PROTOCOLLO STUDIO NAZIONALE

Versione 1.1

25/11/2018

HE.RC.O.LE.S. PROJECT

Hepatocarcinoma Recurrence on the Liver Study

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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 Registry 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 study.

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.

2.2 Objectives

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

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

2.3 Type of Study

This is an observational multicentric retrospective cohort study.

2.4 Study population.

Planned number of subjects to be screened: almost 260 per year (patients treated/year in centres already registered as participating). Total planned number of enrollment during the study period: 2600 patients.

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.
- Patients treated between 2008 and 2017.

2.6 Exclusion criteria

- Surgery as a downstaging therapy for transplant.
- Patients who were treated with liver transplantation.

- 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 retrospective multicentric cohort nation-based study.
It evaluated patient data collected prospectively and anonymized prior to the analysis. The study protocol followed the ethical guidelines of the 1975 Declaration of Helsinki (as revised in Brazil 2013).

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. 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

HCV

HBV

HIV

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 since the retrospective nature.

3.3 Data handling.

Data collection will be performed using an electronic database system. 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 has been performed by surgeons with large experience in liver surgery. The resection technique has ben 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 has been made by CT scan or MRI scan during follow-up on a participating center-base.

3.6 Follow-Up.

All the patients has been followed using the 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 were censored in case of loosed patient at the follow-up screening. Disease-Free Survival (DFS) was defined as time interval (in months) from surgery to recurrence or death. In case of no recurrence, data were 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. This has been defined as death following tumor progression.

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 according to the actual national legislation. 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.
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 register will be conducted in accordance with the Declaration of Helsinki and according to local and regional ethical standards.

5.1 Informed consent form for trial subjects

Since the retrospective observational nature of the study, no written informed consent is provided.

6. Critical documents

Before the Investigator starts the study (i.e., insert data in the database), 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.

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 trial-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 study 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 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 for all the duration of the study analysis period. These National Meetings can be hosted by each center participating to the register. 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 trial if not otherwise notified.
Clinical study documentation must be retained until at least 2 years.