original reports

Long-Term Outcomes and Exploratory Analyses of the Randomized Phase III BILCAP Study

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abstract

PURPOSE The BILCAP study described a modest benefit for capecitabine as adjuvant therapy for curatively resected biliary tract cancer (BTC), and capecitabine has become the standard of care. We present the long-term data and novel exploratory subgroup analyses.

METHODS This randomized, controlled, multicenter, phase III study recruited patients age 18 years or older with histologically confirmed cholangiocarcinoma or muscle-invasive gallbladder cancer after resection with curative intent and an Eastern Cooperative Oncology Group performance status of < 2. Patients were randomly assigned 1:1 to receive oral capecitabine (1,250 mg/m^2 twice daily on days 1-14 of a 21-day cycle, for eight cycles) or observation. The primary outcome was overall survival (OS). This study is registered with EudraCT 2005-003318-13.

RESULTS Between March 15, 2006, and December 4, 2014, 447 patients were enrolled; 223 patients with BTC resected with curative intent were randomly assigned to the capecitabine group and 224 to the observation group. At the data cutoff of January 21, 2021, the median follow-up for all patients was 106 months (95% CI, 98 to 108). In the intention-to-treat analysis, the median OS was 49.6 months (95% CI, 35.1 to 59.1) in the capecitabine group compared with 36.1 months (95% CI, 29.7 to 44.2) in the observation group (adjusted hazard ratio 0.84; 95% CI, 0.67 to 1.06). In a protocol-specified sensitivity analysis, adjusting for minimization factors, nodal status, grade, and sex, the OS hazard ratio was 0.74 (95% CI, 0.59 to 0.94). We further describe the prognostic impact of R status, grade, nodal status, and sex.

CONCLUSION This long-term analysis supports the previous analysis, suggesting that capecitabine can improve OS in patients with resected BTC when used as adjuvant chemotherapy after surgery and should be considered as the standard of care.

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INTRODUCTION

Biliary tract cancer (BTC) includes intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma (pCCA), gallbladder cancer, and distal or lower common bile duct cholangiocarcinoma (dCCA) as described in the International Classification of Diseases (ICD) 11th revision/ICD for Oncology, third edition.[1,2] pCCA and dCCA are often also referred to as extrahepatic cholangiocarcinomas. pCCA is associated with liver flukes and iCCA with causes of hepatic insult similar to those for hepatocellular carcinoma, but for most, the etiology is uncertain.[3] The incidence of iCCA is increasing across the western world[4]; however, BTC remains uncommon cancer, often presenting late with a poor outcome.[3] For those 20% of patients presenting with operable disease, the 5-year survival is 25%, and for those with advanced disease, it is $< 5\%$.[3]

The BILCAP study was a randomized phase III study of oral capecitabine chemotherapy compared with observation alone after curative resection of BTC and established capecitabine as the adjuvant standard of care in the context of other negative studies.[5-7] Although negative for the primary end point, the previously presented data were accepted as sufficient to support a recommendation as the standard of care by the oncologic community in the context of the positive per-protocol (PP) analysis, the positive relapse-free survival data, and the supportive sensitivity analyses. We present the prespecified long-term (5-year) survival outcomes for the BILCAP study and novel exploratory analyses.

METHODS

BILCAP was a randomized, controlled, multicenter, phase III study run across 44 centers in the United Kingdom.[5] Patients age 18 years or older with histologically confirmed cholangiocarcinoma or muscle-invasive gallbladder cancer who had a macroscopically complete

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

The BILCAP study was a randomized, multicenter phase III study that established capecitabine as the adjuvant standard of care for patients after curatively resected biliary tract cancer (BTC), originally published in 2019. This publication presents the long-term data, which not only confirm the original findings but also include further exploratory analyses, possible because these data represent the single largest prospectively assembled data set of patients after curatively resected BTC.

Knowledge Generated

These confirm the role of capecitabine as the adjuvant standard of care in curatively resected BTC. In addition, the novel exploratory outcomes that we describe suggest multiple options for future research.

Relevance

Capecitabine remains the adjuvant standard of care after curatively resected BTC and the control arm of future randomized studies.

resection with curative intent were eligible. All patients underwent radical surgical treatment, which included liver resection, pancreatic resection, or, less commonly, both. The Eastern Cooperative Oncology Group performance status (ECOG PS) had to be < 2, and adequate renal, hematologic, and liver function was required. Patients with pancreatic or ampullary cancer, mucosal gallbladder cancer, or unresolved biliary tree obstruction were ineligible. Patients who had not completely recovered from previous surgery or who had previous chemotherapy or radiotherapy for BTC were also excluded. Criteria are described in full in the study Protocol (online only). The anatomic subgroups have been redesignated according to ICD 10th revision as iCCA, pCCA, muscle-invasive gallbladder carcinoma (GBC), and lower common bile dCCA.[1]

Major protocol amendments included extending the start date of chemotherapy from 8 to 12 weeks from the date of definitive surgery on October 16, 2007, a further extension of study eligibility to 16 weeks after surgery on September 2, 2008, and the inclusion of extrahepatic cholangiocarcinoma after the completion of the ESPAC-3 study[6] on August 26, 2008. These recommendations were made by the independent data monitoring committee on the basis of the accumulating events during blinded patient monitoring rather than because of repeated interim analyses.

Random Assignment and Masking

Patients were randomly assigned 1:1 to the capecitabine group or the observation group. Treatment was not masked, and allocation concealment was achieved using a computerized minimization algorithm that stratified patients by surgical center, site of disease, resection status, and performance status. Concealment remained until the interventions were assigned by a central telephone-based random assignment service hosted by the Cancer Research UK Clinical Trials Unit (Birmingham).

Procedures

Oral capecitabine (1,250 mg/m^2) was given postoperatively twice a day on days 1-14 of a 3-weekly cycle for 24 weeks (eight cycles), and observation commenced within 16 weeks of surgery. After random assignment, chemotherapy was started as soon as possible but with a maximum of 16 weeks from surgery. The protocol permitted dose modifications and cycle interruptions. In cases in which the capecitabine dose was reduced, it was not subsequently increased for any reason. In the case of dose interruptions because of toxicity for longer than 2 weeks, the patient was considered to be off treatment. There were no criteria for removal of patients from the study. Patients had the option to withdraw from trial treatment or follow-up at any stage. The criteria for early treatment discontinuation included safety concerns, patient deterioration, and administration of any other cancer treatment during the study treatment period.

All surgery was undertaken in specialist hepatopancreatobiliary centers, mandated in the United Kingdom. The surgical strategy was to achieve complete microscopic clearance of the disease, including liver or pancreatic resection. Patients with < 1 mm clearance were classified as surgical margin-positive (R1) patients. Patients with iCCA underwent hepatectomy, and lymphadenectomy was not mandated for these patients, consistent with surgical practice at the time. In the case of hilar cholangiocarcinoma, patients underwent hepatectomy, including segment 1, along with radical excision of the extrahepatic biliary tree and standard lymphadenectomy. Patients with muscle-invasive gallbladder cancer were treated by cholecystectomy when the gallbladder was in situ and hepatectomy, including the gallbladder bed. Excision of the extrahepatic biliary tree and the extent of lymphadenectomy were dependent on local practice. Biliary tract excision was commonly performed in patients in whom the tumor involved the cystic duct. For tumors in

TABLE 1. Patient Baseline Characteristics by Treatment Arm, for All Full Model Variables, Plus Age

Characteristic	Observation Arm (n = 224)	Capecitabine Arm (n = 223)
Sex		
Male	113 (50)	111 (50)
Age		
Median (interquartile range), years	64 (55-69)	62 (55-68)
Tumor site		
iCCA	41 (18)	43 (19)
pCCA	63 (28)	65 (29)
GBC		
Incidental[a]	20 (9)	22 (10)
de novo[a]	20 (9)	17 (8)
dCCA	80 (36)	76 (34)
Resection status		
R0	140 (63)	139 (62)
R1	84 (38)	84 (38)
ECOG PS		
0	101 (45)	100 (45)
1	116 (52)	116 (52)
2	7 (3)	7 (3)
Lymph node status		
Negative	121 (54)	115 (52)
Positive	102 (46)	108 (48)
Missing	1 (< 1)	0
Disease grade		
Well	36 (16)	34 (15)
Moderate	120 (54)	110 (49)
Poor	56 (25)	64 (29)
Not known	12 (5)	15 (7)
Missing	1 (< 1)	0

NOTE. Values shown are No. (%) for categorical data and median (interquartile range) for continuous measures.

Abbreviations: dCCA, duct cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder carcinoma; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma.

[a]Incidental is a GBC found in histology after a routine cholecystectomy, and de novo is presentation with a GBC by symptoms and/or imaging.

the lower common bile duct, patients underwent pancreaticoduodenectomy (Whipple's procedure) with excision of the extrahepatic biliary tree and a standard lymphadenectomy.

Computed tomography scans were performed every 3 months in year 1, every 6 months in year 2, and annually thereafter up to 5 years. Full blood count, biochemistry, and liver function tests were performed at baseline, at the beginning of each treatment cycle for the capecitabine group, and every 3 months in year 1 and every 6 months in year 2 for all patients. Follow-up treatment for patients who had disease recurrence was not recorded. Toxicity, quality of life, and cost economic evaluation have been previously described.[5] This trial was run by the Cancer Research UK Clinical Trials Unit, University of Birmingham (United Kingdom), under the auspices of the UK National Cancer Research Institute Upper Gastrointestinal Cancer Studies Group and sponsored by the University of Southampton (United Kingdom). This trial was approved by the West Midlands Multi-Centre Research Ethics Committee (05/MRE07/62), and all necessary regulatory approvals were obtained. All patients were required to give written informed consent, and the trial was conducted in accordance with the Declaration of Helsinki and reported according to CONSORT guidelines.

Outcomes

The primary outcome was overall survival (OS), defined as the time from random assignment until the date of death or last date of follow-up for surviving patients. Prespecified secondary outcomes included a PP analysis of outcomes, recurrence-free survival (RFS), toxicity (not described here), health economics (not described here), and quality of life (not described here). RFS was defined as the time from random assignment until the date of disease recurrence, death from disease, or date of last follow-up.

Statistical Analysis

Details of the statistical analysis were reported previously, and the final analysis, as specified in the Statistical Analysis Plan (SAP; Protocol addendum, online only). Long-term follow-up results reported here replicate the analyses used in the initial report. Primary analyses prespecified by protocol were by intention to treat, including all randomly assigned patients. Analyses were also performed by PP, excluding ineligible patients and those failing to complete at least one cycle of capecitabine, as specified in the SAP. We quantified OS and RFS differences as hazard ratios (HRs) with 95% CIs estimated using Cox proportional hazards models with adjustment for minimization factors. As in the previously reported analysis, we did not adjust by surgical centers because of the number of participating centers (n = 44) leading to flat statistical modeling regions.

We also update the prespecified sensitivity analyses of OS in the intention-to-treat population, adjusting for the same prognostic factors as in the previous analysis. Subgroup analysis used Cox models including the minimization factors such as primary tumor site, resection status, and ECOG PS, with heterogeneity tested via interaction terms.

Reporting of the local and distant recurrence rates was descriptive with no hypothesis testing undertaken. Where appropriate (specifically plots with only two arms), we have followed the Kaplan-Meier plot guidelines previously outlined.[9] Analysis was conducted using Stata 17 software. Full final analysis results were reported previously, as specified in the SAP, and these long-term follow-up results

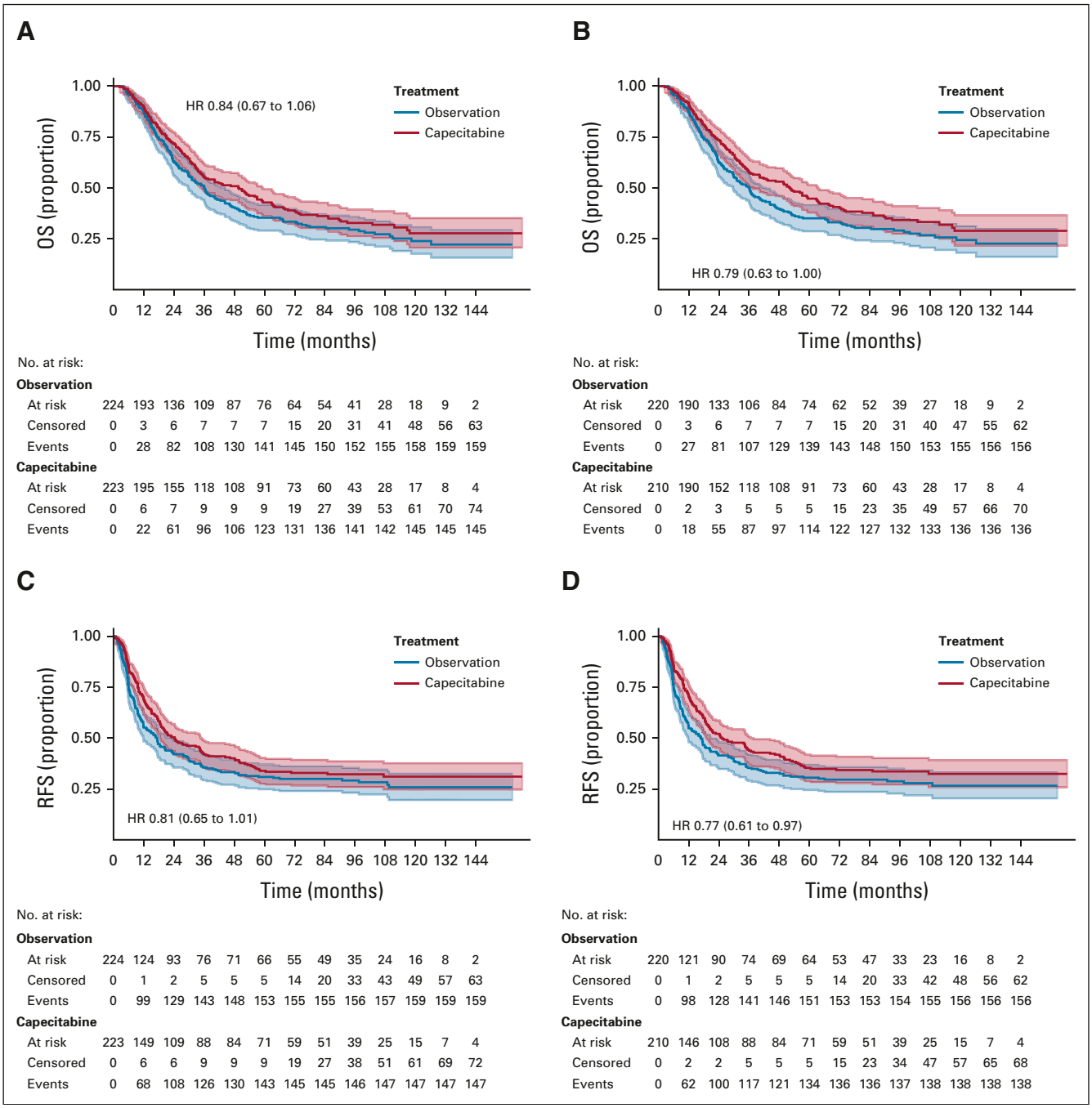

FIG 1. (A) Kaplan-Meier OS curves for ITT population, (B) OS for PP population, (C) RFS for ITT, and (D) RFS for PP. HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PP, per-protocol; RFS, relapse-free survival.

replicate the analyses used in the previously reported results.

Role of the Funding Source

The funder of the study had an advisory role in study design but no role in the running of the study, data collection, data analysis, data interpretation, or writing of the report. Upon completion of patient follow-up, J.P., P.F., and J.B. had full access to all the data and the corresponding authors had final responsibility for the decision to submit for publication. An educational grant was awarded for translational study purposes by F. Hoffmann-La Roche AG who had no input into the study conduct.

RESULTS

Between March 15, 2006, and December 4, 2014, 447 patients (intention-to-treat population) were enrolled and randomly assigned to the capecitabine group (n = 223) or

TABLE 2. Overall Survival, Intention-to-Treat Population

Characteristic	Adjusted HR (95% CI)
Treatment	
Capecitabine	0.74 (0.59 to 0.94)
Site	
dCCA	0.88 (0.67 to 1.18)
iCCA	1.12 (0.79 to 1.60)
GBC	0.88 (0.60 to 1.30)
Resection status	
R1	1.60 (1.25 to 2.04)
ECOG PS	
PS 1	1.09 (0.86 to 1.38)
PS 2	1.28 (0.67 to 2.46)
Sex	
Female	0.78 (0.61 to 0.99)
Nodes	
Positive	2.22 (1.74 to 2.85)
Differentiation grade	
Moderate	1.32 (0.93 to 1.88)
Poor	1.90 (1.30 to 2.78)
Not known	1.34 (0.73 to 2.46)

NOTE. pCCA is the reference category for site, that is, the HR for the other three sites is compared with pCCA. Similarly, R0 is the reference category for R status and PS0 is the reference category for PS. Capecitabine is compared with observation. Male is the reference category for sex, negative for nodes, and well differentiated is the reference category for grade. n = 447, with 304 events.

Abbreviations: dCCA, duct cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder carcinoma; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma.

the observation group (n = 224; Appendix Fig A1, online only). The PP population comprised 430 patients (210 in the capecitabine group and 220 in the observation group) after the exclusion of 17 patients, comprising seven (2%) patients (three in the capecitabine group and four in the observation group) who were found to be ineligible after random assignment, nine (2%) patients who did not receive capecitabine, and one (< 1%) patient was ineligible and also received no drug. Baseline characteristics were well balanced between the two groups (Table 1).

At the time of this long-term follow-up analysis (January 21, 2021), the median follow-up was 106 (95% CI, 98 to 108) months. One hundred forty-five (65%) patients had died in the capecitabine group, and 159 (71%) patients had died in the observation group. Of these deaths, 272 (89%) were related to BTC (129 in the capecitabine group and 143 in the observation group), 12 (4%) were from other causes (six in each group), and 20 (7%) were due to unknown reasons or were missing (10 in each group).

In the intention-to-treat analysis, the median OS was 49.6 (35.1 to 59.1) months for capecitabine and 36.1 (29.7 to 44.2) months in the observation group (Fig 1A). The HR for death of capecitabine versus control was 0.84 (0.67 to 1.06), adjusted for the stratification factors resection status, performance status, and site of disease. In the PP analysis (Fig 1B), the median OS was 52.3 (36.5 to 63.3) months for capecitabine and 36.1 (29.6 to 42.5) months for observation, with an HR of 0.79 (0.63 to 1.00), adjusted for the minimization factors as for the intention-to-treat analysis.

In the intention-to-treat analysis, the median RFS was 24.3 (18.6 to 34.6) months for capecitabine and 17.4 (11.8 to 23.0) months for surveillance (Fig 1C), with a HR of 0.81 (0.65 to 1.01), adjusted for resection status, performance status, and site of disease. In the PP analysis, the median RFS was 25.3 (18.9 to 36.7) months for capecitabine and 16.8 (11.8 to 20.7) months for surveillance (Fig 1D), with a HR of 0.77 (0.61 to 0.97), adjusted for resection status, performance status, and site of disease. As previously reported, the relative difference in risk between treatment groups differed over time, and hence, again, Cox models with time-varying effects were fitted. The adjusted RFS HR was 0.74 (0.57 to 0.96) in the first 24 months from random assignment, with insufficient evidence of a difference from 24 months onward: HR 1.47 (0.86 to 2.52). In the PP analysis, the adjusted RFS HR in the first 24 months was 0.69 (0.53 to 0.90), and again, there was insufficient evidence of a difference after 24 months: HR 1.57 (0.90 to 2.74).

The 5-year RFS proportion for the intention-to-treat population was 34% (28 to 40) for capecitabine and 31% (25 to 37) for observation. Three hundred six (68%) of 447 patients had disease recurrence (or death from disease), of whom 147 (66%) were in the capecitabine group and 159 (71%) in the observation group. Of these 306 patients, 10 first experienced recurrence (or death from disease) over 5 years from random assignment. The highest risk of recurrence appears to be at 24 months for both capecitabine and surveillance groups (Appendix Fig A2, online only).

Planned sensitivity analyses in the intention-to-treat population explored the effect of identified prognostic factors (nodal status, grade of disease, and sex, in addition to the minimization variables site of disease, resection status, and ECOG PS). Adjusting for these prognostic factors resulted in an OS HR for capecitabine of 0.74 (0.59 to 0.94; Table 2, Fig 2). We observed a significantly poorer survival in the R1 population compared with R0: HR 1.60 (1.25 to 2.04), positive node status compared with negative: HR 2.22 (1.74 to 2.85), poorly differentiated tumors compared with well-differentiated: HR 1.90 (1.30 to 2.78), and better survival in female compared with male: HR 0.78 (0.61 to 0.99). There was no evidence that either site of disease (Fig 3) or ECOG PS was associated with differential survival

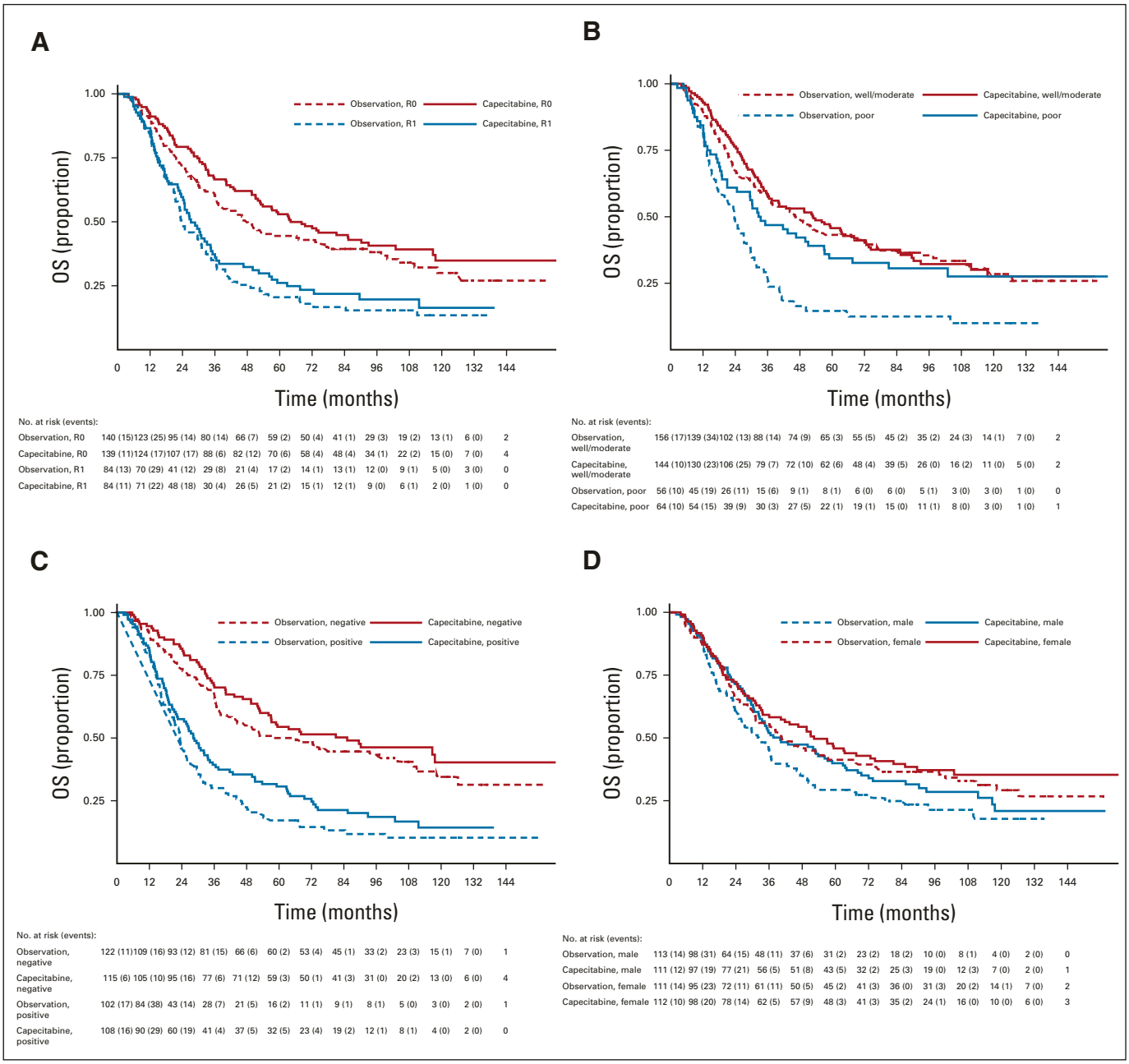

FIG 2. OS in the ITT population by treatment and (A) resection status, (B) tumor grade, (C) node status, and (D) sex. ITT, intention-to-treat; OS, overall survival; R, resection.

(Table 2). RFS by disease site is also reported using Kaplan-Meier plots in Appendix Fig A3, online only).

Subgroup analysis was checked for evidence of a differential treatment effect in some groups and was reported extensively previously. Visually, it appears that poorly differentiated tumors and male sex are associated with a greater benefit of treatment (Figs 2B and 2D respectively); however, testing this by modeling interactions indicated no statistical evidence of heterogeneity.

The presence or absence of local and distant recurrence by treatment and resection status was explored, and the descriptive results are reported in Table 3. In the observation arm, R1 resections are more likely to have a local recurrence alone (24 of 84, 29%) compared with R0 resections (27 of 140, 19%, Table 3). Capecitabine did not appear to have any impact on the local recurrence rate for either R0 (26 of 139 [19%]) or R1 (25 of 84 [30%]) resections.

DISCUSSION

These long-term data confirm the benefit of capecitabine as adjuvant therapy after surgical resection of BTC, which is

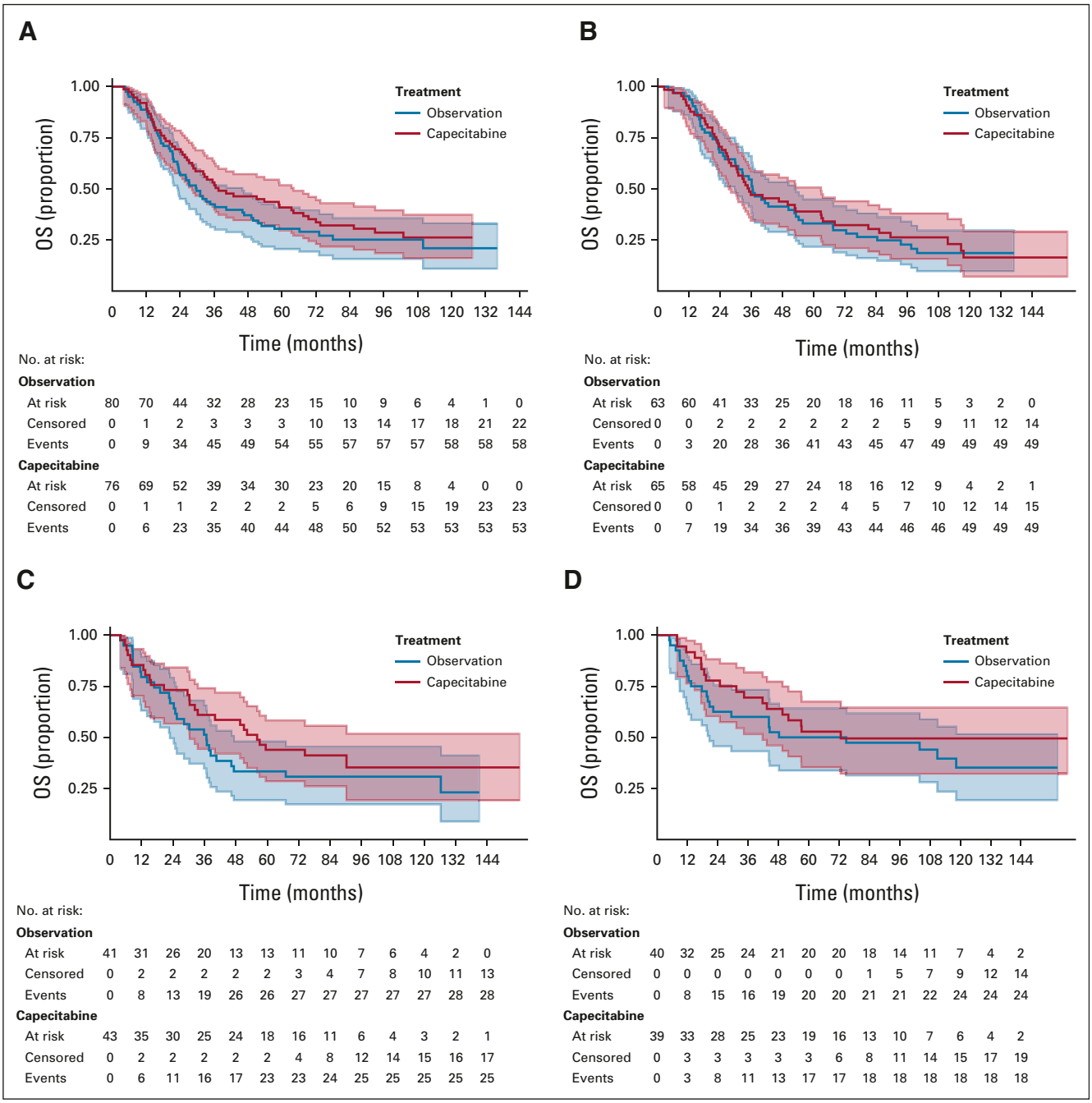

FIG 3. OS in the intention-to-treat population by (A) dCCA, (B) pCCA, (C) iCCA, and (D GBC. dCCA, duct cholangiocarcinoma; GBC, gallbladder carcinoma; iCCA, intrahepatic cholangiocarcinoma; OS, overall survival; pCCA, perihilar cholangiocarcinoma.

now recommended by ASCO guidelines.[9] The results support the view that the benefit, although clinically meaningful, is modest and patients and investigators are encouraged to participate in adjuvant studies aimed at improving outcomes further (eg, the international ACTICCA-01 study [ClinicalTrials.gov identifier: NCT02170090][10]), which compares capecitabine with the ABC-02 regimen of cisplatin and gemcitabine.[11] The results of the ASCOT study in which patients are randomly assigned to receive S-1 compared with surveillance are also anticipated.[12] These studies will increase the knowledge base of the use of adjuvant fluoropyrimidine in BTC and provide valuable material for translational analyses.

BILCAP is the largest prospective randomized data set in this setting, and the control arm offers insights into the natural history of BTC after resection. These data suggest

TABLE 3. No. of Patients With Local or Distant Recurrence, by Treatment Arm and Resection Status

Resection Status	Capecitabine, No. (%)	Observation, No. (%)	Overall, No. (%)
R0 resections			
Local	26 (19)	27 (19)	53 (19)
Distant	30 (22)	31 (22)	61 (22)
Local and distant	19 (14)	21 (15)	40 (14)
Neither	64 (46)	61 (44)	125 (45)
Total	139	140	279
R1 resections			
Local	25 (30)	24 (29)	49 (29)
Distant	22 (26)	28 (33)	50 (30)
Local and distant	17 (20)	17 (20)	34 (20)
Neither	20 (24)	15 (18)	35 (21)
Total	84	84	168

that local recurrence remains a significant issue for up to 50% of all patients after resection, whether the resection is classified as R1, although local recurrence occurs more frequently in patients in R1. The frequency of local recurrence suggests the need to develop novel therapeutic strategies, accepting that more extensive surgery is seldom possible even in the context of expert centers. Neoadjuvant approaches or local therapies such as stereotactic radiotherapy warrant investigation. R1 itself is demonstrated to be a negative prognostic factor as are lymph node involvement, poor differentiation of tumors, and male sex. We did not observe any meaningful difference in treatment benefit in subgroups, including nodal status, resection status, or primary disease site. There was some indication that poorly differentiated tumors and male sex were associated with higher treatment benefits, but the evidence was weak and formal statistical testing did not lead to any definitive results. However, as the study was not powered to detect effects in subgroups, more research is recommended. We conclude that capecitabine remains effective and beneficial in this population regardless of subgroup classification.

These data suggest that capecitabine appears to have little impact on local recurrence or local and distant recurrence for both R1 resections and R0 resections. The main benefit from capecitabine appears to be in the timing of recurrence, with patients on capecitabine experiencing recurrence on average later than those on observation and hence giving an OS advantage in terms of both RFS and OS, particularly in the first 2 years postrandomization.

The BILCAP trial included all anatomic subgroups of cholangiocarcinoma (and gallbladder cancer) accepting that they have clinical and molecular differences.[13] This was a pragmatic approach that made the trial feasible to perform. This does give the opportunity to compare the outcome for different anatomic sites after surgery, with and without capecitabine. The OS curves for the four disease sites (Fig 2) are similar with overlapping 95% CIs although numerically patients with GBC appear to have a survival advantage. This may, however, be influenced by the number of patients with incidental GBC (Table 1) in this subgroup. The survival analysis expressed in HRs shown in Table 2 and corrected for other factors gives a more useful description. In this model, patients with iCCA have a numerically worse outlook compared with the comparator (pCCA) and those with dCCA or GBC. However, there is no clear or statistically significant difference between the disease sites and the trial is not adequately powered to show such.

The recent advances in the management of advanced BTC have been in the targeted therapy of actionable alterations including FGFR, IDH1, and BRAF, among others.[14-16] Understanding the absolute benefit of targeted agents has been hampered by the limited knowledge of the natural history of each subgroup and whether the targeted alterations are also prognostic and predictive. The molecular description of the BILCAP study (currently underway) may provide further insights into the biology of individual subgroups and other prognostic variables such as the R status. Even in this large study, the analysis will be limited by the number of patients in each subgroup emphasizing the importance of cross-study collaboration.

The follow-up of patients after potentially curative resection of a BTC has hitherto been somewhat arbitrary, based mostly on local preference and resource. The long-term BILCAP data suggest a pattern of recurrence that will inform a follow-up program. The possibility of recurrence is still present even at 5 years, and recurrence occasionally develops thereafter. This suggests that follow-up with appropriate imaging should continue at least until 5 years. Although the benefit of imaging over symptomatic surveillance is unlikely ever to be formally demonstrated, the establishment of first- and second-line standard-of-care chemotherapy[11,17] and the potential of benefit from targeted therapies in selected subgroups[14-16] would argue for active rather than symptomatic surveillance.

In summary, the benefit of adjuvant capecitabine after curative resection of BTCs has been maintained with a longer-term analysis of the data. The need to continue clinical trial activity, in particular, the continuous collection of material for translational analysis, is critical.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

All data from our study will be made available to any other by request to the corresponding authors. There is no time limit, and there are no supporting documents.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Long-Term Outcomes and Exploratory Analyses of the Randomized Phase III BILCAP Study

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No other potential conflicts of interest were reported.

APPENDIX 1.

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APPENDIX 2.

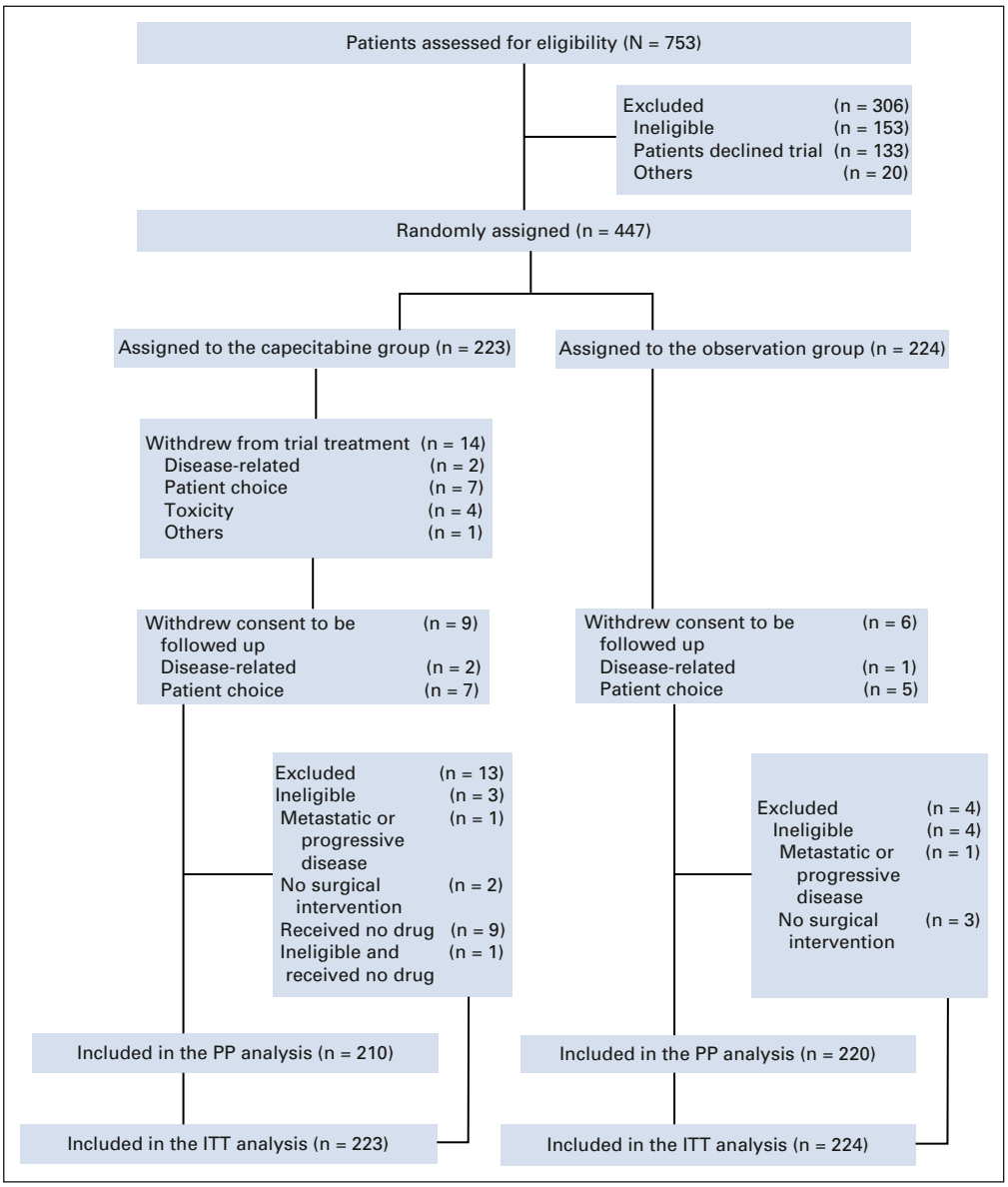

FIG A1. CONSORT diagram. ITT, intention-to-treat; PP, per-protocol.

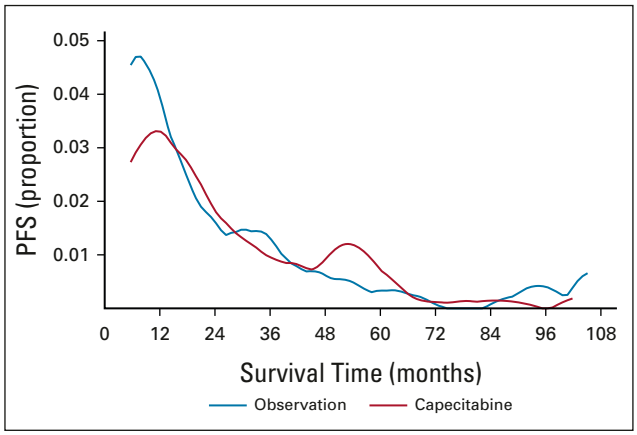

FIG A2. Risk of recurrence by time (hazard plot). RFS, relapse-free survival.

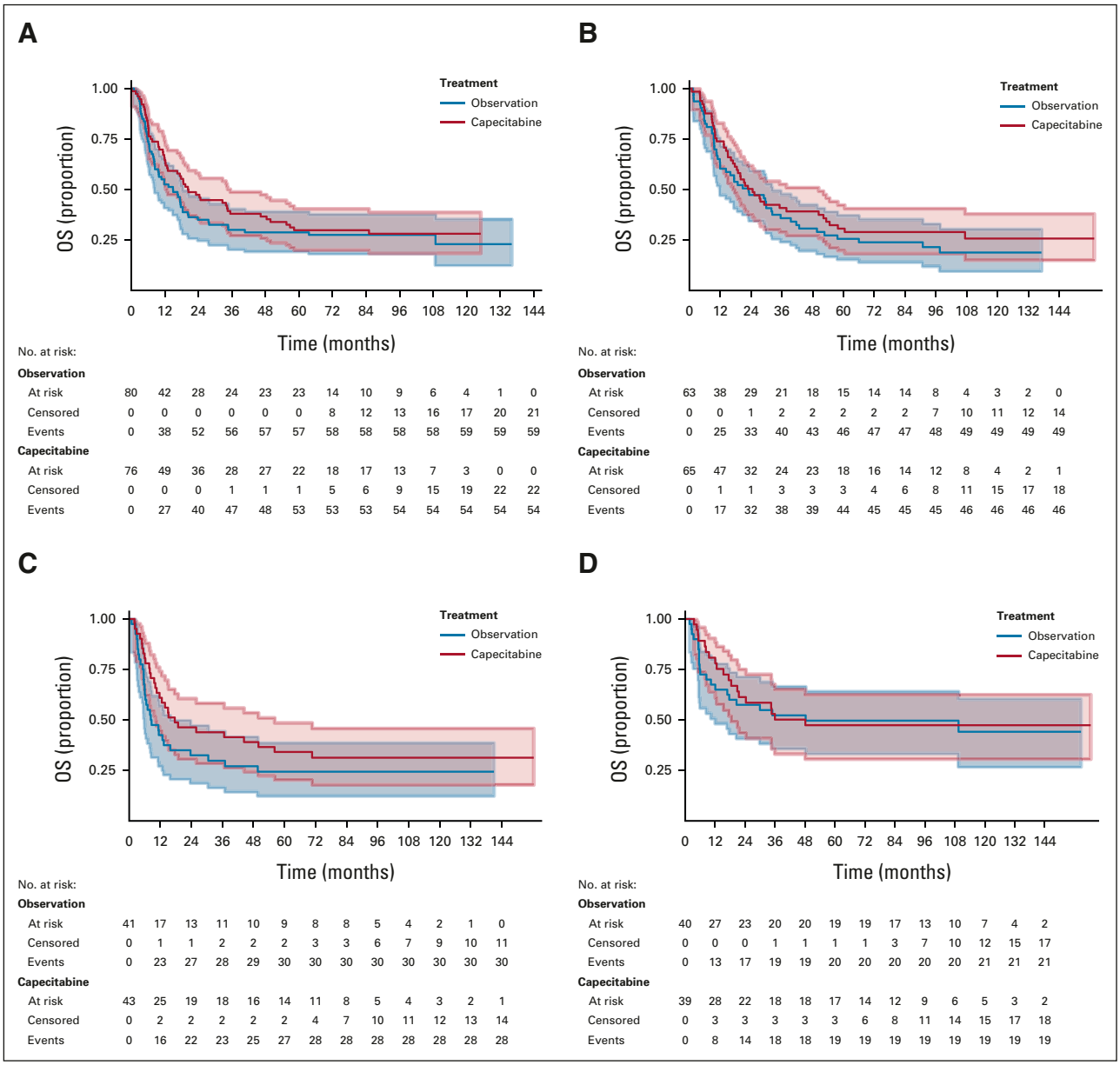

FIG A3. RFS by (A) dCCA, (B) pCCA, (C) iCCA, and (D) GBC. dCCA, duct cholangiocarcinoma; GBC, gallbladder carcinoma; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; RFS, relapse-free survival.