients with iCCA for treatment with RE followed by standard chemotherapy (equivalent to **Figure2, OptionA**) (NCT02167711). A similar design has been followed by the randomised phase II SIRCCA clinical trial (NCT02807181) which is investigating the use of the cisplatin/gemcitabine combination +/- RE as first-line treatment in patients with advanced iCCA. An innovative approach with concomitant chemotherapy

and RE (RE will be administered on day 3 or 4 in combination with cisplatin/gemcitabine in cycles 1 and 2) is being explored by another phase I study (NCT02512692). One study is currently recruiting patients diagnosed with iCCA to explore other LDT approaches such as chemo-saturation (NCT03086993).

While the above aspects will inform sample size calculation and trial design, prognostic factors in patients with iCCAs treated with systemic chemotherapy should be considered for patient stratification. In a large series of patients with BTC treated with cisplatin/gemcitabine, the impact of factors such as haemoglobin, disease status, bilirubin, and neutrophils on both PFS and OS was identified and validated (61). The current post-hoc analysis did not confirm these results, probably due to limitations of sample size in the subgroup analysis presented. Based on the current results, factors such as ECOG performance status and baseline CEA should be considered at time of stratification for patients diagnosed with iCCA. In addition, retrospective studies including patients treated with LDT (specifically with RE), have identified multiple factors impacting survival which should be considered at the time of study design for patient stratification. Patients with ECOG performance status of 2 have been reported to have worse prognosis when treated with RE (42, 56-58), similar trend was identified in the current iCCA population (even though it did not reach statistical significance in the multivariable analysis). Other factors contributing to worse prognosis include multifocal disease (55), infiltrative morphology (42, 55, 57), bilobar disease (55) and liver tumour burden (56, 62). The presence of portal vein thrombosis has been reported to have varying impact on prognosis in different studies (42, 55). The presence of extra-hepatic disease, if low volume, is not necessarily required as an exclusion criteria (58). Most of these previously described prognostic factors, were not explored in the current analysis due to lack of available information, and should be considered at the time of RE study design.

A strength of this work is the fact that all data had been previously produced and quality-assured as part of prospective clinical trials. This provides robustness to the results. In addition, a homogeneous population of patients treated with the same chemotherapy schedule is presented (treatment-naïve patients treated with first-line cisplatin/gemcitabine) and the same chemotherapy protocol for dose reductions and duration of chemotherapy.

Regarding the limitations of this post-hoc analysis, it is worth mentioning that the sample size was modest, since the analysis was focused on a small subpopulation of patients, which could have limited the survival analysis (particularly the Cox-regression for identification of prognostic factors when multiple covariates were included). Some patients had received cediranib as part of the ABC-03 study, but this was not expected to impact on the patients' outcomes (49). In addition, the actual percentage of patients suitable for LDT may have been under or overestimated due to the lack of information for assessing the above criteria, such as tumour spread pattern and technical problems (i.e. liver-lung shunt). In fact, only patients with liver-only disease were classified as suitable for LDT, excluding patients with liver-predominant disease.

In summary, the magnitude of benefit described in some of the studies focusing on iCCA is within the range that would be considered statistically significant if there was no knowledge of the survival of this patient cohort. This post-hoc analysis demonstrates that patients with iCCA have a better outcome than other patients with BTC and these survival figures should be considered at the time of future study design in this patient population. In addition, close to half of the patients diagnosed with iCCA are likely to have liver-only disease, and therefore may be suitable for approaches involving LDT.

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Tables

Table 1: Summary of baseline characteristics of all patients and those with iCCA included in ABC-01, -02 and -03.

Characteristics	All patients with biliary tract cancer (n=534)	Intrahepatic cholangiocarcinoma (n=109)	Patients with iCCA and liver-only disease (n= 52)
	N (%)	N (%)	N (%)
Gender			
Female	278 (52.1)	53 (48.6)	23 (44.2)
Male	256 (47.9)	56 (51.4)	29 (55.8)
Median age, y (range)	64.3 (23.4-84.8)	61.7 (35.0-78.9)	63.1 (35.3-78.4)
ECOG Performance Status			
0	185 (34.6)	43 (38.5)	28 (53.9)
1	297 (55.6)	57 (52.3)	22 (42.3)
2	52 (9.7)	9 (8.3)	2 (3.8)
Primary tumour site			
Gallbladder	188 (35.2)	n/a	n/a
Ampulla of Vater	28 (5.3)	n/a	n/a
Cholangiocarcinoma	318 (59.6)	109 (100)	52 (100)
iCCA	109 (34.3)	109 (100)	52 (100)
Extrahepatic cholangiocarcinoma	122 (38.4)	n/a	n/a
Hilar	57 (17.9)	n/a	n/a
Not specified	30 (9.4)	n/a	n/a
Grade of Differentiation			
Well differentiated	40 (7.5)	7 (6.4)	2 (3.8)
Moderately differentiated	164 (30.7)	30 (27.5)	16 (30.8)
Poorly differentiated	99 (18.5)	22 (20.2)	12 (23.1)
Not specified	231 (43.3)	50 (45.9)	22 (42.3)
Prior treatment			

No	328 (61.4)	82 (75.2)	38 (73.1)
Yes	206 (38.6)	27 (24.8)	14 (26.9)
Surgery	48 (23.3)	10 (37.1)	8 (57.1)
Other*	158 (76.7)	17 (62.9)	6 (42.9)
Stented			
No	491 (91.9)	106 (97.3)	50 (96.1)
Yes	43 (8.1)	3 (2.8)	2 (3.9)
Stage			
Locally advanced	124 (23.2)	23 (21.1)	23 (44.2)
Metastatic	410 (76.8)	86 (78.9)	29 (55.8)
Sites of disease†			
Liver	161 (30.2)	35 (31.1)	52 (100)
Peritoneum	76 (14.2)	10 (9.2)	n/a
Lung	43 (8.1)	13 (11.9)	n/a
Other	44 (8.2)	11 (10.1)	n/a
Extrahepatic disease			
No	250 (46.8)	52 (47.7)	52 (100)
Yes	139 (26.0)	28 (25.7)	n/a
Not specified	145 (27.2)	29 (26.6)	n/a

*Other treatment included radiotherapy, and photodynamic therapy. iCCA: intrahepatic cholangiocarcinoma; ECOG: Eastern Cooperative Oncology Group; n/a: not applicable.
† "Site of disease" was missing for some patients.

Table 2: Progression-free survival and overall survival of patients with iCCA treated with cisplatin/gemcitabine at various time-points.

Outcome	No. of patients eligible for LDT (liver-only disease)/ total (%)	Median, months (95%CI)	Rate, % (95%CI)				
			3 months	6 months	9 months	12 months	18 months
Progression free survival							
All patients diagnosed with iCCA (survival from starting cisplatin gemcitabine)	n/a	8.4 (5.9-8.9)	75.8 (63.5-84.4)	61.9 (49.1-72.5)	38.1 (26.4-49.8)	24.9 (14.9-36.1)	11.2 (4.8-20.5)
Patients with liver-only iCCA at first diagnosis of advanced disease (study entry/baseline) (survival from starting cisplatin gemcitabine)	34/66 (51.5)	8.4 (5.9-10.02)	88.2 (71.6-95.4)	64.3 (45.8-77.9)	42.9 (25.9-58.7)	24.5 (11.6-39.9)	12.3 (3.9-25.8)
Patients with liver-only iCCA after 3 months of cisplatin/gemcitabine first-line chemotherapy (survival from starting cisplatin gemcitabine)	30/66 (45.5)	8.6 (7.6-11.3)	100 (100-100)	72.9 (53.0-85.4)	48.6 (29.8-65.1)	27.8 (13.2-44.5)	13.9 (4.4-28.8)
Patients with liver-only iCCA after 6 months of cisplatin/gemcitabine first-line chemotherapy (survival from starting cisplatin gemcitabine)	21/66 (31.8)	11.1 (8.5-12.9)	100 (100-100)	100 (100-100)	66.7 (42.5-82.5)	38.1 (18.3-57.8)	19.1 (5.9-37.7)
All BTC	n/a	7.9 (6.9-8.4)	79.8 (75.1-83.8)	61.8 (56.3-66.9)	38.1 (32.1-44.0)	20.3 (15.4-25.6)	8.8 (5.4-13.0)
Non-iCCA BTC	n/a	7.8 (6.5-8.4)	80.8 (75.5-85.1)	61.8 (55.6-67.4)	38.1 (32.1-44.0)	20.3 (15.4-25.6)	8.8 (5.4-13.0)

Overall survival							
All patients diagnosed with iCCA (survival from starting cisplatin gemcitabine)	n/a	15.4 (11.1-17.9)	90.6 (80.2-95.6)	79.4 (67.2-87.5)	68.1 (55.0-78.1)	61.4 (48.1-72.2)	36.5 (24.4-48.6)
Patients with liver-only iCCA at first diagnosis of advanced disease (study entry/baseline) (survival from starting cisplatin gemcitabine)	34/66 (51.5)	16.7 (8.7-20.2)	100 (100-100)	81.3 (62.9-91.1)	68.8 (49.7-81.8)	62.5 (43.5-76.7)	43.8 (26.5-59.8)
Patients with liver-only iCCA after 3 months of cisplatin/gemcitabine first-line chemotherapy (survival from starting cisplatin gemcitabine)	30/66 (45.5)	17.9 (11.7-20.9)	100 (100-100)	85.7 (66.3-94.4)	75.0 (54.6-87.2)	67.9 (47.3-81.8)	50.0 (30.6-66.6)
Patients with liver-only iCCA after 6 months of cisplatin/gemcitabine first-line chemotherapy (survival from starting cisplatin gemcitabine)	21/66 (31.8)	18.9 (16.7-25.9)	100 (100-100)	100 (100-100)	90.5 (67.0-97.5)	85.7 (61.9-95.2)	61.9 (38.1-78.8)
All BTC	n/a	12.2 (10.7-13.6)	90.3 (86.4-93.1)	77.8 (72.7-82.0)	61.7 (55.9-66.9)	51.0 (45.1-56.6)	27.4 (22.2-32.9)
Non-iCCA BTC	n/a	11.7 (10.2-12.6)	90.2 (85.7-93.3)	77.4 (71.6-82.1)	59.9 (53.4-65.9)	48.2 (41.5-54.5)	24.8 (19.2-30.9)

*Median PFS, OS and survival rates have been calculated both from the time of starting palliative chemotherapy. PFS and OS were also measured from 3 and 6 months of starting chemotherapy in order to inform all possible trial design sample size calculation (such information can be found in **Supplementary Table 4**). iCCA patients at risk / number of events for each time point are as follows for PFS [at 3 months 66/16; at 6 months 50/9;at 9 months 40/15; at 12 months 23/8; at 18 months 15/8] and OS [at 3 months 64/6; at 6 months 57/7;at 9 months 50/7; at 12 months 41/4; at 18 months 36/14]. Data for additional time-points (month 24, 30 and 36) can be found in **Supplementary Table 4**. CI: confidence interval; LDT: liver-directed therapy; iCCA: intrahepatic cholangiocarcinoma; BTC: biliary tract cancer.

Table 3: Prognostic factors of overall survival for patients with iCCA treated with cisplatin/gemcitabine

Factor	All patients diagnosed with iCCA (n=66)				Patients diagnosed with iCCA and liver-only disease (n=34)			
	Univariate analysis		Multivariable analysis*		Univariate analysis		Multivariable analysis*	
	HR (95%CI)	*P*†	HR (95%CI)	*P*†	HR (95%CI)	*P*†	HR (95%CI)	*P*†
Gender								
Female	1.00 (Ref)	-	-	-	1.00 (Ref)	-	-	-
Male	1.35 (0.79-2.31)	0.28	-	-	1.41 (0.67-2.98)	0.37	-	-
Age, y	0.99 (0.97-1.03)	0.91	-	-	1.01 (0.97-1.04)	0.99	-	-
ECOG Performance Status								
0	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-	-	-
1	1.43 (0.81-2.55)	0.22	1.11 (0.52-2.37)	0.79	1.59 (0.76-3.32)	0.22	-	-
2	5.21 (1.68-16.19)	0.004	7.54 (0.87-65.21)	0.07	n/a	-	-	-
Grade of differentiation								
Well differentiated	1.00 (Ref)	-	-	-	1.00 (Ref)	-	-	-
Moderately differentiated	2.58 (0.33-19.94)	0.36	-	-	$1.96x10^9$ ($7.84x10^8$-$4.89x10^9$)	<0.001	0.39 (0.08-1.92)	0.25
Poorly differentiated	3.30 (0.41-26.58)	0.26	-	-	$2.51x10^9$ (nc)	<0.001	nc	-
Prior treatment								
No	1.00 (Ref)	-	-	-	1.00 (Ref)	-	-	-
Yes	1.02 (0.58-1.79)	0.95	-	-	0.79 (0.36-1.76)	0.57	-	-

Stented								
No	1.00 (Ref)	-	-	-	1.00 (Ref)	-	-	-
Yes	0.48 (0.11-1.99)	0.31	-	-	0.54 (0.07-4.04)	0.55	-	-
Stage								
Locally advanced	1.00 (Ref)	-	-	-	1.00 (Ref)	-	-	-
Metastatic	1.49 (0.76-2.94)	0.25	-	-	1.33 (0.62-2.86)	0.47	-	-
White cell count baseline, $\times 10^9$/L	1.10 (1.02-1.19)	0.02	0.82 (0.52-1.28)	0.38	1.13 (0.99-1.29)	0.07	-	-
Platelets baseline, $\times 10^9$/L	1.003 (0.99-1.006)	0.09	-	-	1.004 (1.001-1.008)	0.04	1.01 (1.001-1.02)	0.04
Haemoglobin baseline, g/dL	0.89 (0.75-1.05)	0.17	-	-	0.55 (0.36-0.83)	0.005	1.07 (0.56-2.05)	0.83
Neutrophils baseline, $\times 10^9$/L	1.16 (1.06-1.26)	0.001	1.69 (0.97-2.96)	0.06	1.17 (1.01-1.34)	0.03	0.99 (0.72-1.37)	0.96
Bilirubin baseline, µmol/L	1.03 (0.97-1.09)	0.40	-	-	0.99 (0.91-1.09)	0.90	-	-
ALT baseline, IU/L	1.01 (0.98-1.02)	0.89	-	-	1.01 (0.99-1.02)	0.65	-	-
AST baseline, IU/L	1.001 (0.99-1.01)	0.77	-	-	1.01 (0.99-1.03)	0.46	-	-
CEA‡ baseline, µg/L	1.05 (1.02-1.09)	0.002	1.07 (1.03-1.12)	0.002	1.06 (1.02-1.10)	0.003	1.09 (1.02-1.17)	0.009
Ca19.9‡ baseline, IU/mL	1.03 (1.01-1.05)	0.03	0.97 (0.93-1.02)	0.18	1.04 (1.01-1.07)	0.02	1.06 (0.98-1.14)	0.16
Ca125 baseline, IU/mL	1.001 (0.99-1.01)	0.15	-	-	1.001 (0.99-1.01)	0.17	-	-

* The test of proportional-hazards assumptions was tested in both multivariable analyses and showed that proportionality assumption in the cox regression was held (p-value for iCCA model 0.6544; p-value for iCCA with liver-only disease model was 0.9550). HR: Hazard Ratio; CI: confidence interval; iCCA: intrahepatic cholangiocarcinoma; n: number of patients; Dif: differentiation; Ref: group of reference; ECOG: Eastern Cooperative Oncology Group; nr: not reached; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CEA: carcinoembryonic antigen; Ca 19.9: Serum carbohydrate antigen; Ca125: cancer antigen 125; nc: not calculated (due to collinearity); n/a: not applicable.

† Cox Regression was employed for this analysis; P values are two-sided.

‡ For the purpose of survival analyses, CEA and Ca19.9 variables were modified in order to obtain a clinically meaningful HR; CEA is presented as CEA/10 and Ca19.9 as CA19.9/10.000. Therefore, HR represents increase risk of death by every increase of 10 units and 10,000 units of CEA and Ca19.9, respectively.

$

Table 4: Reported studies of radioembolisation in intrahepatic cholangiocarcinoma

Reference	Study design	No. of patients	Patient outcomes	Level of evidence*
Al-Adra *et al* 23014 (40)	Systematic review	298	Median OS: 15.5 months. Radiological response: partial response in 28% and stable disease in 54% of patients at three months.	Level C
Mouli *et al* 2014 (55)	Prospective single centre	46	Radiological response: partial response (n=11; 25%), stable disease (n = 33; 73%), and progressive disease (n=1; 2%).One patient did not have information regarding response to treatment.	Level C
Edeline *et al* 2017 (45)	Prospective phase II study	45	Cisplatin/gemcitabine day 1 and 8 of a 21-days cycles; radioembolisation delivered during cycle 1 (unilobar disease), or cycles 1 and 3 (bilobar disease). Radiological response: partial response (39%, 90% CI = 26-53); disease control rate 98% (all 40 evaluable patients had disease control). Median PFS and OS from time of starting chemotherapy were Median PFS was 13 months (95%CI = 7-nr) and 21 months (95%CI = 14-nr), respectively.	Level C
Hoffmann *et al* 2012 (56)	Prospective single centre	33	Radiological responses: 12 patients had a partial response, 17 had stable disease, and 5 had progressive disease after 3 months. Median OS from the time of diagnosis and first radioembolisation procedure was 43.7 months and 22 months, respectively. Median TTP was 9.8 months.	Level C
Saxena *et al* 2009(57)	Prospective study	25	The median OS (following radioembolisation): 9.3 months. Radiological response: partial response to treatment was observed in 6 patients (24%), stable disease in 11 patients (48%), and progressive disease in 5 patients (20%).	Level C
Rafi *et al* 2013 (58)	Prospective single centre	19†	Median OS from the time of diagnosis and first radioembolisation procedure was 24.7 months (752 days, 95%CI = 374-1130) and 11.3 months (345 days; 95%CI = 95-595), respectively.	Level C

Hyder *et al* 2013 (38)	Retrospective multicentre review	198‡	Median OS: 11.3 months.	Level C
Gangi et al 2018 (59)	Retrospective single centre	85§	Median OS from diagnosis and from radioembolisation was 21.4 (95%CI = 16.6-28.4) and 12.0 months (95%CI = 8.0-15.2), respectively. At 3 months, 6.2% of patients had partial response,	Level C
Edeline *et al* 2015 (60)	Retrospective single centre	24	Sequencing of chemotherapy and radioembolisation: concomitant chemotherapy in 10 patients (42%), chemotherapy as induction before RE in 13 (54%) or after RE in 1 (4%). From the start of any treatment, the median PFS was 16.0 months. Median OS: not reached.	Level C
Ibrahim *et al* 2008 (42)	Open-label cohort study	24	Radiological response: 22 patients evaluable: 6 (27%) achieved a partial response, 15 (68%) stable disease and 1 patient (5%) progressive disease. The median OS was 14.9 months.	Level C

*The following definitions of level of evidence were used (52): Level A: there exists a meta-analysis of high standard or several randomised trials with consistent results; Level B: if randomised studies (level B1), therapeutic trials, quasi-experimental trials, or comparisons of populations (level B2) provide consistent results when considered together; Level C: there exist studies, therapeutic trials, quasi-experimental trials, or comparisons of populations, of which the results are not consistent when considered together; Level D: if either scientific data does not exist or there is only a series of cases; expert agreement: data does not exist but the experts are unanimous in their judgment. TTP: time-to-progression; PFS: progression-free survival; OS: overall survival; nr: not reached; CI: confidence interval.

† All patients were refractory to standard chemotherapy

‡ Patients in total (23.2%; 45 patients were intrahepatic cholangiocarcinoma)

§ Consecutive patients

Figure titles and legends

Figure 1: Prognosis of cisplatin/gemcitabine-treated patients.

Median overall survival estimated by Kaplan-Meier for each subgroup is shown. Patients for whom survival data was not available are excluded from this graph. Therefore, number of patients at risk [BTC (309 patients), BTC (non-iCCA) (245 patients), iCCA (64 patients); iCCA (liver-only) (32 patients) and iCCA (non-liver-only) (32 patients)] may not match with the total number of patients included in each group [BTC (328 patients), BTC (non-iCCA) (262 patients), iCCA (66 patients); iCCA (liver-only) (34 patients) and iCCA (non-liver-only) (32 patients)]. Univariate and multivariable Cox Regression results (as per **Supplementary Table 3**; if applicable) are provided: **Figure 1.A** shows OS for all BTC patients. **Figure 1.B** shows comparison between other BTC (non-iCCA) (Reference group) and iCCA. **Figure 1.C** shows comparison between other BTC (non-iCCA) (Reference group) and iCCA (liver-only). **Figure 1.D** shows comparison between iCCA (liver-only) and iCCA (non-liver-only) (Reference group). All statistical tests were two-sided.

uHR: Univariate hazard ratio; aHR: adjusted multivariable hazard ratio; 95%CI: 95% confidence interval; BTC: biliary tract cancer (includes gallbladder, ampulla and cholangiocarcinoma); iCCA: intrahepatic cholangiocarcinoma; m: months.

Figure 2: Potential trial designs for incorporating liver-directed therapy (LDT) to the management pathway of patients with iCCA. Figure includes details regarding percentage of patients potentially eligible for LDT (defined as liver-only disease; calculated using the

whole iCCA population as reference) and expected outcomes with cisplatin/gemcitabine for each potential scenario.

R: randomisation; iCCA: intrahepatic cholangiocarcinoma; LDT: liver-directed therapy; PFS: progression-free survival; OS: overall survival; 95%CI: 95% confidence interval; % percentage.

Figure 1 color

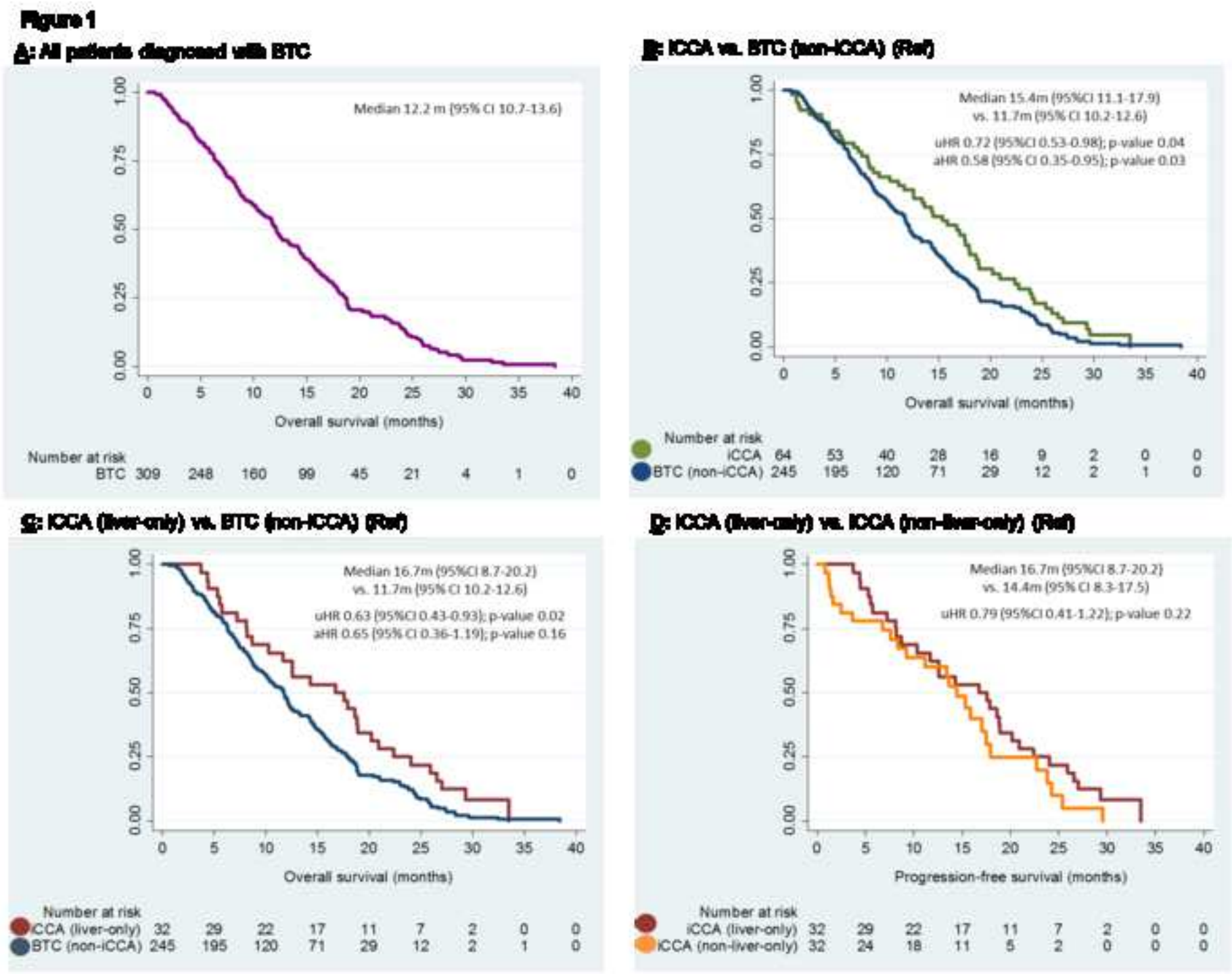

Figure 1 blackandwhite

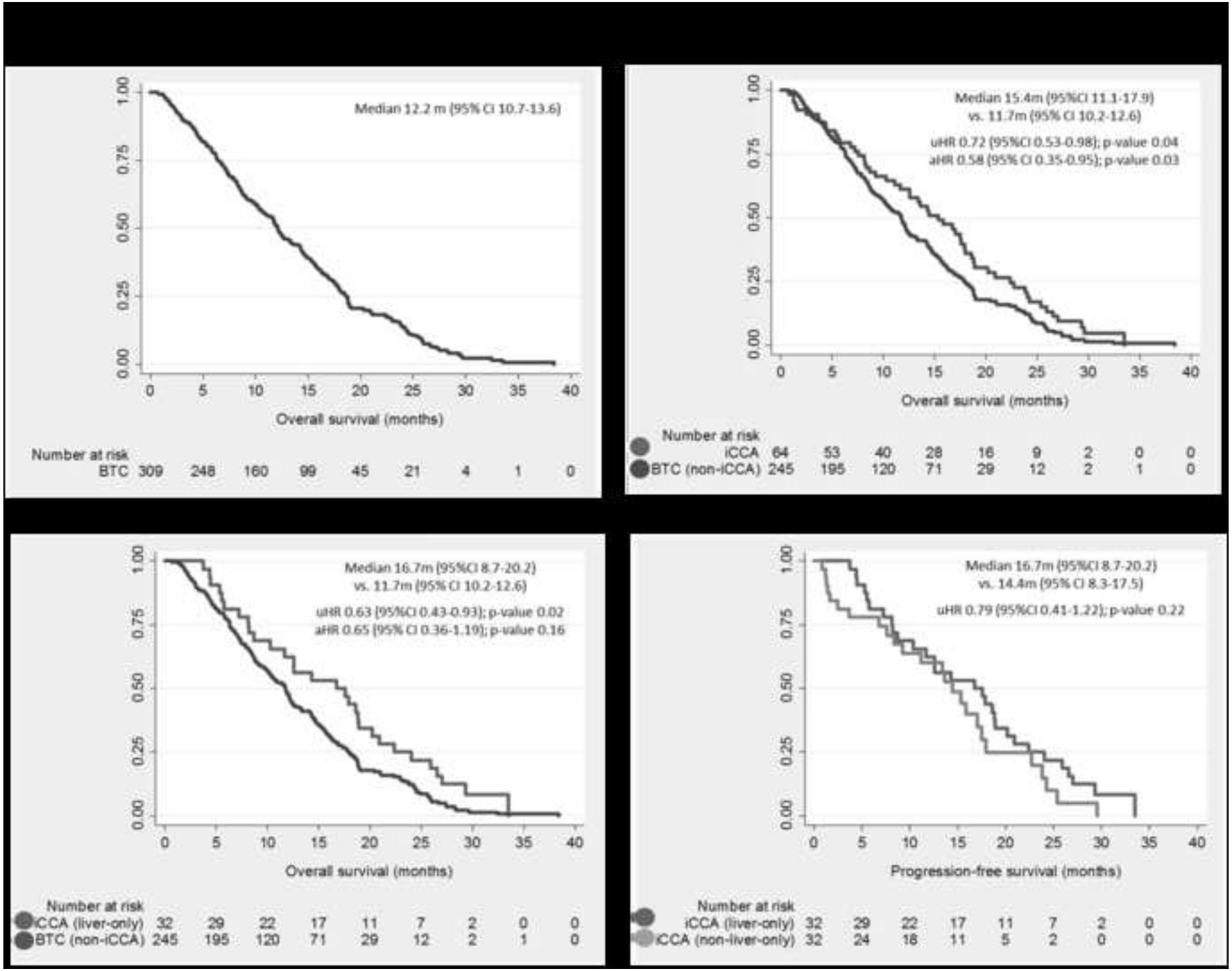

Figure 2 blackandwhite

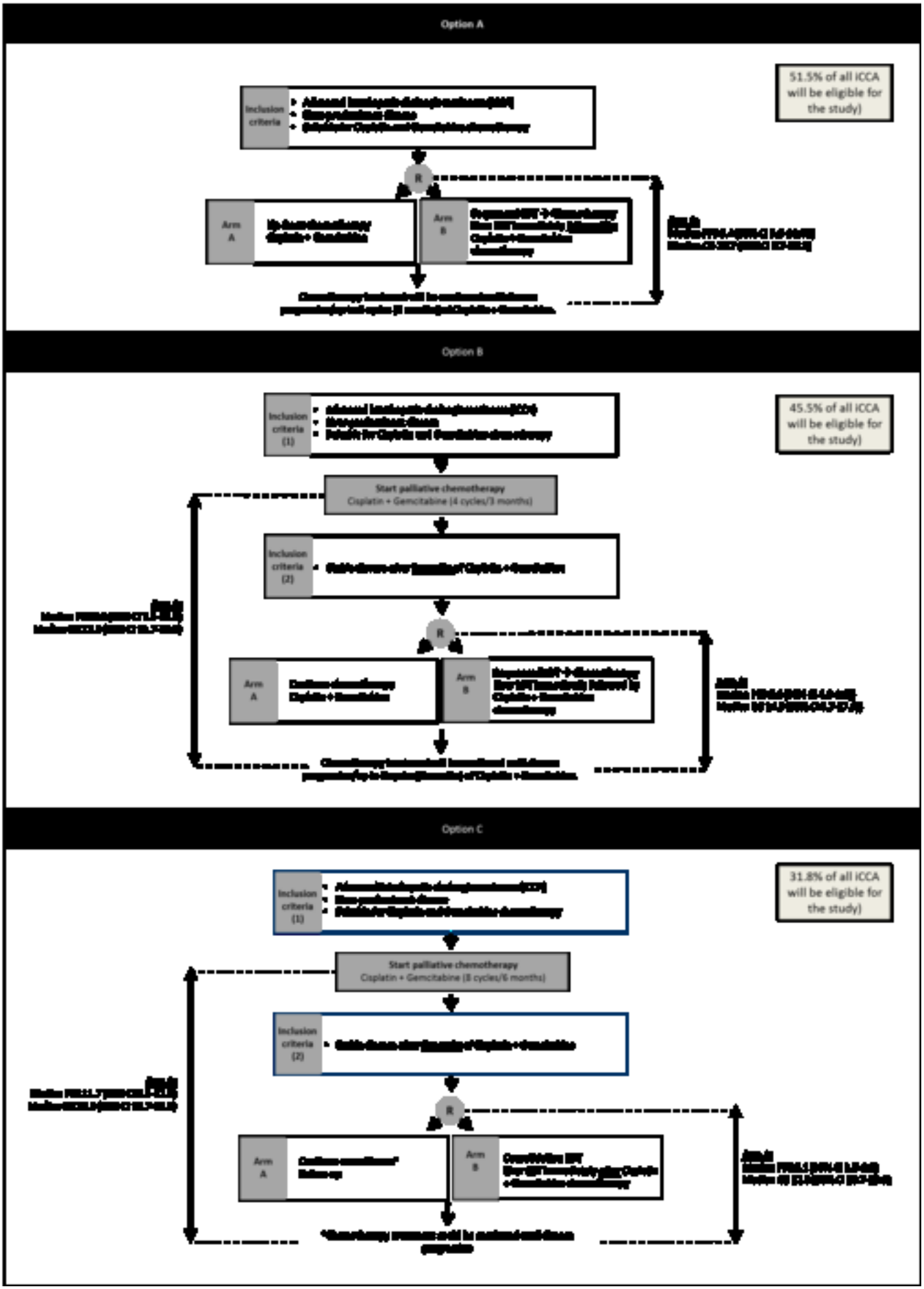

Figure 2 color