PROTOCOLLO NAZIONALE

HE.RC.O.LE.S. PROJECT

Hepatocarcinoma Recurrence on the Liver Study Group

- Fase 2 -

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1. Introduction.

Hepatocellular carcinoma (HCC) is 1 of the 5 most common malignancies worldwide and the third most common cause of cancer related mortality of 500,000 deaths globally every year. Although more common in East Asia, the incidence of HCC is increasing in the Western world. Hepatic resection is the first-line therapeutic option and it is accepted as a safe treatment with a proven impact on prognosis, with a low operative mortality as the result of advances in surgical techniques and perioperative management. Nevertheless, surgical resection is applicable in only about 20% to 30% of patients with HCC, since most have poor hepatic reserve function caused by underlying chronic liver disease and multifocal hepatic distributions of HCC.

Although hepatic resection is one of the curative treatments for hepatocellular carcinoma, the recurrence rate of HCC even after curative resection is quite high, estimated to be approximately 50 % during the first 3 years and more than 70 % during the first 5 years after curative resection, and so the postoperative long term results remain unsatisfactory. In this scenario the role of liver transplantation has been, in the last years, predominant, due to the ability of transplant to reduce disease recurrence, because of the treatment of liver cirrhosis associate to HCC which represent the most important driver to recurrence. Otherwise the scarcity of organ source has been a boost to the spread of liver resection, not only confined in the boundary taken into account in the BCLC algorithm (guidelines endorsed by EASL and AASLD), but even in patients considered not suitable for curative treatment as well as liver resection.

Although surgical treatment has been adopted in the last years in more patients outside the Guidelines with satisfactory results in term of mortality, morbidity and Short term oncological outcomes, the limits of this approach remain the long term disease free survival.

Risk factor for recurrence has been yet identified in the last years as hcc dimension, grading, microvascular invasion and satellitosis. The evidence that these two prognostic factors could negatively impact on the long term prognosis enhancing the risk of recurrence, has led many Author to propose anatomical resection (segmental resection) as the ideal surgical treatment

to reduce these risks in HCC patients. Otherwise literature results are in conflict regarding the real benefit of this approach. In fact in many patients with HCC and underlying cirrhosis the anatomical approach is not feasible due to the risk of postoperative liver failure. So a parenchyma-sparing technique has been developed and compared to anatomical resection in term of oncological outcomes. Even if radiological and clinical pictures seems to predict the prognosis of resected HCC, the pathophisiology behind the recurrence is still unclear.Currently, data suggests two type of recurrence presentation: intrahepatic metastatization (IM) and multicentric occurrence (MO) of de novo HCC based on the precancerous status of the remnant diseased liver. Several effort has been done to preoperatively identified the 2 pattern of recurrences. Genetical studied has been performed, especially in eastern countries to better clarify and understand the impact of the 2 phenomena. In the japanese guidelines are described histo-pathological hallmarks able, in retrospect, to define the type of recurrence, metastases or de novo tumor. Moreover, several recent studies including a metanalysis, seems to show that de novo recurrence could have a better prognosis when approached surgically, with a significant improvement in overall and disease-free survival rates. The model of HCC recurrence is not yet well clarified as well as the best treatment of hcc recurrence. On these data is based the proposal to create an Italian study project on surgical treatment and surgical outcomes of hepatocellular carcinoma in term of disease free survival. The idea growth up from the finding that, although the curative intent of surgical approach, results are not so satisfactory and it seems to not ameliorate the long term patient's prognosis and long term disease-free outcome without the need for therapies, conditioning the real everyday life of patient. In Italy is not yet present a study group that draw togher the experience of surgical centers with low,medium or high volume of surgical procedures on HCC, with the intent to offer radical cure through surgery as the first choice treatment. The intent is to collect Big Data through a common database, with high power of analysis and high scientific impact, to better understand the mechanism which regulate HCC recurrence and to identify the best clinical treatment option for these patients.

2. EXPERIMENTAL DESIGN

2.1 Rationale for the trial.

To evaluate the impact of surgery on hepatocarcinoma recurrence. Thus, to evaluate the impact of different clinical, radiological, histopathological variables on recurrence after surgical treatment. The nature of this study will allow to observe, over time, the distribution of the considered collection variables, allowing a strictly observational monitoring of possible associations able to suggest models or interpretations, which can then be the basis for the construction of prospective and randomized studies.

2.2 Objectives

- Primary objective: to evaluate and to monitor the impact of surgery, on Disease-Free-Survival, Overall Survival and Tumor-Specific-Survival on a nation-based point of view.

- Secondary objective: to evaluate and to monitor the role of different clinical, biochemical, radiological and histopathological variables in determining the recurrence after surgery.

2.3 Type of Study

This is a nation-based multicentric observational study on hepatocellular carcinoma surgical and oncological outcomes after curative treatment.

2.4 Study population.

Planned number of subjects to be screened: almost 260 per year (patients treated/year in centres already registered as participating).

2.5 Inclusion criteria.

- No age limit.
- Hepatocarcinoma diagnosis confirmed at histological specimen
- Every single patients with first HCC diagnosis or with a recurrence/persistence disease evaluated and treated with surgery at the participating center.
- the assessment for patient enrollment must have been performed starting from 02/02/2019.

2.6 Exclusion criteria

- Surgery as a downstaging therapy for transplant
- Patients treated with surgery in case of not-curative intent (palliation, best supportive care, etc).
- Histopathological specimen of combined liver primary neoplasms (e.g. 'epatocolangiocarcinoma').
- Patients with other tumors in the previous past.

2.7 Design.

This study is an observational prospective multicentric cohort nation-based study.
This study will evaluate patient data collected prospectively and anonymized prior to the analysis. The study protocol follows the ethical guidelines of the 1975 Declaration of Helsinki (as revised in Brazil 2013). This study is considered the second stage of the study-group foundation "HERCOLEStudy Group", started with the proposal of the observational retrospective study named "HERCOLES", who had the aim to merge similar data with this protocol, during the last decade.
In this protocol, every single patient currently undergoing liver resection for hepatocellular carcinoma in one of the centers will be evaluated for enrollment. If suitable for inclusion, data will be collected no later than 1 month after treatment. Confirmation of enrollment, and associated procedures (see above), will be decided and communicated to the patient at the first post-operative out-patients visit. Follow-up data will be collected according to follow-up schedule (read above), and they will be updated in the database–at least twice per year (once every semester at least) for all the patients enrolled.

2.8 Withdrawal criteria

The subject may withdraw at will at any time. The patient may be withdrawn from the trial at the discretion of the investigator for safety concerns. Patients who will meet the exclusion criteria after a prior inclusion in this study will be withdrawn. A patient withdrawn analysis will be made to clarify the related rate and possible impact on the study results.

3. Methods and assessments

3.1 Variables.

3.1.1. Anagraphic Data

Patient ID (anonymously assigned by the center in consecutive order)
Date of Birth
Gender

3.1.2. Anamnestic Data

Performance Status
ASA score
Charlson Comorbidity Index
BMI
Diabetes
Cardiopathy
Pneumopathy

Nefropathy

Previous Surgery

3.1.3 Liver Anamnestic Data

Presence of Cirrhosis

Presence of Steathosis

Child-Pugh GRADE (A-B-C)

CHILD SCORE (5-15)

MELD

HIV

HCV

HBV

Alcool consumption

HCV eradicated by DAA

Presence of Varices

Presence of Splenomegaly

3.1.4 Pre-operative biochemical data (collected at recovery)

AST

ALT

Total Bilirubine

Albumine

Sodiemia

Creatinine

White Blood Cells

Lymphocyte and Neutrophil

Hb

INR

Platelet Count

Indocyanine Green Ritention Test at 15 minutes

Alfa-feto-protein

3.1.5 Pre-op radiological data

Date of radiological diagnosis

Type of imaging (TC vs MRI)

Liver Biopsy executed

Number of nodules

Liver segmental localization

Size of the nodule

Bilobar disease

Macrovascular portal invasion

Extra-hepatic disease

BCLC

Milano in/out

% Liver remnant volume

Total Liver volume

3.1.6 Neoadjuvant treatments

Type of neoadjuvant therapy

Date of execution

Radiological Restaging and response

3.1.7 Surgical Data

Date of Surgery

Number of resected nodules

Localization

Type of resection

Laparoscopic resection

Portal embolization

ALLPS

Intraoperative US

Presence of Portal Trombosis

Clamping

Total time of clamping

Lenght of surgery

Ablative therapies during surgery

Bleeding

Transfusion

Lenght of in-hospital stay

Presence of post-operative complications

Grade of complication (Clavien-Dindo Score and Comprehensive Complication Index)

Liver related complications

90-day-mortality

Re-do surgery for complication

3.1.8 Histopathological findings

Histological type

pT

Grading (Edmondson)

Number of nodules

Size

Micro or macro-vascular invasion

Presence of satellithosis

Surgical Margin (R)

3.1.9 Follow-up

Death event

Date of dead/last follow-up available

Dead cause

Recurrence event

Date of recurrence/last follow-up available

Single or multiple recurrence

Intra-hepatic or extra-hepatic recurrence

Local Recurrence

Number of recurrent nodules

Localization

Size of recurrent nodule

Alfa-feto-Protein at recurrence

Recurrence treatment

Grading of the recurrent nodules if surgically treated

3.2 Study supplies and products.

Patients will be treated according to local hospital procedure. No additional costs (materials, salaries, other) due to the study will be charged to the hospital. Study products will be those commonly used in the hospital according to the local rules.

3.3 Data handling.

Data collection will be performed using an electronic database system, in accordance with the European Statement 679/2016/UE. The submitted data will be then checked centrally, at San Gerardo Hospital (Monza) and, where missing data may be identified, the local investigator will be contacted and asked to complete the record. Once examined, the record will be accepted into the dataset for analysis.

3.4 Surgical methodology.

All operations will be performed by surgeons with large experience in liver surgery. The resection technique will be at surgeon preference, according to local protocol, good clinical practise and national guidelines. All surgeons adopted the same criteria to select the surgical strategy: baseline variables of liver function, tumour location and diameter, and number of nodules. Restaging Ultrasonography (US) will be performed intra-operatively for each patient.

3.5 Analysis of recurrence pattern.

The recurrence patterns will be evaluated as follow. Local recurrence will be defined as a recurrence on the same liver segment in case of PSR, or on the surgical hedge of the nearest segments in case of AR. Thus, it will be evaluated the number of recurrent nodules (single versus multiple), the location of recurrence (intrahepatic versus extrahepatic or both), the size of the main recurrent nodule and the liver segment. All this evaluations on recurrence will be made by CT scan or MRI scan during follow-up, as the local follow-up protocols provide.

3.6 Follow-Up.

All the patients will be followed using a local protocol including measurement of serum α-FP, ultrasound, contrast Computed Tomography (CT) or magnetic Resonance Imaging (MRI) and office visits. Patients usually are checked every 3 months during the first postoperative year and every 6 months thereafter. When the recurrence occurred, the cases are discussed in a multidisciplinary setting, involving radiologist, hepatologist, surgeon, interventional radiologist, radiotherapist and oncologist. Overall-Survival (OS) is defined as time interval (in months) from surgery to patient death. Data will be censored in case of loosed patient at the follow-up screening. Disease-Free Survival (DFS) is defined as time interval (in months) from surgery to recurrence or death. In case of no recurrence, data will be censored at the date of the last available follow-up. Tumor-Specific-Survival (TSS) is defined as the time interval in months between surgery and tumor-related death.

3.7 Statistical analysis.

Data will be expressed as median and interquartile range (IQR), number and relative percentage, or hazard ratio (HR) with related 95% confidential intervals (CI). Normal distribution of continuous variables will be assessed by Kolmogorov-Smirnov test. To compare baseline characteristics of the groups in the univariate analysis, continuous variables will be analysed using the Mann-Whitney test or ANOVA according to the type of distribution. Categorical variables will be analyzed by Fisher exact test or Chi-Square Test as appropriate. A 1:1 propensity-score-analysis, with a caliper of 0.1SD, may be conducted for significant variables ($p<0.05$) at univariate to reduce the retrospective bias of selection.

Multivariate analysis will be performed by logistic regression analysis or Cox regression as appropriate. DFS, OS and TSS will be evaluated by Kaplan-Meier method. Comparison between groups will be performed with the log-rank test. All statistics will be 2-tailed and statistical significance will be accepted when $p<0.05$.

3.8 Data management.

Data will be stored in an electronic database. Each investigator may have the access to the whole dataset.
The subject will be identified by an alphanumeric code linked to the name of the patient that the enrolling investigator can see. Appropriate measures such as encryption or deletion will be enforced to protect the identity of human subjects in all presentations and publications as required by local/regional/national requirements.During the patients entering in the database, data quality will be ensured.
At least one report analysis will be performed each year.
Major protocol deviations will lead to exclusion of data from the analysis, while data will not be excluded because of minor protocol deviations. The list of major protocol deviations will be detailed and documented in the clean file document prior to database release.

4. CRF

4.1 Rules for completing CRFs

The investigator staff must ensure that all information derived from source documentation is consistent with the source information. By uploading the complete dataset, the Investigator confirms that the information is complete and correct.

4.2 Corrections to CRFs

Corrections to the data on the CRFs can only be made by communicating to the Data Manager the alphanumeric code linked to the name of the patient and asking to modify the data.

5. Ethics

The study will be conducted in accordance with the Declaration of Helsinki and according to local and regional ethical standards.

5.1 Informed consent form for study subjects

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirements and adhere to the requirements in the Declaration of Helsinki. A voluntary, signed and personally dated, informed consent form will be obtained from the subject prior to the study inclusion. In those cases where the patient will not be able to sign the informed consent, an informative module will be given to relatives to ask the temporary permission to collect data; once the patient will have recovered the possibility to express the consensus, if positive, data will be inserted into the database. The responsibility for obtaining informed consent must remain with that of a medically qualified person and cannot be delegated to a non-medically qualified person. The written informed consent must be signed and personally dated, by the person who obtained the informed consent.
If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the Investigator must inform the subject in a timely manner, and a revised written informed consent must be obtained. Each investigator is responsible to correctly refer the provided documentation to the candidate and to acquire the written consent to study participation and to the privacy statement.

6. Critical documents

Before the Investigator starts the study (i.e., obtains informed consent from the first subject), the following documents must be available:

• Regulatory approval and/or notification as required

• Signed and dated agreement on the final protocol

• Signed and dated agreement on any substantial amendment(s), if applicable

• Approval/favourable opinion from IEC clearly identifying the documents reviewed: the protocol, any substantial amendments, subject information/informed consent form and any other written information to be provided to the subject, subject recruitment Procedures.

7. Responsibilities

The Investigator is accountable for the conduct of the study. If any tasks are delegated, the Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant study-related duties.

The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician.

The Investigator will take all necessary technical and organizational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The Investigator will prevent any unauthorized access to data or any other processing of data against applicable law.

8. Reports and publications

The information obtained during the conduct of this trial is considered confidential and belongs to the investigator group for the purpose of scientific publications. No confidential information shall be disclosed to others. Such information shall not be used except in the performance of this study group.

All the investigators may decide after a consensus, to share the data with other groups or trials occasionally. In this case, the agreement of the whole study group is needed.

8.1 Database Rules

Any investigator can propose a specific study on the data available. This proposal may be done during the meetings of the study group. Afterwards, each proposal has to be voted by the whole group. Proposal who meets at least ⅓ of the investigators votes during the meeting will be accepted as a study group specific project. The center who proposed the project become the Principal Investigator of the project, and he/she will have the responsibility to conduct and carry out the project, from the design to the publication. If another center will be interest in direct participation at the project, it become the Co-Principal Investigator. If more than 1 center would be part of the project, they have to decide between them who will be the Co-PI. This decision should be based on the weight of the sample size considered shared by each participating center. The PI, or in alternative the Co-PI, has the responsibility to update the rest of the Study Group on the project progress at least during group meetings by presenting the current results. Before submission, the manuscript should be approved by each center participating at the study group. In the event of any disagreement about the content of any publication, all Investigators' opinions shall be fairly and sufficiently represented in the publication.

8.2 Authorship

Authorship of publications should be in accordance with guidelines from The International Committee of Medical Journal Editors' Uniform Requirements.
The first author will be the project PI. The last author will be the Co-PI. Each center participating to the project can express two researchers for authorship. All the participating members of the study group will be cited using the wording "on behalf of He.RC.O.Le.Study Group", and listing all the name of the whole study group. Specific accordance may need to be taken, prior submission, with the specific journal to permit this type of authorship.

9. Study Group National Meetings

The Study Group must meet at least twice per year and once per semester. These National Meetings can be hosted by each center participating to the study. At each meeting should be indicated who will be the next center hosting the reunion. This last one will have the

responsibility of organization and accommodation. The date of each meeting should be decided by majority. The group can decide to organize other specific events, dedicated commission or web-meetings. These events do not replace the National Meeting.

10. Retention of clinical trial documentation

Subject notes must be kept for the maximum period permitted by the hospital, institution or private practice.
The Investigator must agree to archive the documentation pertaining to the study in an archive after completion or discontinuation of the study if not otherwise notified.
Clinical study documentation must be retained until at least 2 years.

Data

Firma Responsabile del Centro di Arruolamento

Firme Ricercatori del Centro di Arruolamento (max 3)

INDIRIZZI EMAIL CONFERMATI:

Responsabile Centro:

Ricercatori del Centro (max 3):