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Clinical Trial

Gemcitabine plus cisplatin versus chemoradiotherapy in locally advanced biliary tract cancer: Fédération Francophone de Cancérologie Digestive 9902 phase II randomised study ☆

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KEYWORDS
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Gemcitabine
Oxaliplatin
Biliary tract cancer

Abstract ***Background:*** Chemoradiotherapy (CHRT) is often advocated for locally-advanced biliary tract cancer (LABTC). However there was not comparative study with chemotherapy alone (CH).
Patients and methods: Patients with hilar or extrahepatic non-metastatic, LABTC could be included in this phase II trial. The inclusion criteria required World Health Organisation (WHO) performance status $\leqslant 2$, bilirubinemia $\leqslant 50$ μM/L after biliary drainage if necessary, and possibility of external radiotherapy. Fluorouracil (5 FU) infusion and cisplatin, were given in association to radiotherapy (50 Gy) in the CHRT arm. Gemcitabine + oxaliplatin (GEMOX) was planned for 6 months in the CH arm. End-points were progression-free survival (PFS), overall survival (OS), toxicity and rate of biliary complications.
Results: The trial was closed before completion due to slow recruitment. Eighteen and 16 patients were included in the CHRT and CH arms, respectively. Median follow up was 27.9 months (±2.8). Grade III–IV toxicities were mostly haematological (23% and 25%), and gastrointestinal (11% and 6%), in the CHRT and CH arm, respectively. Biliary complications occurred in 28% of patients in the CHRT arm and 44% of patients in the CH arm (risk ratio (RR): 1.60 [0.65–3.92]). Median PFS was 5.8 months in the CHRT group and 11.0 months in the CH group (hazard ratio (HR): 0.65 [0.32–1.33]). Median OS was 13.5 months in the CHRT group and 19.9 months in the CH group (HR: 0.69 [0.31–1.55]).
Conclusions: Combination of gemcitabine plus cisplatin seems to be at least as efficient as chemoradiotherapy (50 Gy plus 5 FU and cisplatin) in LABTC.

1. Introduction

Biliary tract cancer accounts for 3% of digestive cancers with approximately 2000 new cases a year in France [1]. A population-based study on intra- and extra-hepatic biliary tract cancer (except ampulla of Vater and gallbladder) conducted in two areas in Burgundy (France) showed a non-significant change in incidence over a 30-year period (1976–2005), 1.4 and 0.7/100,000 in men and women, respectively [2]. Surgery is the only curative treatment. The proportion of patients undergoing resection for cure increased over the 30-year period from 4.8% to 14.2% ($p < 0.001$). However, most patients have an unresectable or metastatic tumour and prognosis is worse with an overall 5-year relative survival rate of 6.8%. Until recently, there was no standard chemotherapy for the treatment of unresectable or metastatic biliary tract cancer and gemcitabine was often given because it is used in pancreatic cancer. In 2010 a phase III trial on advanced or metastatic biliary tract cancer showed better overall survival with gemcitabine and cisplatin than with gemcitabine alone [3].

The role of radiotherapy or chemoradiotherapy (CHRT) remains unclear in the treatment of locally-advanced, but non-metastatic biliary tract cancer (LABTC) [4]. Radiotherapy or chemoradiotherapy has been considered a possible option according to non-randomised studies [5–11], even though no standard has emerged. No randomised trial had compared chemoradiotherapy to chemotherapy alone. The Fédération Francophone de Cancérologie Digestive (FFCD) therefore designed a randomised trial in 1999. In the absence of an established regimen, cisplatin and protracted fluorouracil were selected as radiosensitisers in the CHRT arm. The association of gemcitabine and oxaliplatin was recommended in France in 1999 and was used as the control arm. This randomised study is the first attempt to compare efficacy and safety of chemoradiotherapy and chemotherapy in LABTC.

2. Patients and methods

2.1. Procedures

This study was an open, multicentre, randomised, controlled phase II trial. After obtaining informed consent, eligible patients were randomised at the 'Federation Francophone de Cancérologie Digestive (FFCD)' data centre. Randomisation was stratified using minimisation techniques according to centre, World Health Organisation (WHO) performance status (PS 0–1 versus 2, tumour location (gallbladder, intra-hepatic and/or hilar, and extra-hepatic) and initial biliary tract drainage (performed versus not performed). The protocol was reviewed and approved by the Ethics Review Committee of Burgundy (Dijon, France) and registered at Clinicaltrials.gov, number NCT00304135.

2.2. Patients

All patients provided written informed consent before inclusion in the trial. Patients were eligible if they were

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18 years old or older, and had a histopathological or cytological diagnosis of biliary tract carcinoma. Intra-hepatic or extra-hepatic, or gallbladder cancers could be included provided non-metastatic on standard computerised tomography (CT)-scan. When the histopathological report was not contributory, inclusion was accepted in cases of biliary stenosis with a tumour mass >1 cm on abdominal spiral computed tomography and no recent medical history of biliary surgery, hydatid cyst, alveolar echinococcosis or intra-arterial hepatic chemotherapy. Other inclusion criteria were WHO performance status 0–2, adequate haematologic parameters (haemoglobin >10 g/100 ml, neutrophils $\geqslant 1500/mm^3$, platelets $\geqslant 75{,}000/mm^3$), total bilirubin blood concentration less than 50 μmol/L (with or without biliary drainage) and a glomerular filtration rate (creatinine clearance) of 60 ml per minute or higher. The main exclusion criteria were adenocarcinoma from the ampulla of Vater or from the glandular pancreas with infiltration of the biliary tract, previous chemotherapy or radiotherapy, previous malignant disease (except basal cell carcinoma or in situ carcinoma of the cervix), and pregnancy.

2.3. Treatment

In the CHRT arm, external beam conformal radiotherapy delivered a dose of 50 Gy in 25 fractions, prescribed at the International Commission on Radiation Units point, using 10–25 MV X-rays. All fields were treated each day, 5 days a week. The target volumes and normal tissues were delineated on a CT scan performed in treatment position. Intravenous contrast and <1 cm thick slices were required. MRI (magnetic resonance imaging) and cholangiography findings were also used for delineation. The clinical target volume included the macroscopic tumour volume, lymph nodes from the hilar, pedicular and coeliac areas, with a safety margin of 2 cm in all directions taking into account organ motion and daily variation in patient positioning in order to create the planning target volume. Respiratory gating could be used in order to decrease the internal margin. Each treatment plan was evaluated with a cumulative Dose Volume Histogram, in order to respect PTV (Planning Target Volume) coverage and dose constraints to normal tissues and minimise liver irradiation. The concurrent chemotherapy was fluorouracil (5 FU, 300 mg/m^2 per day) by continuous infusion, 5 days a week, for 5 weeks and cisplatin, 20 mg/m^2 per day from day 1 to 4 and from day 29 to 32 (cisplatin 80 mg/m^2 at day 1 or 2 and day 29 or 30 was accepted). Prophylactic medication consisted of hydration (1 L over 2 h before and after cisplatin). An antiemetic medication by Setron was recommended. Adjuvant chemotherapy was not allowed after completion of CHRT.

In the CH arm, treatment was IV gemcitabine, 1000 mg/m^2 over 100 min on day 1 and IV oxaliplatin, 100 mg/m^2 over 2 h, starting 1 h after the end of the gemcitabine infusion (GEMOX). An antiemetic medication by Setron was recommended. The treatment was repeated every 14 days and continued for 12 cycles over 6 months or until disease progression, unacceptable toxicity, or patient refusal. In the event of toxicity, dose reductions and treatment delays were planned in the study protocol.

A second line of treatment was authorised at progression in both arms. It was not defined by the trial design and let to the investigator's choice.

2.4. Tumour evaluation

Within the month before randomisation, patients underwent a CT scan of the thorax and the abdomen (hepatic magnetic resonance imaging could replace the CT of the abdomen). Biliary and pancreatic endoscopic ultrasonography was optional. A complete medical history was recorded with a complete physical examination, including body weight, height, WHO performance status, and a quality of life questionnaire. Routine laboratory studies (blood cell count, serum creatinine, bilirubin, AST (Aspartat aminotransferase), ALT (Alanine aminotransferase), alkaline phosphatase, gamma-glutamyltransferase, prothrombin time) were performed. During the treatment, physical examinations, laboratory tests and toxicity signs were weekly recorded in the CHRT arm and every 2 weeks in the CH arm. After completion of the treatment, physical examinations and laboratory tests were done and toxicity was recorded every 3 months until progression or death. Patients were followed up using the same imaging technique as for the initial examination (mostly CT scan) every 3 months for the first 2 years and then every 6 months until documented progression. Tumour response was evaluated by RECIST (Response Evaluation Criteria In Solid Tumors) V1.0 criteria to determine progression.

2.5. Statistical analyses

The initial primary end-point was progression-free survival (PFS) at 3 months. The criteria were changed as a median time because few patients presented a progression at 3 months. The overall PFS was defined as the time from inclusion until progression or death. The expected number of patients was calculated according to one-step Fleming's design permitting the validation of efficacy of the experimental arm before any further comparison to the control arm in a phase III. Treatment failure was defined as a PFS rate at 3 months less than 50%; a 70% PFS rate was expected. With a one-sided alpha risk of 5%, a total of 72 patients (36 patients per arm) was required to achieve 80% power under the formulated hypotheses. If 23 patients or more were not progressive at 3 months then the experimental

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treatment was declared as efficient. This study was not designed to make comparisons between treatment arms.

Secondary end-points were safety, overall survival (OS), rate of biliary complications and duration of hospitalisation. OS was defined as the time from inclusion to death. Intention-to-treat (ITT) analyses were done for PFS and OS using the Kaplan–Meier's method. Per-protocol analyses were performed on patients who completed the planed treatment. The frequency and grading of toxicity were tabulated according to the National Cancer Institute-Common Terminology Criteria (NCI-CTC) v2.0. At 6 months, quality of life data were complete for only three patients in the CHRT arm and four patients in the CH arm, and we therefore decided not to analyse these data.

3. Results

3.1. Patients

The study was closed before inclusion of the planned number of patients due to slow recruitment. Between July 2006 and December 2010, 34 patients were included in 12 centres (18 in the CHRT and 16 in the CH arm). Patients' characteristics were balanced betweens arms (Table 1). Patients were slightly older in the CH arm (median age 75 years) than in the CHRT arm (69.5 years). Most patients were in good performance status. Tumour location and necessity of bile drainage were similar in both arms. The mean bilirubin concentration, at inclusion, was 23 (±19) μmol/L in the CH arm and 34 (±49) μmol/L in the CHRT arm. All patients but one had histological or cytological proof of biliary tract tumour. No histological proof could be recorded for 1 patient from the CHRT arm; cytological samples being negative despite two biliary tract catheterisations. Median follow up was 27.9 (±.8) months. Analyses were performed on as intention-to-treat principle in 34 patients whereas per-protocol analyses were performed in 27 patients. Reasons for exclusion were less than six cycles of GEMOX in three patients from the CH arm, metastatic progression before the first dose of radiotherapy in one patient, radiotherapy less than 50 greys in two patients from the CHRT arm and one patient had less than 50 greys of radiotherapy and metastatic progression before radiotherapy (Fig. 1).

Table 1
Baseline characteristics.

	Chemoradiotherapy (CHRT) $n = 18$ *N* (%)	Chemotherapy (CH) $n = 16$ *N* (%)
Sex		
Male	7 (39)	8 (50)
Female	11 (61)	8 (50)
Age, years		
Median	69.5	75
Range	53–80	54–81
WHO performance status		
0 or 1	17 (94)	16 (100)
2	1 (6)	0
Primary tumour location		
Gallbladder	2 (11)	2 (13)
Hilum	4 (22)	5 (31)
Intra-hepatic biliary duct	10 (56)	8 (50)
Extra-hepatic biliary duct	2 (11)	1 (6)
Biliary drainage		
No	4 (22)	4 (25)
Yes	14 (78)	12 (75)

3.2. Safety and treatment compliance

Patients in the CHRT and CH arms presented 47% and 75% of grade 3–4 toxicity, respectively. Main toxicities were haematological (23% and 25%, respectively), gastrointestinal (11.8% and 6.3%, respectively). Peripheral neurological toxicity linked to oxaliplatin was only recorded in the CH arm (18%) and the dose was adjusted as a consequence (67% of the planned dose of oxaliplatin was delivered).

In the CHRT arm, no cases of grade 3 or 4 neutropenia were reported whereas four patients presented grade 3 neutropenia in the CH arm. No episode of febrile neutropenia, or treatment-related death was reported in both arms.

Biliary complications occurred in 28% of patients in the CHRT arm and 44% of patients in the CH arm (risk ratio (RR): 1.60 [0.65–3.92]). They were mainly obstruction (27% and 18%) or angiocholitis (20% and 36%). In the CHRT arm, one patient presented a recurrent hepatic abscess, one patient had an infected bilioma and three patients had jaundice. The biliary stent was changed once for one of these patients. In the CH arm, two patients had recurrent infections, one patient developed jaundice and another patient had an obstruction of the biliary stent.

Six patients had at least one hospitalisation not linked to treatment administration in the CHRT arm (total number of hospitalisation among these patients: 13), and eight in the CH arm (total number of hospitalisation among these patients: 12). The mean duration of hospitalisation per patient was 6.6 (±10.9) days in the CHRT arm and 5.9 (±9.95) in the CH arm. The main reason for hospitalisation was supportive care in 38.5% of cases in the CHRT arm and in 16.7% in the CH arm. One patient in the CHRT arm presented three recurrent episodes of upper gastrointestinal bleeding linked to radiation-induced antral gastritis.

At the end of CHRT treatment, 13 patients (77%) had received 5 weeks of 5 FU-cisplatin with 78% of the planned dose of 5 FU and 90% of the planned dose of cisplatin. Fourteen patients (82%) received 5 weeks of

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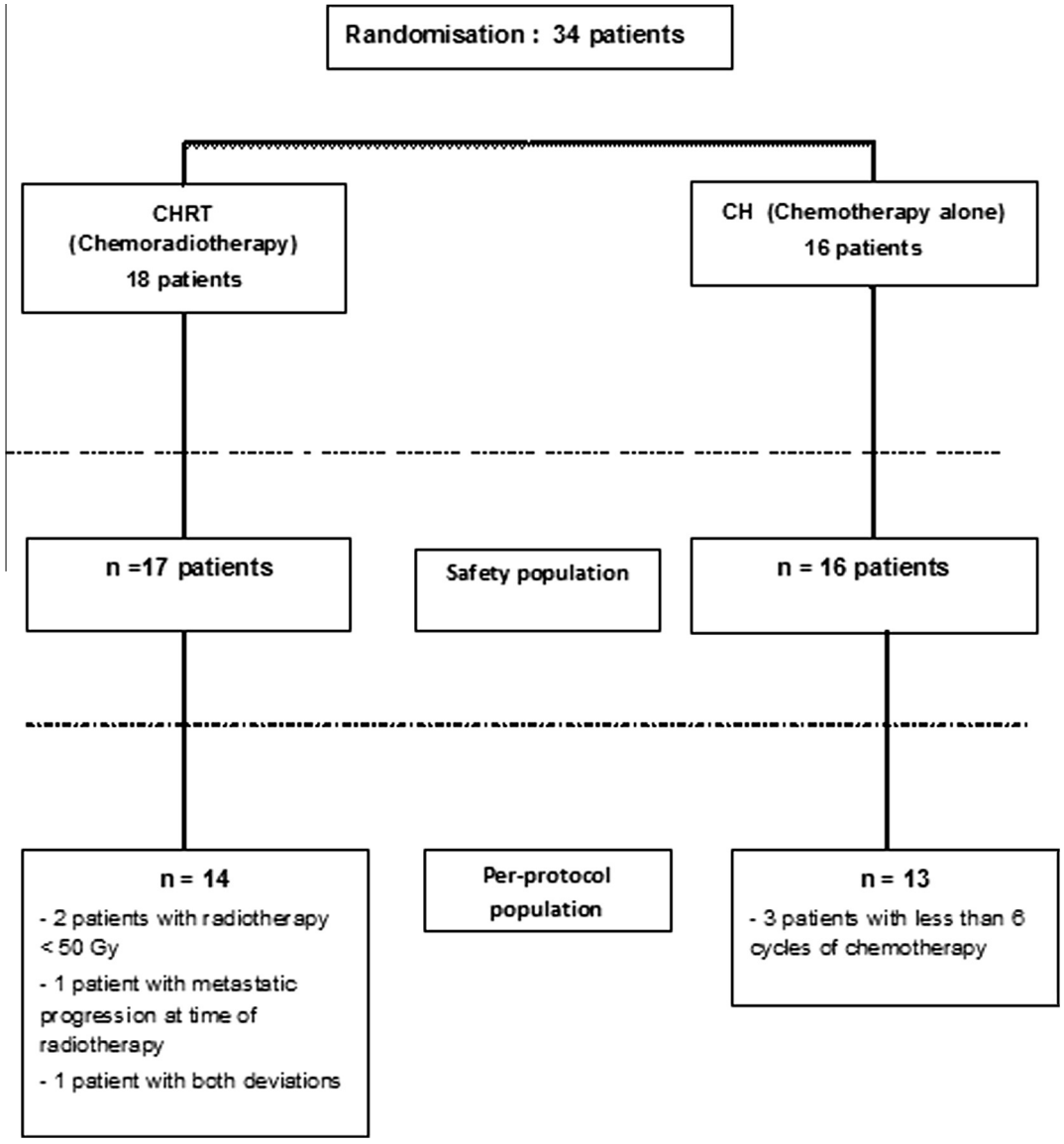

Fig. 1. Flow-chart of the study.

radiotherapy and 86% of the planned dose. In the CH arm, 10 patients (63%) received 12 cycles of GEMOX and 70% of the planned dose of gemcitabine and 67% of the planned dose of oxaliplatin. Fourteen cycles were delayed for haematological toxicity in the CH arm versus none in the CHRT group.

3.3. Efficacy

The ITT median PFS was 5.8 months in the CHRT arm (95% confidence interval (CI): 2.8–11.8), and 11.0 months in the CH arm (95% CI: 6.3–14.3) [hazard ratio (HR): 0.65 (0.32–1.33)] (Fig. 2). Overall survival was 13.5 months in CHRT arm (95% CI: 7.8–22.6) and 19.9 months in the CH arm (95% CI: 11.0–29.2) [HR of 0.69 (0.31–1.55)] (Fig. 3). The per-protocol analysis

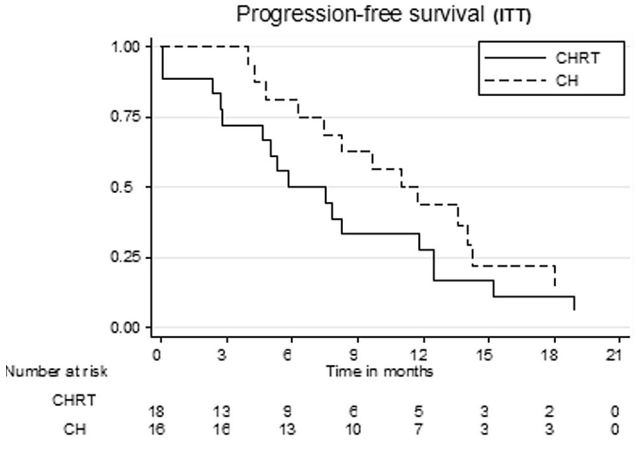

Fig. 2. Intent-to-treat progression-free survival.

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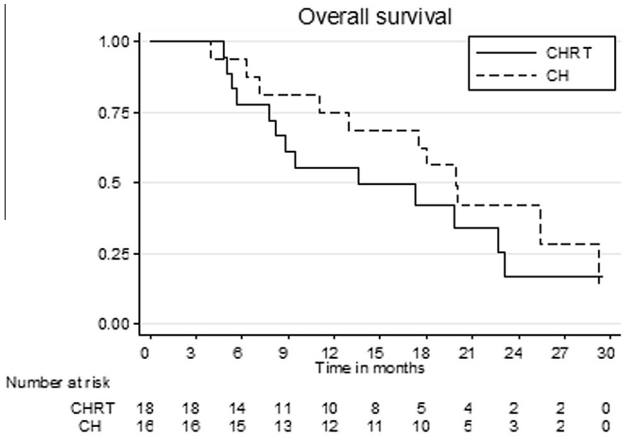

Fig. 3. Intent-to-treat overall survival.

confirmed the trend of longer PFS and OS in the CH arm: median PFS of 7.5 months (95% CI: 2.8–12.5) in the CHRT arm versus 11.7 months (95% CI: 7.4–14.3) and median OS of 13.5 months (95% CI: 7.8–22.6) in the CHRT arm versus 19.9 (95% CI: 11.0–29.2) in CH arm.

Second-line therapy after progression was documented for 41% of patients (56% in the CHRT arm and 25% in the CH arm). In the CHRT arm, GEMOX was used for seven patients, gemcitabine alone for two patients and leucovorin/5 FU for one patient. In the CH arm, patients received leucovorin/5 FU + irinotecan, leucovorin/5 FU and cisplatin or gemcitabine alone. One patient in the CH arm received chemoradiotherapy after progression. Efficacy of second line treatments was weak.

No patient had a resection of the tumour after the first line treatment.

4. Discussion

When the FFCD 99-02 trial was designed in 1999, chemoradiotherapy was considered as a valuable option for the treatment of locally-advanced biliary tract cancer. The alternative option was chemotherapy alone [10]. A randomised trial was then designed by FFCD to compare both options. Unfortunately the FFCD 99-02 trial was closed in 2010 before the completion of planned inclusions due to low recruitment (34 patients in 4.5 years in 12 active centres). Even if enrolment was limited, population of each arm was comparable and the trial could be analysed with caution. No trend towards an advantage of CHRT was detected. Instead, there was a slight advantage for CH alone, both in terms of progression free survival (median 11 versus 5.8 months) and overall survival (20 versus 13.5 months). Treatment tolerance was quite similar in both groups, except the specific oxaliplatin-related neurotoxicity. Biliary complications (obstruction and infections) were less frequent in the CHRT arm. There were more cases of biliary infection in the CH arm probably induced by immunosuppression. Nevertheless this potential benefit of local irradiation is doubtful to advocate CHRT.

Despite its limitations, chemoradiotherapy is still used worldwide for treatment of LABTC [4–11]. The retrospective analysis of 3839 patients with intrahepatic cholangiocarcinoma collected from the Surveillance, Epidemiology, and End Results (SEER) database with overall survival (OS) as the end-point suggested that definitive radiation treatment extended survival, while cure rates remained low [9]. Meanwhile the efficiency of chemotherapy has improved with use of gemcitabine combined with platinum compounds. Our trial suggests that chemotherapy alone is not detrimental and should be preferred to CHRT for LABTC in current clinical practice even if radiotherapy is technically feasible.

Causes of failure of CHRT in the present trial have to be analysed. An obvious difference is the lack of adjuvant chemotherapy in the CHRT arm. However, one argument for CHRT is the shortness of treatment compared to an unlimited time for chemotherapy. Evaluation of impact of adjuvant chemotherapy would imply that a new trial is implemented. However difficulties to include in the present trial are a bit daunting. Lack of efficiency in the CHRT arm was not related to the regimen toxicity because 82% of patients received more than 80% of the planned dose of radiotherapy. The main difficulties for inclusion came from the lack of consensus and standardisation among radiotherapists, and the fear of radiation-induced hepatitis on a large volume of liver. Only a few number of radiation oncologists are experienced in the treatment planning and delineation for such a disease, which is often infiltrative. Even if an accurate definition of the target volumes was provided in the protocol, the consistency was not validated between centres in this multicentre protocol and not validated by a dedicated quality assurance programme. The use of 3D combined approach and selected irradiation of the target volume as well as relevant protection of organ at risk were not uniform. Nevertheless this trial was a 'true life' snapshot of clinical practices in France in the years 2000–2010. Our results indicate that CHRT must no longer be proposed in such conditions as the standard treatment for LABTC.

Conventional chemoradiotherapy, with a total dose of 50 Gy is not enough to cure the tumour. It cannot be excluded that better results could be obtained by optimising techniques. LABTC comprises a variety of diseases: intrahepatic, hilar, gallbladder, or extra-hepatic biliary tract carcinomas. These entities have a different natural history, different routes for metastatic propagation and perhaps different degrees of chemo- and radiosensitivity. The small number of patients in our trial did not allow us to perform subgroup analyses. In retrospect, it was probably naive to gather these different anatomical sites in a single trial. Chemoradiotherapy could be of great interest

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in some locations. For example, neoadjuvant CHRT followed by high dose rate brachytherapy could have a major interest when followed by liver transplantation for non-resectable localised perihilar cholangiocarcinoma. A large US series of 287 patients reported a survival rate of 53% at 5 years [12]. Development of imaging techniques, improvements in radiotherapy modalities, mainly IMRT (Intensity-Modulated Radiation Therapy) and, stereotactic hypofractionated radiation and the proven efficacy of chemoradiotherapy for some other digestive tumours (oesophagus, rectum) suggest that it would be useful to evaluate these new methods in the field of LABTC, with selection of the technique according to the tumour location. Whatever new radiotherapy techniques or CHRT regimen, they should be evaluated through randomised studies involving a chemotherapy arm as control.

Our present findings on locally-advanced biliary tract carcinoma are quite similar to those found on locally-advanced pancreatic cancer (LAPC) in the FFCD 2000–01 phase III trial [13]. CHRT and adjuvant gemcitabine was not better than gemcitabine alone. Median overall survival was higher in the gemcitabine arm than in the CHRT arm (13.0 months versus 8.6 months, respectively, $p = 0.03$). Except for the intensity of the radiotherapy (60 Gy in pancreatic tumours versus 50 Gy in LABTC), combination of 5 FU and cisplatin with radiation was the same in both trials. In conclusion, it was suggested that CHRT should not be the standard first line treatment for LAPC. The conclusion could be the same for LABTC.

The choice of the combination of gemcitabine and oxaliplatin (GEMOX) as control could be discussed nowadays. In 1999, GEMOX was considered one of the most active regimens for cholangiocarcinoma after several phase II studies [14–17] Gemcitabine plus cisplatin (GEMCIS) combination chemotherapy became a standard only in 2010 after the ABC-02 phase III trial, which compared gemcitabine alone with GEMCIS [3]. Median overall survival was 11.7 months in the GEMCIS group and 8.1 months in the gemcitabine group (HR: 0.64: [0.52–0.80]; $p < 0.001$). There have been no direct comparisons between GEMOX and GEMCIS. The GERCOR study reported a 14% response rate, 35% of stable disease and median overall survival of 8.8 months with GEMOX for advanced and metastatic biliary tract cancer [15]. Interestingly, the 20-month median survival in the CH arm in our trial was higher than the 8.8 months' median survival in the GERCOR study. As the drug doses were the same for both trials, it can be concluded that locally-advanced disease has a better prognosis than metastatic disease, as soon observed for pancreatic cancer [18]. The 20 month survival in the CH arm in our trial is also higher than in ABC 02 study with GEMCIS (median survival of 11.1 months), which included both locally-advanced and metastatic diseases [3]. Subgroup analysis in ABC 02 showed that GEMCIS was more effective than gemcitabine for the locally-advanced group (HR: 0.47: [0.29–0.74] than for the metastatic group (HR: 0.74: [0.57–0.95]. All these findings supported the conclusion that the prognosis of LABTC is better in non-metastatic patients and that both entities must be evaluated through separate trials.

In conclusion, conventional radiotherapy with 50 Gy combined to 5-fluorouracil and cisplatin is not superior to a chemotherapy regimen with gemcitabine and oxaliplatin in locally-advanced non-resectable biliary duct cancers. Chemotherapy based on gemcitabine and a platinum compound must be selected for clinical practice outside of clinical trials.

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Conflict of interest statement

Pr. Jean Marc Phelip: Sanofi regional board for colorectal cancer. Other authors declared no disclosures.

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