ABC-07 Trial Summary

Title:	Addition of stereotactic body radiotherapy (SBRT) to systemic chemotherapy in locally advanced biliary tract cancers
Short Title/acronym:	ABC-07
EUDRACT no:	2014-003656-31
Sponsor name & reference:	University College London; UCL 14/0174
Funder name & reference:	Cancer Research UK; A18752
Design:	Multicentre phase II study (with a feasibility stage) with 2:1 randomisation between cisplatin and gemcitabine (CisGem) chemotherapy + SBRT and CisGem chemotherapy alone, respectively
Overall aim:	**Feasibility:** The overall aim of the feasibility component of the trial is to determine if it is feasible to deliver SBRT in a multicentre trial setting in a rare disease. In particular, will clinicians recruit to the trial and will sufficient patients accept randomisation. If the feasibility component proves successful, the trial would continue into the full phase II trial. **Phase II:** The overall aim of the phase II trial is to evaluate the efficacy of 6 of cycles of CisGem chemotherapy followed by SBRT compared to 8 cycles of CisGem.
Target accrual:	**Feasibility:** Approximately 18 patients with locally advanced inoperable cholangiocarcinoma. **Phase II:** 81 patients with locally advanced inoperable cholangiocarcinoma, which will include the patients recruited in the feasibility stage.
Primary endpoint:	**Feasibility:** An average recruitment rate of at least 1 patient per month once 6 sites have been activated. **Phase II:** To evaluate the relative merits of adding SBRT to CisGem chemotherapy in terms of progression free survival.
Secondary endpoints:	**Feasibility & Phase II:** • Progression free survival at 9 months after randomisation • Worst grade of AE (CTCAE v4.03) • Best overall response rate (according to RECIST v1.1 criteria) • Progression free survival • Duration of response • Overall survival • Patterns of treatment failure • Time to treatment failure • Achieving downstaging facilitating surgery • Quality of Life (EQ 5D and EORTC QLQ- BIL21)

Inclusion & exclusion criteria:	The main inclusion criteria are: • A histopathological/cytological diagnosis of locally advanced, non-resectable biliary tract carcinoma (intra- or extra-hepatic), (excluding cancer of the gall bladder and ampullary carcinoma) • Not suitable for radical surgery, or medically unfit for surgery as decided by a hepatobiliary MDT Measurable disease (according to RECIST criteria v1.1). (If disease is not measurable using RECISTv1.1, tumour must be visible for targeting with radiation). • Tumour (and nodes if involved) visible on cross-sectional imaging ≤12 cm in the longest dimension. For patients with non-measurable disease, sites should use the CT reconstructions (coronal or sagittal views) to measure tumour size. • Adequate biliary drainage • WHO PS 0 or 1 • Adequate bone marrow, renal & liver function • Life expectancy >12 weeks • 16 years or over • Patient consent The main exclusion criteria are: • Metastatic disease • Direct tumour extension in the duodenum, stomach, small bowel or large bowel • Previous abdominal radiotherapy or previous selective internal radiotherapy such as hepatic arterial Yttrium therapy • Previous hypersensitivity to platinum salts • Uncontrolled systemic disease (diabetes with established sensory peripheral neuropathy) • Other/prior malignancy or intercurrent disease precluding trial entry • Other concomitant anti-cancer therapy (except steroids) • Pregnancy/breast-feeding
Planned number of sites:	Approximately 18 sites (to include SBRT sites and recruiting sites) within the UK
Treatment summary	All patients will be **registered** to receive 6 cycles of chemotherapy consisting of cisplatin 25 mg/m^2 plus gemcitabine 1000 mg/m^2 on days 1 and 8 of a 21-day cycle. Patients will then be **randomised** to receive either: **Investigational arm:** 5 or 15 fractions of SBRT given over 5-21 days (number of fractions and duration of therapy depends on the size of the tumour as measured on the end of cycle 4 imaging scan). SBRT should start not more than 6 weeks after day 1 of cycle 6, and not less than 2 weeks after the last dose of CisGem chemotherapy. Or **Standard arm:** 2 further cycles of CisGem (8 cycles in total)

Anticipated duration of recruitment:	**Feasibility:** 18 months **Phase II:** Up to 6 years (including feasibility)
Duration of patient follow up:	Patients will be followed up 3-monthly until disease progression or for up to two years after registration. Following progression patients will be followed up as per standard practice and survival data will be collected.
Exploratory research:	The following types of samples will be collected and stored for future research: • Archival paraffin-embedded tissue • Whole blood for ctDNA • Whole blood for germline DNA • Serum samples (optional for trial sites)
Radiotherapy Quality Assurance	Quality Assurance will be conducted by the National RTTQA group. Pre-trial QA will involve a radiotherapy specific protocol and a pre-trial test case will be delineated by all participating investigators and planned by the corresponding RT department – feedback will be provided on the delineated volumes and plan prior to patients being entered into the trial. In addition, this study requires a rapid review of segmented GTV and normal tissue and radiotherapy plans PRIOR to delivery of radiation treatment for at least the first 3 patients to be treated in each SBRT site, including at least one patient with a tumour ≤6cm and at least one patient with a tumour >6cm.
Central imaging Quality Assurance	Central review of CT images (and additional imaging if required) will be performed for 100% of patients from each centre, to exclude patients who have not been randomised. Images from registration up until 6 month follow up would be reviewed. The following sets of scan images (CT, and MRI if available) should be pseudonymised and sent for central assessment to confirm disease status: baseline (pre-registration), end of cycle 4, completion of treatment, 3 and 6 month follow-up and confirmation of disease progression scan (if applicable).