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Non-Colorectal Liver Metastases Undergoing Liver Resection: The NONCOLMET Study Group

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Abstract
Introduction: While the resection of colorectal liver metastases is a well-established procedure, with survival rates superior to chemotherapy alone, controversial data still exist on liver resection for non-colorectal liver metastases (NCRLM). These patients comprise a diverse and heterogeneous group usually excluded from surgery. To date, only few retrospective reports are available on the surgical treatment of NCRLM. The NONCOLMET study aimed to build a comprehensive registry of patients undergoing liver resection for NCRLM, providing robust retrospective and prospective data to describe clinical practices, outcomes, and identify prognostic factors. ***Methods:*** The study consists of two phases: (1) retrospective collection of data from patients treated between 2010 and 2024 and (2) prospective enrolment from 2025. Patients aged ≥18 years with histologically confirmed NCRLM undergoing liver resection will be included. Data will be recorded via a standardized electronic case report form on the RedCap platform. The following endpoints will be evaluated: oncological outcomes including overall survival, disease-free survival, and disease relapse; post-operative mortality at 30 and 90 days with causes of death; post-procedural complications; predictor variables of short- and long-term outcomes. These outcomes will be used to elaborate a risk score model. ***Conclusions:*** NONCOLMET will offer crucial insights into the surgical management of NCRLM, helping refine patient selection criteria and informing future clinical guidelines.

Introduction

Liver metastases (LM) are common in various types of malignant diseases, either at the diagnosis of the primary tumour or a later point [1]. While the resection of colorectal LM (CRLM) is a well-established procedure, with survival rates superior to chemotherapy alone, controversial data still exist on liver resection for non-colorectal LM (NCRLM) [2, 3]. These patients comprise a diverse and heterogeneous group usually excluded from surgery due to advanced tumour stage or the presence of concomitant extrahepatic disease [4, 5]. To date, no randomized clinical trial on the surgical treatment of NCRLM has been conducted, and only few retrospective reports are available.

NCRLM includes neuroendocrine tumours, oesophageal cancer, stomach cancer, pancreatic and periampullary cancer, small intestine cancer, urogenital tract tumour, breast cancer, melanoma, sarcoma, gastrointestinal stromal tumours, uveal cancer, and others. One of the reasons why liver resection remains controversial in NCRLM is due to the difference in underlying tumours, with a significantly lower survival when all possible tumour entities are considered, depending on the biological aggressiveness of the tumour [4]. Still, case series with large sample sizes have documented a 5-year survival rate of up to 42%, while without treatment, the 5-year survival rate is only <5% [6, 7]. Besides, recent data have shown that good patient selection, technical advances in medical oncology and surgical therapy have resulted in significantly better outcomes [8, 9]. Classical risk factors for poor survival, coming from studies on CRLM [10–12], included (a) aggressiveness of the primary tumour; (b) presence of extrahepatic tumour manifestation; (c) time interval between primary tumour and liver resection; (d) disease burden of the LM.

However, what has not been considered is an updated analysis of patients with non-colorectal LM evaluating: tumour biology according to contemporary biological markers; adherence to current principles of surgical oncological and response to contemporary systemic agents (including targeted therapies and immunotherapy when indicated). Therefore, it is no longer justifiable to systematically withhold the option of liver resection or other interventional locoregional therapies for patients with NCRLM. It is of paramount importance to provide updated large-scale data on the chance to cure patients with NCRLM to provide individualized indication for liver resection or other interventional therapies. Therefore, with the intent of building a new registry on surgery for NCRLM, the following Study Protocol of Non-Colorectal Liver Metastases (NONCOLMET) undergoing liver resection was established. This study protocol includes two phases: (1) retrospective collection of data on patients with NCRLM that underwent liver resection; (2) prospective collection of data on patients with NCRLM.

Methods

Design and Setting

All patients with a diagnosis, based on imaging methods and histologically confirmed, of NCRLM, consecutively referred to centres with expertise in hepatobiliary surgery will be evaluated for inclusion. No specific protocols or recommendations for the diagnostic evaluation, management or treatment of the neoplasm will be suggested. For the diagnosis and staging of disease, the participating centres will refer to the guidelines for NCRLM, together with the established clinical habits present in each centre.

Due to the strictly observational nature of the study, there will be no mandatory follow-up visits for patients. In any case, the participating centres will always record any events occurring to the patient, including death, in a timely manner, and will also collect, as far as possible, information on vital status at least once a year.

This study protocol includes two phases. Phase 1: The duration of enrolment for the retrospective phase will be from January 1, 2010, to December 31, 2024. Phase 2: The duration of enrolment for the prospective phase will be 36 months. The duration of follow-up for each patient will be a minimum of 24 months and a maximum of 60 months. Therefore, the total duration of the study (including enrolment) will be 60 months.

Eligibility Criteria

Inclusion criteria will be signatured informed consent, age ≥18 years, histologically confirmed diagnosis of NCRLM (first diagnosis or relapse), liver resection performed. Exclusion criteria will be ASA IV, severe psychiatric pathology, patient unable to follow a clinical examination pattern during observation, patient submitted exclusively to interventional locoregional procedures other than liver resection.

Outcomes

The primary objective of the NONCOLMET study is to describe the clinical epidemiology of patients with NCRLM coming to surgical observation and the surgical diagnostic-therapeutic approach adopted in the participating centres. It is, therefore, not possible to define primary and secondary efficacy endpoints for the study. The following endpoints will, however, be evaluated during the statistical analysis.

1. Oncological outcomes with the following:
   a. overall survival, defined as the time elapsed between the date of resective surgery of the NONCOLMET and the date of death for any reason. Patients who are surviving at the end of observation will be considered "censored" at the date of the last available follow-up.
   b. disease-free survival, defined as the time from resective surgery of the NONCOLMET to the date of first relapse or last available follow-up, whichever occurs first. Disease relapse is defined as disease recurrence in any site.
   c. disease relapse.
2. Post-operative mortality at 30 and 90 days with causes of death.
3. Post-procedural complications, defined according to the Clavien-Dindo classification [13] and Comprehensive Complication Index (CCI) [14].
4. Predictor variables of short- and long-term outcomes. These outcomes will be used to elaborate a risk score model. The observational cohort from the retrospective dataset (Phase 1) will be used as a training set for the model and the prospective dataset (Phase 2) as a validation set.

Recruitment

The call for this study protocol will be addressed to centres with expertise in hepatobiliary surgery, both community hospitals and academic hospitals. The University Maggiore Hospital della Carità of Novara (Novara, IT) will serve as the coordinating centre. Other national or international centres will be invited to participate in this study. The recruitment for the NONCOLMET project will be continuous throughout its duration, targeting surgeons, oncologists, academic communities, potential stakeholders in biostatistics and clinical research, physicians in general medicine, and the public. The study is currently endorsed by the Società Italiana di Chirurgia Oncologica (SICO) and will be submitted for evaluation to other national and international scientific societies. Strategies for achieving adequate participant enrolment will include creating a website with regular newsletters on updates and promotion throughout social media, national and international conferences.

Data Collection and Management

Data for the NONCOLMET study will be collected by the investigators solely using an electronic case report form (eCRF) built using the RedCap environment. RedCap is designed to comply with Good Clinical Practice (GCP) guidelines and the International Conference on Harmonisation (ICH), ensuring adherence to regulatory standards. Each local investigator will be responsible for entering data into a RedCap online form for each patient included in the study. Personal patient identifying data (name, birthdate, address, phone number, etc.) will not be recorded, while a progressive identification code and number will be adopted. Epidemiological, clinical, and related to medical and surgical therapy data will be collected on an eCRF, which can be completed by accessing a protected data system. A link to the eCRF will be sent to a designated contact person (Local Lead) at each participating centre, ensuring that no patient identifying data are transmitted. The variables collected at baseline will include those listed in the online supplementary Appendix 1 (for all online suppl. material, see https://doi.org/10.1159/000548423). Definitions for each variable included are provided in online supplementary Appendix 2.

Data Monitoring and Auditing

An independent Data Monitoring Committee will not be constituted due to the observational nature of the study and the use of already collected data. However, internal monitoring procedures will be established. This will involve periodic reviews of the data collection and entry processes to identify and rectify any discrepancies or missing information. Data quality will be assessed through random checks of the data against source documents for a subset of participants. Any amendments to data entry or collection procedures will be documented and communicated to all team members involved in the study.

Observation will be suspended if the patient withdraws consent. Patients who leave the study or cannot be found will be considered until the date of last available observation. For patients who present disease progression, or adverse events related to comorbidities not related to the neoplasm under study during remote observation, information on remote vital status will be collected.

Statistical Analysis

Statistical analyses will include all patients enrolled in the study undergoing liver resection. Continuous variables collected in the eCRF will be summarized by calculating numerosity, mean, standard deviation, minimum, median, maximum, first and third quartiles. Categorical variables will be presented by calculating absolute frequency and percentage. The 95% confidence interval of the mean and proportions will be provided to assess the level of precision of the calculated estimates. The time-dependent parameters (overall survival, disease-free survival) will be analysed with the methods of survival analysis (Kaplan-Meier curves and Cox model). All patients enrolled in the study will be evaluated for statistical analysis. Missing data will not be replaced. Exploratory analyses will be conducted using logistic regression models as appropriate. The univariable analysis will be used to test the association between baseline clinical characteristics, type of surgical procedure and study endpoints. The analysis will be performed by performing a chi-square test or Fisher's exact test, where appropriate, for categorical variables and analysis of variance for continuous variables. All variables found to be statistically significant in the univariable analysis will be included in a multivariable analysis model with the aim of identifying predictors of all-cause mortality and disease recurrence. Additionally, machine learning techniques, including Artificial Neural Networks (ANN) will be used for the multivariable analysis. These analytic results will be used to elaborate contemporary risk score models. The observational cohort from the retrospective dataset (Phase 1) will be used as a training set for the model and the prospective dataset (Phase 2) as a test set. All statistical tests will be performed using a two-tailed approach. p values <0.05 will indicate the presence of statistical significance. Data analysis will be performed using the Stata software version 16.0 (StataCorp) or higher and R version 4.2.0 or higher.

Discussion

The NONCOLMET registry aims to fill a relevant gap in current literature by providing an updated analysis of patients with NCRLM according to: tumour biology according to contemporary biological markers; response to contemporary systemic agents and adherence to current principles of surgical oncological. It will offer crucial insights into the surgical management of NCRLM, helping refine patient selection criteria and informing future clinical guidelines.

The protocol has been written following the SPIRIT 2025 Guideline [15], and the study will be conducted in accordance with the ICH, GCP, ethical standards of the Declaration of Helsinki, and current Italian regulation. The protocol and its annexes have been subject to review and approval by the Independent Ethics Committee of University Maggiore Hospital della Carità, University of Piemonte Orientale, Novara, Italy (CE387/2024), and the study protocol has been published on clincaltrials.gov (NCT06542926). The study will be formally communicated to the Ethics Committee of each participating centre, proceeding only upon obtaining authorization from each institution from the hospital.

Informed consent will be obtained from participants or their parent/legal guardian/next of kin to participate in the study. All records identifying the subject will remain confidential and, to the extent applicable by General Data Protection Regulation (GDPR) and Italian privacy laws, will not be made available to the public. The patient's name will not be requested or recorded by the Data Centre. A sequential identification number will be automatically assigned by the electronic archive software to each patient entered the practice. This number will identify the patient and must be included in all data collection forms. The investigator will keep a logbook at the centre where, to avoid identification errors, the patient's initials and date of birth will also be entered alongside a sequential code that can be traced back to the

patient identifier recorded in the database. All patient information or documentation concerning clinical study is subject to the provisions of data protection laws ("privacy"). They will only be identifiable by the authorized investigators at each centre by means of the double encryption "key," which will no longer be available outside the centre, making the patient information or documentation anonymous.

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Statement of Ethics

The study proposal was approved by the Comitato Etico Territoriale (CET) Interaziendale AOU Maggiore della Carità di Novara (Ethics Committee), under Protocol No. CE387/2024. Written informed consent will be obtained from participants to participate in the study.

Conflict of Interest Statement

Guido Torzilli and Matteo Donadon are both members of the Digestive Surgery Editorial Board at the time of submission.

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Author Contributions

Conceptualization and methodology, data curation, software, and original draft preparation: M.D.M. and M.D. Reviewing and editing: M.D., M.D.M., and G.E. Final review and approval: M.D.M., G.E., F.C., G.B., R.B., M.C., A.F., F.G., G.G., S.G., G.M., R.M., F.P., F.R., A.R., M.S., G.A.T., G.T., R.T., and M.D.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author upon reasonable requests.

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