

The effect of preoperative chemotherapy on liver regeneration after portal vein embolization/ligation or liver resection in patients with colorectal liver metastasis: a systematic review protocol

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Protocol

Keywords: liver regeneration, liver resection, portal vein embolization, colorectal cancer liver metastasis, neoadjuvant chemotherapy

Posted Date: August 2nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-50168/v1>

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Version of Record: A version of this preprint was published on December 4th, 2020. See the published version at <https://doi.org/10.1186/s13643-020-01545-w>.

Abstract

Introduction The primary objective of this systematic review is to assess the effect of neoadjuvant chemotherapy on liver regeneration after liver resection (LR) or portal vein embolization (PVE) in patients with liver metastasis from colo-rectal cancer. The secondary objectives are to evaluate the impact of the type of chemotherapy, number of cycles and time between end of treatment and procedure (LR or PVE) and to investigate whether there is an association between degree of hypertrophy and postoperative liver failure. **Methods** The design of this systematic review will follow the current recommendations of PRISMA. After an exhaustive literature search with pre-established criteria, two researchers will individually screen the identified records, according to a list of inclusion and exclusion criteria. Primary outcome will be future liver remnant regeneration rate. All data will be registered in a predesigned database. In the event of a substantial heterogeneity of selected articles, a narrative systematic review will be performed. **Discussion** The results of this systematic review may help to better identify the patients affected by liver metastasis that could present low regeneration rates after neoadjuvant chemotherapy. These patients are at risk to develop liver failure after extended hepatectomies and therefore are not good candidates for such aggressive procedures. Systematic Review Registration PROSPERO registration number: CRD42020178481 (July 5th 2020).

Background

Description of the condition

Colorectal cancer is the fourth most frequently diagnosed cancer and the second cause of death related to cancer(1). More than 50% of the patients diagnosed with colorectal cancer will develop metastases in the course of their disease(2). 20-30% of these will be confined exclusively in the liver (CRCLM)(3). To date, liver resection (LR) remains the only curative option for patients with CRCLM(2,4,5), with survival rates that may reach 50% and 26% at 5 and 10 years, respectively(6). The importance of complete treatment of all liver disease is reflected by the fact that up to 97% of 10-year survivors do not develop recurrence after CRCLM resection(7).

However, more than 80% of CRCLM patients will have unresectable disease at the time of diagnosis(2,8,9). Several prospective trials have shown encouraging results for preoperative chemotherapy, with conversion rates to resectable disease of 12.5-60%, depending on tumor biology and type of regimen used(10–14). Furthermore, current guidelines recommend preoperative chemotherapy for the majority of CRCLM patients with resectable disease(4,5). The justification for this type of recommendations is to lower the probability of microscopic disease, to test the response to the treatment and to identify the patients with aggressive disease in whom resection would not be indicated(15). Therefore, the majority of CRCLM patients who reach LR will have received some form of neoadjuvant chemotherapy.

One of the most important complications after LR is liver failure, which leads to a higher probability of major postoperative complications and death(16). Major post-LR complications are usually associated with a significant increase in hospitalization time and higher postoperative costs(17,18). Current data demonstrates a correlation between liver failure and the extent of LR, highlighting the importance of planning a sufficient future liver remnant (FLR) (i.e. the volume of liver to be preserved after LR) when undertaking liver resection (19,20). In the context of CRCLM, in order to avoid liver failure, a minimum FLR of 30% is recommended(19,21,22). For smaller FLRs, strategies for manipulating liver volume may be used, such as portal vein embolization (PVE), two-stage hepatectomy or associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)(19,22,23).

Preoperative chemotherapy may cause liver histological changes, such as sinusoidal obstruction syndrome (SOS) and non-alcoholic steatohepatitis (NASH)(21). SOS has been associated with oxaliplatin regimens, while NASH is described particularly with irinotecan-based chemotherapy(24,25). Both syndromes may cause an increase in postoperative complications index, although NASH has especially been associated with higher rates of postoperative liver failure(21,24).

One of the key events in the liver response to the injury (i.e. LR) is the occurrence of regeneration or hypertrophy. At a cellular level this process is more accurately described as a compensatory hyperplasia, given that the remaining liver tissue expands in order to meet the organism requirements(26). In healthy livers, regeneration restores liver volume to more than 80% of the preoperative value, three months after major LR(27). However, several factors may impair adequate hepatic regeneration. The majority of these are also associated with postoperative liver failure: steatosis, fibrosis or cirrhosis, obstructive cholestasis, ischemia etc.(19,28). Since preoperative chemotherapy causes proven histological changes in the liver, a link between neoadjuvant treatment and insufficient hypertrophy of the liver remnant may exist. However, to date, the available data remains controversial. Details about this matter are offered in the subchapter "How the intervention might work?".

Description of the intervention

Current US and European guidelines establish the preferred neoadjuvant chemotherapy depending on the liver disease characteristics (4,5). However, there is a great degree of variability on the indications for neoadjuvant chemotherapy and on the type of treatment used, depending on each hospital's local protocol. For this reason, definitive conclusions concerning the oncological results as well as the occurrence of postoperative complications related to the chemotherapy are difficult to obtain outside randomized control trials or systematic reviews. The effect of neoadjuvant chemotherapy on postoperative liver regeneration is subject to the same variability and remains uncertain.

How the intervention might work

The effect of neoadjuvant chemotherapy on liver regeneration may be considered from several different perspectives.

First, neoadjuvant chemotherapy can cause histological changes in the liver which may impair regeneration after surgery or post-embolization. As shown by several studies, steatosis and NASH are related to preoperative chemotherapy(21,24,25). Liver steatosis reduces hypertrophy after major hepatectomy in animal models(29). In addition, some publications have shown lower regeneration rates after major hepatectomy in obese patients(30). Furthermore, there are studies that have demonstrated a direct correlation between lobular inflammation or fibrosis and liver regeneration rate(31). Other authors mention the association of SOS with lower liver regeneration rates and increased indicators of liver failure(32). However, the deleterious effect of neoadjuvant chemotherapy on liver regeneration are probably less evident in patients submitted to minor hepatectomies, since in these cases the percentage change in future liver volume is lower than after major hepatectomy(33).

Second, the impact of the number of preoperative chemotherapy cycles on liver regeneration is still not known. Some studies describe lower regeneration rates with more than six cycles of treatment(34), while other studies did not find such differences in the post-procedure hypertrophy rates(31).

Third, the time interval between completion of chemotherapy and the procedure could be important. Some studies report differences in the post-procedure regeneration rates in patients with less than eight weeks of chemotherapy-free interval, especially when dealing with bevacizumab regimens(35). However, other studies have failed to reproduce the same results(31).

Finally, the type of chemotherapy might be important. This debate is generally related to regimens containing bevacizumab. This molecule is a monoclonal antibody that targets vascular endothelial growth factor (VEGF)(36). Its addition to classical chemotherapy regimens has showed an improved response and prolonged disease-free survival rates in patients with initially unresectable disease(37). Concerns about the possible deleterious effect of bevacizumab on liver regeneration have been raised after experimental studies have shown that neutralization of VEGF inhibited proliferative activity of hepatocytes(38). However, this effect in human patients is still debated(35).

This systematic review will study the effect of neoadjuvant chemotherapy and of its characteristics (type, number of cycles and time from the end of treatment until intervention) on liver regeneration.

In accordance with current guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on July 5th 2020 (registration number CRD42020178481).

OBJECTIVES

The main objective is to assess the effects of neoadjuvant chemotherapy on liver regeneration after LR or PVE in patients with CRCLM when compared to patients without chemotherapy before the procedure

(defined as LR or PVE).

Secondary objectives are as follows:

- evaluate the impact of type of chemotherapy, number of cycles and time between end of treatment and procedure on liver regeneration after LR or PVE in patients with CRCLM
- assess the association between liver hypertrophy rate (defined below in *Outcomes*) and index of postoperative liver failure/liver dysfunction in patients with neoadjuvant chemotherapy.

Methods

Study Eligibility Criteria

Studies selection will be performed according to the PICO criteria of PRISMA described below(39).

Types Of Studies

Randomized controlled trials (RCTs), including cluster RCTs, controlled (non-randomized) clinical trials (CCTs) or cluster trials, controlled before-after (CBA) studies, prospective and retrospective comparative cohort studies, and case-control or nested case-control studies will be included. Cluster randomized, cluster non-randomized, or CBA studies will be included only if there are at least two intervention sites and two control sites. Cross-sectional studies, case series, and case reports will be excluded.

Type Of Participants

We will include adult patients with CRCLM and with indication to perform LR or PVE, irrespective of the number of lesions or their localization. At least two volumetric estimations of FLR, one before and one after the procedure (LR or PVE) will be required for the inclusion of the study in the current review. The usual indication to perform PVE is an insufficient FLR. Accordingly, a separate analysis for LR and PVE indications will be performed.

Type Of Interventions

In order to achieve the primary objective, the type of intervention to be taken into account will be neoadjuvant chemotherapy, irrespective of type, number of cycles or other characteristics. According to the National Cancer Institute, neoadjuvant chemotherapy is defined as “treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery”(40).

In order to achieve the secondary objectives, we will perform sub-analysis for the following type of interventions:

- Type of chemotherapy –addition of bevacizumab to the chemotherapy regimen.

- Number of cycles: the intervention will be administration of more than 6 cycles of neoadjuvant chemotherapy. Depending on the data found in the selected studies, this number may be changed.
- Time between the end of chemotherapy and the procedure (LR or PVE): the intervention will be considered when this wait is less than 8 weeks. Depending on the analysis performed in the selected studies, this number may be changed.

Comparators

For the primary objective, the control group will include patients without chemotherapy submitted to the procedure (defined as LR or PVE). We will accept studies in which the control group contains patients with benign disease or other types of neoplasia. However, these studies will be carefully analyzed to detect possible biases of selection.

For the secondary objectives, the control group can include patients with chemotherapy that do not meet the type of intervention mentioned above, patients without chemotherapy (similar to primary objective) or both.

Outcomes

Primary Outcomes:

- *Liver regeneration/hypertrophy rate: future liver remnant regeneration rate (FLR³)*, calculated as follows:

$$FLR^3 = \frac{FLR_f - FLR_i}{FLR_f}$$

Where FLR_f is the final future liver remnant (after the procedure – LR or PVE) and FLR_i is the initial future liver remnant (before the procedure). The timing of FLR_f will depend on the data reported in the selected studies, but we expect mainly volumetric data in the first month after the procedure, giving that the most part of the hypertrophy occurs in this interval.

- *Surrogate volumetric data:*
 - Total liver volume changes.
 - Changes in the volume of the liver to be resected (derived from pre- and post-procedure volumes in the case of PVE and pre-procedure volumes and weight of the resected liver in the case of LR).

Secondary Outcomes:

- *Postoperative liver failure or liver dysfunction.* Accepted definition of liver failure will be:

- 50-50 criteria as proposed by Balzan – association of a prothrombin time of less than 50% and serum bilirubin of more than 50 µmol/L on 5th postoperative day(16).
- Bilirubin peak of more than 120 µmol/L during the postoperative period of a major hepatectomy(41).
- Grade B and C of post-hepatectomy liver failure according to International Study Group of Liver Surgery(42).

Review eligibility criteria

We will include studies independently of geographic location or year of publication. We will accept unpublished material and abstracts from congresses. There will be no language restrictions. Editorials, letters or commentaries will be excluded during the screening of titles and abstracts. Experimental studies on animals will also be excluded.

Information sources

Electronic Searches

Literature search strategies will be conducted using medical subject headings (MeSH) and text words related to the objectives of this systematic review. We will search the following electronic databases:

- PubMed (1990 to present)
- Scopus (1990 to present)
- Web of Science (1990 to present)
- Embase (1990 to present)
- Cochrane Central Register of Controlled Trials (1996 to present)

The key words used to perform the search in each electronic database are shown in Appendix 1.

Before proceeding to write the manuscript draft, the search of the literature will be updated, in order to identify any new publication which could be relevant to the objectives of this systematic review.

Searching Other Resources

Reference lists of all primary studies and review articles will be manually searched for additional references. Authors of identified studies will be contacted if needed in order to ask them to identify other published and unpublished studies. Errata or retractions from eligible studies will be searched on PubMed and the date this was done will be reported in the review.

Data Collection and Analysis

Data Management

Literature search will be loaded in a specially created Mendeley folder in order to access to titles and abstracts and will be listed in a specially created Excel file with the following coding: included, not included and 2nd look. Several methods will be used to identify duplicate publications: juxtaposing author names and comparing sample sizes, outcomes and text of the abstract.

Selection process

Two review authors (MP and RC) will independently screen titles and abstracts of all the potential studies identified as a result of the search, and code them as “included”, “not included” or “2nd look”. Full text of study reports coded as “included” or “2nd look” will be retrieved and two review authors (MP and RC) will independently analyze the full text, identifying studies for inclusion and recording reasons for exclusion of the ineligible studies. Study authors will be contacted when additional information will be needed to resolve questions about eligibility. Any disagreement between the two authors will be solved by a 3rd reviewer (RJ). Duplicates and collate multiple reports of the same study will be identified and excluded, thus each study rather than each report will be the unit of interest in the review. The selection process will be recorded in sufficient detail to complete a PRISMA flow diagram and a table of excluded studies features.

Data collection process

An Excel-based data collection form will be used to register study characteristics and outcome data. The data collection will be piloted on five studies previously identified as significant for this review. Two review authors (MP and RC) will independently extract study characteristics and outcome data from included studies. Any disagreement between the two authors will be solved by a third reviewer (RJ). To ensure consistency across reviewers, calibration exercises will be conducted before starting the review. Study corresponding authors will be contacted to resolve any uncertainties (three e-mail attempts at maximum). In order to extract data not reported in a numeric format, graphically presented data will be translated into usable format using OriginPro v 7.5 from OriginLab. Before final revision of the draft, another search will be performed in order to identify duplicate publications among the selected articles, following the same previously described methodology.

Data Items

The following study characteristics and outcomes will be extracted:

1. *Methods*: study design, total duration of study and run-in period, number of study centers and location, study setting, withdrawals, date of study.
2. *Participants*: number, mean age, age range, gender, inclusion criteria, exclusion criteria.
3. *Interventions*: intervention, comparison, and any cointerventions.
4. *Outcomes*: primary and secondary outcomes specified and collected, time points reported.

5. *Notes:* funding for trial, notable conflicts of interest of trial authors.

Outcomes And Prioritization

The main outcome of this systematic review will be FLR³, which represents the hypertrophy of the remnant liver after surgery. This outcome is derived from the estimated volume of the remnant before and after the intervention (LR or PVE). Even though both interventions induce liver hypertrophy, presumably FLR³ after LR or PVE will not be comparable. Therefore, FLR³ will be analyzed separately after each one of the interventions. FLR³ data will be expressed as mean \pm SD. If data is offered in other forms (median – range or median – IQR), mean \pm SD will be calculated following the recommendations of Cochrane Handbook for Systematic Reviews of Interventions, whenever possible.

Regarding the timing of post-procedure volume calculation, homogenous data are expected in PVE studies. The majority of preoperative PVE protocols plan surgery four weeks after the embolization procedure. However, the timing of remnant volumetry after LR could vary between studies. The majority of included studies most likely perform volume calculation one month after the procedure, when 80% of liver hypertrophy has occurred. Whenever remnant volume has been calculated at several time points, the one obtained at one month after LR will be chosen. The time of post-procedure volumetry will be registered for each study.

The secondary outcome will be liver failure/dysfunction as defined above. This outcome will be calculated only for patients submitted to LR. This outcome will try to determine whether there is a correlation between a possible lower hypertrophy rate in patients with neoadjuvant chemotherapy and subsequent liver dysfunction rate.

Assessment of bias

Two investigators (MP and RC) will independently assess risk of bias for the included studies. Risk of bias will be assessed by the ROBINS-I tool for non-RCT studies(43). In this tool, risk of bias is assessed within specified domains, including (1) bias due to confounding, (2) bias in selection of participants into the study, (3) in classification of interventions, (4) bias due to deviations from intended interventions (5) bias due to missing data, (6) bias in measurement of outcomes, (7) bias in selection of the reported result, and (8) overall bias. Since assessments are inherently subjective and there are no strict and objective criteria to judge bias within the ROBINS-I tool, disagreements will be resolved via discussion between the two investigators or by the intervention of a third (RJ).

Quality assessment

The quality of each selected article will be assessed by one reviewer and verified by another. The quality of evidence will be determined with the Grading of Recommendations Assessment, Development and

Evaluation (GRADE) system(44).

Data Synthesis

If selected studies are sufficiently homogeneous in design and comparators, we will perform a meta-analysis of reported results.

Measures Of Treatment Effect

Dichotomous data (liver failure or dysfunction as previously defined or presence of ascites, encephalopathy) will be analyzed by using risk ratio (RR) with 95% confidence interval (CI) and continuous outcomes (FLR³ or surrogate volumetric data - total liver volume changes and changes in the liver volume to be resected) as mean difference or standardized mean difference when different scales are used (e.g. FLR³ vs surrogate volumetric data).

If a study is suspected of comprising skewed data, this is commonly indicated by reporting medians and interquartile ranges. When this is found, transformations to mean differences will be carried out. If this is not possible due to lack of data, the data will be considered as skewed. If the data are skewed, a meta-analysis will be not performed, though a narrative summary will be provided instead.

Unit Of Analysis Issues

The unit of analysis will be individual participants affected by liver metastasis and candidates for LR or PVE. If any cluster-randomized studies are unexpectedly found, the data will be included in the analysis if the results are adjusted for intra-cluster correlation. If any cross-over randomized studies are found, the data prior to the cross-over will be included. When a study has more than two treatment groups, the additional treatment arms will be presented. Where the additional treatment arms are not relevant, they will not be taken into account.

Dealing With Missing Data

Investigators or study sponsors will be contacted to verify key study characteristics and obtain missing numerical outcome data (e.g. when a study is presented as abstract only). If this information is not available from the study authors, it will be obtained, where feasible, by using calculations provided in the Cochrane Handbook for Systematic Review Interventions. The impact of including such studies will be assessed in a sensitivity analysis. If we are unable to calculate the standard deviation from standard error, interquartile range, or P values, we will impute standard deviation as the highest standard deviation in the remaining studies included in the outcome.

Assessment Of Heterogeneity

Clinical heterogeneity will be tested by considering the variability in participant factors among trials (for example age) and trial factors (randomization concealment, blinding of outcome assessment, losses to follow-up, treatment type, co-interventions). Statistical heterogeneity will be tested using the Chi² test (significance level: 0.1) and I² statistic (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). If high levels of heterogeneity among the trials exist (I² >=50% or P <0.1) the study design and characteristics in the included studies will be analyzed. The source of heterogeneity by subgroup analysis or sensitivity analysis will be explained.

Data Synthesis

Each outcome will be calculated using the statistical software RevMan 5.1, according to the current version of the Cochrane Handbook for Systematic Reviews of Interventions. The Mantel-Haenszel method will be used for the fixed effect model if tests of heterogeneity are not significant. If statistical heterogeneity is observed (I² >=50% or P <0.1), the random effects model will be chosen. Data will be presented in text and tables, in order to summarize the characteristics and findings of included studies. The analysis will describe the findings and associations within individual studies as well as among all the studies included in this review.

Subgroup Analysis And Investigation Of Heterogeneity

Subgroup analysis will be used to investigate possible sources of heterogeneity, based on the following parameters:

- General characteristics of included patients (age, sex)
- Timing of post-procedure volumetry
- Type of procedure (hepatectomy vs PVE)

Sensitivity analysis will be performed to explain the source of heterogeneity:

- Analysis of the material retrieved (full text vs abstract only, preliminary data vs final results, published vs unpublished material)
- Risk of bias (performing analysis by omitting studies evaluated as of high risk of bias)

Amendments

If there is a need to amend this protocol, the date of each amendment will be registered, describing the change and giving the rationale in this section. Changes will not be incorporated into the protocol.

Reaching conclusions

Conclusions will be based on findings from the quantitative or narrative analysis of the studies included in this review. We will avoid making recommendations for clinical practice but we will focus on the remaining uncertainties in the field and the need for future clinical investigation.

Discussion

To date, there is sufficient data to conclude that postoperative liver regeneration is a key factor in avoiding postoperative liver failure. Factors associated with postoperative liver failure are also associated with impaired liver regeneration(19,28). Furthermore, predicted insufficient FLR volume represents an indication to perform alternative techniques in order to stimulate liver hypertrophy such as preoperative PVE, two-stage hepatectomy or ALPPS(19,45). Since liver failure is associated with higher rates of postoperative death, it is important to evaluate whether neoadjuvant chemotherapy may cause a deficit in liver regeneration.

However, there are no systematic reviews that analyze specifically the association between chemotherapy characteristics and post-procedure hypertrophy. A number of important prospective randomized controlled trials establish as a primary objective the oncological results or the postoperative complication rates(3,37,46,47). Furthermore, the heterogeneity of regimens used, the different protocols of treatments and the lack of volumetric data in published studies makes it difficult to draw definitive conclusions regarding the role of neoadjuvant chemotherapy in liver regeneration without a properly conducted systematic analysis. Therefore, the need of a systematic review centered on this issue is evident.

Abbreviations

ALPPS - associating liver partition and portal vein ligation for staged hepatectomy

CBA – controlled before-after study

CCT – controlled clinical trial

CRCLM – colorectal cancer liver metastases

FRL – future liver remnant

FLR³ – future liver remnant regeneration rate

LR – liver resection

NASH – non-alcoholic steatohepatitis

PVE – portal vein embolization

RCT – randomized controlled trial

SOS – sinusoidal obstruction syndrome

Declarations

Ethics approval and consent to participate

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

Funding

The study was performed exclusively by members of the HBP Unit of University Hospital of Tarragona Joan XXIII. No funding has been received for this study.

AUTHORS' contribution

Conceiving the protocol: Mihai-Calin Pavel, Laia Estalella

Designing the protocol: Mihai-Calin Pavel, Raquel Casanova, Rosa Jorba

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Designing search strategies: Mihai-Calin Pavel, Raquel Casanova

Writing and reviewing the protocol: Mihai-Calin Pavel, Raquel Casanova, Laia Estalella, Robert Memba, Erik Llacer, Mar Achalandabaso, Elisabeth Julia, Justin Geoghegan, Rosa Jorba

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ACKNOWLEDGEMENTS

We would like to thank Miss Gemma Falcó, medical librarian, for her valuable help provided to perform the literature search.

AUTHORS' INFORMATION

The HBP unit of Hospital Universitari de Tarragona Joan XXIII is an emergent group, formed by several surgeons with an important background in HBP surgery. Our unit is the only one in Tarragona province approved to perform liver resections for colorectal liver metastasis.

MCP is currently the coordinator of the HBP Committee of Tarragona province, Spain. Together with LE, he is responsible for the management of the waiting list of patients with CRCLM for the University Hospital of Tarragona Joan XXIII.

RJ is the chief of General Surgery Department of University Hospital of Tarragona Joan XXIII. RM is the coordinator of the HBP unit.

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