Protocol title:

**Adjuvant Therapy after resection for Distal Cholangiocarcinoma (ATDC). A retrospective multicentric study.**

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Version and protocol data: 1 - 19/10/22

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1. Summary.

**Title:** The role of the adjuvant therapy after resection for Distal Cholangiocarcinoma. A retrospective multicentric study.

**Coordinator centre:** Humanitas Research Hospital

**Study coordinator:** Prof. Alessandro Zerbi, Chief of Pancreatic Surgery Unit at Humanitas Research Hospital, Milan.

**N. of protocol:**

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**Background and rationale:** Adjuvant therapy after radical resection for distal cholangiocarcinoma is still debated. The main evidence supporting adjuvant chemotherapy is the BILCAP study [[1]](#endnote-1), a phase III randomized open-label study testing capecitabine versus observation in cholangiocarcinoma patients (any subsite) undergoing macroscopic complete surgical resection. Per-protocol analysis of this study showed a median survival of 53 months in patients treated with capecitabine versus 36 months in observation group patient (p = 0.028). On the basis of this study, international guidelines recommend adjuvant capecitabine for a period of six months following curative resection of cholangiocarcinoma as the current standard of care [[2]](#endnote-2). Apart from the BILCAP study, two phase III clinical studies in which patients with resected biliary tract cancer (any subsite) were randomized to observation alone versus gemcitabine (BCAT study) [[3]](#endnote-3) or gemcitabine and oxaliplatin (PRODIGE-12 study) [[4]](#endnote-4) failed to show any benefit from chemotherapy. The available literature was considered to be of low quality due to the heterogeneity of patients resulting from the inclusion of also gallbladder carcinomas, the risk of bias due to the lack of study participant and medical personnel blinding, and the smaller samples sizes in different institution. Particularly, no relevant studies focusing on the role of adjuvant therapy after distal cholangiocarcinoma (DC) have been published.

**Phase**: Observational

**Selection criteria:** patients undergoing radical resection for DC.

**Design and study’s duration:** Multicentre retrospective study, no profit.

**Aim of the study**: to evaluate the prognostic role of adjuvant therapy after resection for distal cholangiocarcinoma.

**Methods and statistical analysis**: The obtained data will be analyzed adopting for each variable the more appropriate statistical model.

**Ethical consideration**: the protocol will be conducted in agreement with Helsinki declaration and with good clinical practice.

1. Background and rationale.

Adjuvant therapy after radical resection for distal cholangiocarcinoma (DC) is still debated. The main evidence supporting adjuvant chemotherapy is the BILCAP study [[5]](#endnote-5), a phase III randomized open-label study testing capecitabine versus observation in cholangiocarcinoma patients (any subsite) undergoing macroscopic complete surgical resection. Per-protocol analysis of this study showed a median survival of 53 months in patients treated with capecitabine versus 36 months in observation group patient (p = 0.028). On the basis of this study, international guidelines recommend adjuvant capecitabine for a period of six months following curative resection of cholangiocarcinoma as the current standard of care [[6]](#endnote-6). Apart from the BILCAP study, two phase III clinical studies in which patients with resected biliary tract cancer (any subsite) were randomized to observation alone versus gemcitabine (BCAT study) [[7]](#endnote-7) or gemcitabine and oxaliplatin (PRODIGE-12 study) [[8]](#endnote-8) failed to show any benefit from chemotherapy. The available literature was considered to be of low quality due to the heterogeneity of patients resulting from the inclusion of also gallbladder carcinomas, the risk of bias due to the lack of study participant and medical personnel blinding, and the smaller samples sizes in different institution. Particularly, no relevant studies focusing on the role of adjuvant therapy after distal cholangiocarcinoma (DC) have been published.

For this reason, the AICEP (Associazione Italiana Chirurgia Epato-Bilio-Pancreatica) group decide to perform a retrospective evaluation of all resected distal cholangiocarcinoma, in order to evaluate the rate and the prognostic role of adjuvant therapy.

3. Aims of the study

3.1 General aim.

The general aim is to evaluate the prognostic role of adjuvant chemotherapy after radical resection for DC.

3.2 End-points

3.2.1 Primary end-point.

The primary endpoint is to evaluate the prognostic role (in terms of Overall Survival (OS) and Disease Free Survival (DFS)) of adjuvant chemotherapy after radical resection for DC.

3.2.2 Secondary end-points.

Secondary endpoints are:

- to evaluate the rate of adjuvant chemotherapy;

- to evaluate the different adopted chemotherapy regimens;

- to evaluate the prognostic impact of different chemotherapy regimens;

- to identify significant prognostic factors after resection;

- to identify factors associated with failure of administration or completion of adjuvant chemotherapy.

4. Selection criteria.

4.1. Inclusion criteria.

Inclusion criteria are the following:

- age > 18 years;

- resection (pancreatoduodenectomy (PD), total pancreatectomy (TP)) for histologically confirmed DC with radical intent, including R0 and R1 resections, performed from January 2010 to date.

4.2. Exclusion criteria.

Exclusion criteria are the following:

- intraoperative distant metastases;

- associated hepatic resection (i.e. after biliary margin positivity);

- R2 resection.

5. Study design.

The study is a multicentre retrospective study. All resected cases of DC will be retrospectively collected from a multicentric database.

6. Statistical analysis.

Stata 15.0 TM statistical software will be used for statistical analysis. For every variable considered in the CRF(s) descriptive analysis will be done: mean and standard deviation for continuous numerical variables; median and interquartile range for discrete variables; relative frequency and C.I. 95% for categorical and binomial variables. Monovariate analysis will be done for principal and secondary endpoints using χ2-test. A p-value of 0.05 and a statistical power of 0.9 is set for statistical significance. Multivariate analysis will be done using stepwise logistic regression. OR and CI 95% will be calculated for primary objective and for every covariates included in the model. A sensitivity analysis will be done to control how the logistic regression model fit.

7. Source documents and data collection.

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. The investigator will permit audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

Study data will comprise demographic, pre-, intra- and post-operative results. Long-term results will include recurrence rate, site of recurrence, overall survival (OS) and disease-free-survival (DFS).

A multicentre database will be created to collect data. All the patient data will be anonymised and stored in a database according to good clinical practice (GCP).

**8. Ethical aspects.**

The Ethical Review Boards (ERBs) will review the protocol as required. Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB vote on the approval of the protocol.

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. The investigator, head of the medical institution, or designee will promptly submit the protocol to applicable ERB(s). An identification code assigned [by the investigator] to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other trial-related data. The investigator must retain any records related to the study according to local requirements.

10. Conflict of interests.

Each researcher has to declare any kind of conflict of interests, if present.

11. Ownership of data.

The study is performed on behalf of AICEP. According the guidelines of Good Clinical Practice, the study coordinator (Humanitas Research Hospital) is the owner of the results of the study. All researchers involving in the study are invited to not share these results without the consent of the study coordinator.

12. Completion of the study, final report and publications.

The physician will conduct this study in compliance with the protocol and all other applicable regulatory and legal requirements. The physician may terminate the study at their site for reasonable cause.

At the end of the study, a study report will be written by the principal investigator. This report will contain a description of the objectives of the study, the methodology of the study and its results and conclusions. The results of this study may be published by one of the participating investigators after agreement with all the other centres.

Authorships will be based on the recommendations from the international committee of medical journal editors (ICMJE). The first author will be reserved for the coordinator center. The last authorship position is reserved for the mentee of this group (Prof. Alessandro Zerbi). The other authorship will be decided according to the number of enrolled patients:

- 1-20 patients: 1 collaborator (that will be listed under the study group AICEP);

- 21-49 patients: 2 collaborators (that will be listed under the study group AICEP);

- 50-99 patients: 1 author and 2 collaborators (that will be listed under the study group AICEP);

- more than 100 patients: 2 authors and 2 collaborators (that will be listed under the study group AICEP).

13. Study duration.

Study duration will be about 12 months: 6 months for data collection and 6 months for the data analysis and final report.

14. References.

1. Primrose JN, Fox RP, Palmer DH, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol 2019:20:663-73. [↑](#endnote-ref-1)
2. Shroff RT, Kennedy ER, Banchini M, et al. Adjuvant therapy for resected biliary tract cancer: ASCO clinical practice guideline. J Clin Oncol 2019;37:1025-27. [↑](#endnote-ref-2)
3. Ebata T, Hirano S, Konischi M, et al. Randomzed clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. Br J Surg 2018;105:192-202. [↑](#endnote-ref-3)
4. Edeline J, Benabdelghani M, Bertaut A, et al. Gemcitabine and oxaliplatin chemotherapy or surveillance in resected biliary tract cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): a randomized phase III study. J Clin Oncol 2019;37:658-67. [↑](#endnote-ref-4)
5. Primrose JN, Fox RP, Palmer DH, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol 2019:20:663-73. [↑](#endnote-ref-5)
6. Shroff RT, Kennedy ER, Banchini M, et al. Adjuvant therapy for resected biliary tract cancer: ASCO clinical practice guideline. J Clin Oncol 2019;37:1025-27. [↑](#endnote-ref-6)
7. Ebata T, Hirano S, Konischi M, et al. Randomzed clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. Br J Surg 2018;105:192-202. [↑](#endnote-ref-7)
8. Edeline J, Benabdelghani M, Bertaut A, et al. Gemcitabine and oxaliplatin chemotherapy or surveillance in resected biliary tract cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): a randomized phase III study. J Clin Oncol 2019;37:658-67. [↑](#endnote-ref-8)