Current Trial Report

Improving Outcome of Selected Patients With Non-Resectable Hepatic Metastases From Colorectal Cancer With Liver Transplantation: A Prospective Parallel Trial (COLT trial)

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Abstract

Background: Patients with unresectable Colorectal Liver Metastases (CLM) receiving palliative chemotherapy have a 5-year overall survival (OS) of less than 30%. Liver transplantation (LT) can improve OS up to 60%-83% (SECA-I and SECA-II trials). The aim of the study is to assess the efficacy of LT in liver-only metastatic CRC compared with a matched cohort of patients included in a phase III trial on triplet chemotherapy + antiEGFR. **Patients and Methods:** The COLT trial is an investigator-driven, multicenter, non-randomized, open-label, controlled, prospective, parallel trial (ClinicalTrials.gov NCT03803436). Hyperselected patients with liver-limited unresectable CLM, *RAS* and *BRAF* wild-type and curatively removed primary colon cancer are included. The observed post-transplant outcomes will be prospectively compared 1:5 with those obtained in a matched cohort from the TRIPLETE trial (NCT03231722). **Results:** Primary endpoint is to compare the 3 and 5-years OS of patients enrolled in the COLT trial with COLT-eligible population enrolled in the TRIPLETE trial. An expected gain in OS of 40% at 5-years is predicted for the COLT population (the expected OS at 5-years in COLT vs. TRIPLETE is 70% vs. 30%). Secondary endpoints are to compare the 5-years disease-

Abbreviations: CLM, Colorectal Liver Metastases; OS, Overall Survival; DFS, Disease-free survival; ALPPS, Associating Liver Partition and Portal vein ligation for Staged hepatectomy; TBS, Tumor Burden Score; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MSS, Microsatellite Stable; LT, Liver Transplantation; CRC, Colorectal Cancer; CT, chemotherapy; CRCC, Centralized Review and Control Committee; RECIST, Response Evaluation Criteria In Solid Tumors; NGS, Next Generation Sequencing; PBMC, peripheral blood mononuclear cell.

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free survival and to assess the safety of LT (Dindo-Clavien Classification and the Comprehensive Complication Index). **Conclusion:** LT offers the longest OS reported in selected patients with CLM. Improving the selection strategies can give patients a 5-year OS similar to other indications for LT and a better outcome than those undergoing chemotherapy alone.

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Keywords: Chemotherapy, Colorectal liver metastasis, Liver resection, Transplant oncology, Liver tumor

Introduction

In patients with unresectable metastatic colorectal cancer, modern first-line chemotherapy regimens are able to achieve a median overall survival (OS) of 30 months.[1,2] On the other hand, patients with resectable liver-only colorectal liver metastases (CLM) can reach median OS exceeding 80 months with liver resection.[3] Liver transplantation (LT), which would provide R0 tumor removal in patients with unresectable CLM, used to be performed about 40 years ago, but this field of investigation was abandoned due to poor outcomes (18% survival at 5-years).[4,5] Since then, CLM have been considered an absolute contraindication to LT up to recent years.[6]

In 2013 the results of the SECA-I study, reporting a 5-year OS of 60% for 21 patients with unresectable CLM who prospectively underwent LT, prompted renewed interest in this field.[7] In fact, despite an almost 100% recurrence rate, long-term survivors were identified in patients with a maximum tumor diameter before LT < 5.5 cm, level of carcinoembryonic antigen (CEA) before LT < 80 μg/L, response to chemotherapy and interval from resection of the primary to LT > 6 months. Based on this experience the SECA-II trial, that included 15 patients with more stringent selection criteria, reported an estimated 83% 5-year OS after LT for patients with unresectable CLM, and 3-years disease-free survival of 35%. Of the 15 patients included, 11 patients had no evidence of disease at the end of follow up.[8] The present prospective parallel study is aimed at confirming these preliminary experiences with LT in comparison to patients undergoing only highly effective chemotherapy for unresectable CLM.[9]

Patients and Methods

The COLT trial is an investigator-driven, multicenter, non-randomized, open-label, controlled, prospective parallel trial aimed at assessing the efficacy (in terms of OS) of LT in liver-only metastatic colorectal cancer (CRC), compared with a matched cohort of patients with the same tumor characteristics, collected during the same time period, and included in a phase III trial on triplet chemotherapy + antiEGFR (TRIPLETE trial, NCT03231722, investigating modified FOLFOXIRI plus panitumumab vs. mFOLFOX6 plus panitumumab) coordinated by the GONO Group (Gruppo Oncologico Nord Ovest).

Study Endpoints

The primary endpoint is to compare the 3-and 5-years OS of patients enrolled in the COLT trial with the COLT-eligible subpopulation of patients enrolled in the parallel TRIPLETE trial conducted over the same period of time.

The secondary endpoints are to compare the 5-years disease-free survival and the pattern of recurrence/progression of transplanted patients enrolled in the COLT trial with the OS in the liver-limited population enrolled in the ongoing TRIPLETE trial converted to potentially curative surgical resection. The safety of LT, by means of Dindo-Clavien Classification and the Comprehensive Complication Index, integrated with a specific list of complications possibly related to LT, will also be assessed. Translational genomics, transcriptomics and proteomics analyses on blood, plasma, peripheral blood mononuclear cell samples and fresh-frozen tumor tissue samples will be retrospectively and prospectively collected in order to identify early tumor relapse and monitor tumor recurrence.

Inclusion Criteria

The main inclusion criteria for patients' enrollment will be:

- Age ≥ 18 and ≤ 69 years.
- Adenocarcinoma of the colon or the upper rectum, pT1-3, pN0 or pN1 (metastases in < 4 regional lymph nodes, a minimum of 12 lymph nodes should be examined), absence of peritoneal tumor deposits, absence of mucinous component >50%, confirmed R0 resection with adequate tumor free margin.
- *RAS* wild-type, *BRAF* wild-type and MSS molecular status
- Absence of extra-hepatic metastatic disease or local recurrence according to CT scan + MRI + PET/CT scans.
- Liver metastases not eligible for curative liver resection.
- Objective response according to RECIST 1.1 to first-line treatment, with sustained response for at least 4 months, OR disease control (CR+PR+SD) during second-line treatment for at least 4 months.
- A maximum of 2 prior chemotherapy treatment lines.
- Performance status, ECOG 0.
- CEA<50 ng/ml
- Absence of hereditary syndromes including familial adenomatous polyposis and Lynch syndrome.
- No prior extra hepatic metastatic disease or primary tumor local relapse.

A crucial requirement for the determination of study eligibility will be the assessment of CLM non-resectability. Non-resectability will be determined according to at least one of the following conditions, as detailed in Table 1:

- Impossibility to achieve an R0 resection
- Estimated risk of perioperative mortality > 5% to achieve R0 resection

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Table 1 Criteria for Non-Resectability

No chance to achieve R0 resection
- Resections with high likelihood of *suboptimal R1 tumor removal* will be considered as eligible for the COLT study if focal microscopic tumor infiltration is predicted in one or more anatomic sites (ie, main hepatic vein, portal vein, biliary bifurcation)
- *Vanishing lesions* after first-line chemotherapy (complete radiologic responses) should be considered for the study as for vital metastases with a diameter of less than 1-cm
- *Residual intrahepatic metastases* that can be treated only by thermal ablation should be considered as non-resectable and therefore are eligible for the study
No chance to preserve enough liver volume in case of tumor resectability
- The predicted liver remnant after tumor removal should not be < 25%-30% of the total liver volume (in case of healthy liver) or <40% (in case of post-chemotherapy histology-confirmed fibro-steatosis)
No chance to achieve R0 resection by means of complex parenchyma-regenerating procedures with a predicted risk of perioperative mortality ≤ 5%
- Examples of operations to be considered in this "complex procedures group" are: ALPPS, liver resections with replacement of vascular segments, ex-situ and ante-situ liver resection, resections with of veno-venous bypass, failed fist-stage of a planned 2 stage hepatectomy with portal vein embolization or ligation, major hepatectomies combined with multiple ablations
Tumor burden score (sum of maximum size in cm and number of nodules) ≥ 9 According to large international datasets these patients, if resected, show 19.8%-29.9% OS at 5 years (Sasaki K et al., Ann Surg 2018)[10], which is similar to that one achieved with hyper-intensive first-line chemotherapy regimens applied in non-resectable patients
Abbreviations: ALPPS = Associating Liver Partition and Portal vein Ligation for Staged hepatectomy; OS = Overall Survival

- Tumor burden score (TBS) ≥ 9, defined according to the following formula[10]: TBS=$\sqrt{}$(maximum tumor diameter)^2 + (number of liver lesions)^2

The final evaluation of non-resectability, as well as the confirmation of fulfillment of inclusion criteria, will be assessed by a multidisciplinary centralized review board.

Centralized Review and Control Committee

A multidisciplinary Centralized Review and Control Committee (CRCC) is the crucial component of the study, in order to validate patients' inclusion in the COLT trial and collect essential information on trial conduction. The CRCC will meet at least every month (or more often if required by Centers asking to include patients) on an Internet Platform allowing for teleconference and data sharing (digital imaging).

The CRCC will include:

- Five expert hepato-biliary surgeons: one from Coordinating Center, 1 surgeon with large experience in liver resection and no direct participation to the study, 3 surgeons from the participating Centers on a voluntarily based candidacy.
- Two medical oncologists from those Centers participating to the study planning.
- One radiologist from Coordinating Center.

At the CRCC meetings, any participating Center wishing to include a patient in the trial will extensively present patients' history and upload baseline and updated post-treatment CT scans/MRI scans. These latter will be permanently stored on the Internet platform. Patients will be given a trial number at this time point, that is after a final judgment by the Committee on patients' eligibility will be made.

Study Design

Patients fulfilling the inclusion criteria of the study will undergo clinical, translational and regulatory steps summarized in Figure 1.

The main steps of the study can be summarized as follows:

- Patients consent to be included in the trial by a written informed consent.
- The clinical cases are discussed the CRCC.
- Once the CRCC confirms patient's eligibility, patients should be activated on the transplant waiting list within 1 month from signing the informed consent.
- In case of radiological progression according to RECIST 1.1 or CEA > 50 ng/mL, the patient will be suspended from the transplant waiting list (early drop-out). Drop-outs during first line chemotherapy may be reactivated on the list if disease control is maintained during second-line treatment for at least 4 months. Drop outs during second-line chemotherapy won't be reactivated on the list.
- The chemotherapy regimens allowed in the COLT study are fluorouracil, oxaliplatin and irinotecan-based schemes with or without anti-EGFRs, with dosages according to local guidelines. Bevacizumab and aflibercept or other anti-VEGF are not allowed.
- During liver transplantation, a careful abdominal exploration will be performed to exclude extrahepatic disease. Intraoperative evidence of extrahepatic disease should be considered a controindication to proceed with LT. Once extra-hepatic disease has been ruled out, LT should be carried out according to local standards.
- Follow up after LT will be conducted according to institutional standards. Oncologic outcomes will be checked at least every 4 months for the first 3 years and every 6 months afterwards. Immunosuppression will follow local standards.

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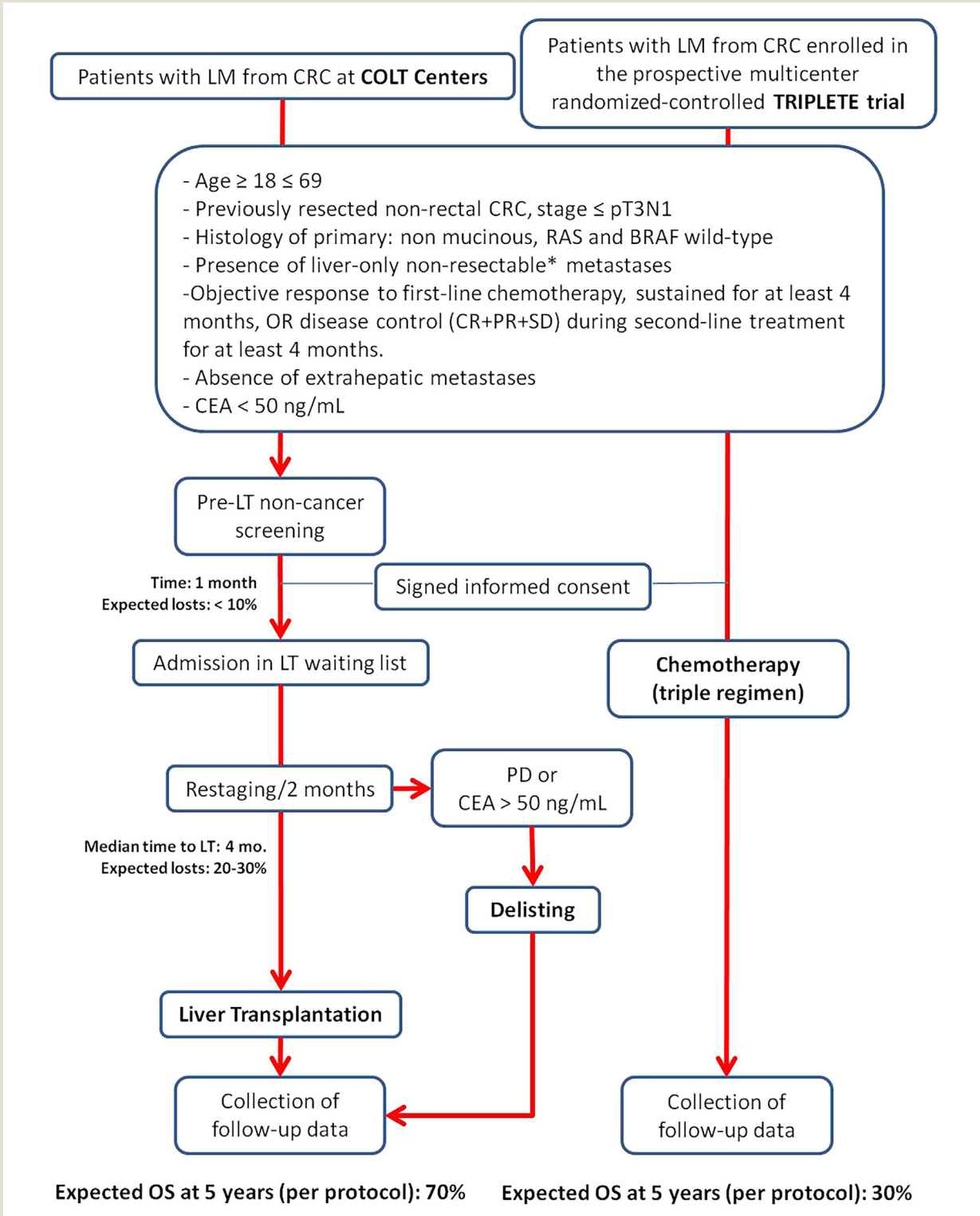
Figure 1 Study design.



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- Control arm: patients with liver-limited metastases, disease response according to RECIST 1.1 and progression free survival of at least 4 months will be asked through informed consent to be included in the COLT trial as part of the matched, non-randomly allocated control arm.

Sample Size Calculation and Statistical Analysis

An expected gain in OS of 40% at 5 years is predicted for the per-protocol COLT population in comparison with the parallel TRIPLETE trial (the expected OS at 5 years in COLT vs. TRIPLETE populations is 70% vs. 30%). Assuming that 80% of patients enrolled in the COLT study will undergo transplantation, and that the 5-year survival (OS) of patients will be 70% and 30% respectively for patients whether or not they have undergone transplantation, the expected 5-year OS of the COLT study patients will be 62%. The 5-year OS of patients in the TRIPLETE study is assumed to be 30% at 5 years. A hazard ratio (HR) = 0.40 will be detected with 5% two-sided type α-error and 80% power. Assuming a 1:5 allocations between the COLT and TRIPLETE study, a total number of 68 events will be needed. To ensure sufficient robustness of the estimates, it will be necessary to enroll at least 25 patients in the COLT study, in an expected time of 2 to 3 years, with a follow-up of 5 years from the end of the enrollment.

Both primary and secondary endpoints will be analyzed in an intention-to-treat and per-protocol fashion. The primary analysis will be performed using the restricted mean survival time method, as described by Royston P. and Parmar M.K.B.[11]

The following secondary analyses will also be carried out:

1 Multivariate analysis: a propensity score analysis will be performed to control for selection biases.
2 Transplantation efficacy: a stratified log-rank and Cox model will be adopted for the analysis and the product limit method will be used to compute the survival over time for the 2 groups.
3 Evaluation of post-transplant survival and disease-free survival
4 A descriptive safety analysis will be performed.

Ethics

The trial was approved by the competent authorities, by the ethics committee at Milan-INT and by the responsible ethics committees of all participating Centers.

Discussion

Metastatic CRC is associated with a poor prognosis, with a 5-year OS of less than 30%. While resectable CLM can be potentially cured with liver resection, the only current therapeutic option for unresectable CLM is palliative chemotherapy. Two recent trials from the Oslo group[7,8] have demonstrated that LT could offer a chance of cure for hyperselected patients with unresectable CLM, with 5-year OS of 60-83%: since then, several studies have been designed and are ongoing aiming at confirming such results.[12]

The COLT trial is the first Italian prospective study on LT in liver-only metastatic CRC, with some distinctive features with respect to the other ongoing trials. Firstly, it aims at comparing the results of LT to those of chemotherapy-only regimens with a parallel rather than a randomized design. This choice was made for ethical reasons, since the expected outcome of LT is strikingly different from that of chemotherapy only, and randomization would not seem completely acceptable from a medical and patient perspective. The parallel prospective design, together with a robust post-hoc statistical matching, is expected to guarantee a meaningful comparison between the outcomes of the 2 therapeutic strategies.

The second peculiar feature of the COLT trial is the definition *a priori* of the criteria for unresectability of liver lesions (as shown in Table 1). The opinions on resectability in fact are often heterogeneous even between HPB surgeons,[13] and depend on several factors that may prescind from the pure technical aspect. In this trial, unresectability is defined as eligible according to 3 domains that cover the different aspects of surgical evaluation (1) technical: impossibility of achieving R0 resection (also considering vanishing lesions as present) (2) short term outcomes: > 5% expected mortality in case of resection (3) long term outcomes: TBS $\geq$ 9, with expected 5-yr OS < 30% in case of resection.

Finally, with respect to other trials, the inclusion criteria of the COLT trial are very restrictive and aim at selecting those patients who may have a better survival and reduced risk of recurrence after LT. In particular, restrictions according to location (non-rectal), pN status (<pN2) and pT status (<pT4) of the primary tumor have been defined in order to reduce the risk of post-LT lung or peritoneal recurrence. Moreover, eligibility has been restricted to tumors with favorable molecular status (RAS and BRAF wild-type & MSS) and response/stability at maximum 2 lines of chemotherapy, in order to possibly select chemoresponsive tumors.

Conclusion

Results from this trial will shed some light on the safety and efficacy of LT as a curative treatment option for hyperselected patients with unresectable liver-only CLM. Combined with the results of other ongoing trials on LT for CLM, these findings will help establish whether LT for unresectable CLM can be offered to an identifiable patient's subgroup.

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Disclosure

The authors have stated that they have no conflicts of interest.

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