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Original Article - Technique

PROTOCOL FOR LIVER TRANSPLANTATION IN UNRESECTABLE COLORECTAL METASTASIS

PROTOCOLO DE TRANSPLANTE HEPÁTICO PARA METÁSTASE COLORRETAL IRRESSECÁVEL

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ABSTRACT – **BACKGROUND:** Colorectal cancer (CRC) is the third most common neoplasm, and half of the patients with CRC develop liver metastasis. The best prognostic factor for colorectal liver metastasis (CRLM) is the possibility of performing a resection with free margins; however, most of them remain unresectable. The justification for performing liver transplantation (LT) in patients with CRLM regards an increase in the number of resectable patients by performing total hepatectomy. **AIM:** The aim of this study was to provide a Brazilian protocol for LT in patients with unresectable CRLM. **METHOD:** The protocol was carried out by two Brazilian institutions, which perform a large volume of resections and LTs, based on the study carried out at the University of Oslo. The elaboration of the protocol was conducted in four stages. **RESULT:** A protocol proposal for this disease is presented, which needs to be validated for clinical use. **CONCLUSION:** The development of an LT protocol for unresectable CRLM aims to standardize the treatment and to enable a better evaluation of surgical results.

HEADINGS: Transplantation. Liver Transplantation. Colorectal Neoplasms. Neoplasm Metastasis.

RESUMO – **RACIONAL:** O câncer colorretal é a terceira neoplasia mais frequente e metade dos pacientes desenvolvem metástase hepática. O melhor fator prognóstico na metástase hepática de câncer colorretal (MHCCR) é a possibilidade de ressecção com margens livres, porém a maioria permanece irressecável. O racional em realizar transplante hepático (TH) em pacientes portadores de MHCCR está na ampliação do número de pacientes ressecáveis através de uma hepatectomia total. **OBJETIVO:** Apresentar protocolo brasileiro para realização de transplante hepático em pacientes com MHCCR irressecável. **MÉTODO:** O protocolo foi realizado por duas instituições com grande volume de ressecções e transplantes hepáticos no Brasil, baseado no trabalho realizado pela Universidade de Oslo. A elaboração foi dividida em 4 etapas. **RESULTADO:** É apresentada proposta de protocolo para esta doença a ser validada na aplicação clínica. **CONCLUSÃO:** Foi possível elaborar protocolo de transplante hepático para MHCCR irressecável a fim de uniformizar o tratamento e melhor avaliar os resultados cirúrgicos.

DESCRITORES: Transplante. Transplante de Fígado. Neoplasias Colorretais. Metástase.

Protocolo de transplante hepático para metástase colorretal irressecável

Central Message

Liver transplantation in patients with unresectable colorectal metastasis achieves good results when a careful preoperative selection is carried out. This protocol aims to standardize the operating procedures for liver transplantation in patients with unresectable colorectal metastasis.

Perspective

This protocol aims to standardize the operating procedures for liver transplantation in patients with unresectable colorectal metastasis and to enable a better assessment of surgical results, disease-free survival, and overall survival. The regulation of this protocol is currently in progress in the National Transplant System (SNT—Sistema Nacional de Transplantes) of the Brazilian Ministry of Health.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common type of cancer in both genders. At the time of diagnosis, nearly 25% of patients have metastasis and the liver is the most affected organ (present in 80% of cases); it is estimated that half of the patients with CRC will develop liver metastasis at some point in the course of the disease[13, 14].

Currently, the treatment of metastatic CRC (stage IV) is based on a multidisciplinary and multimodal approach[13,18]. The possibility of performing a resection with free margins is the best prognostic factor for colorectal liver metastasis (CRLM)[14]. In this scenario, hepatectomy has become the main treatment of CRLM, having an overall survival rate of 30–55% in 5 years and 20–25% in 10 years[1,7,14,18]. Several strategies have been used to expand the possibility of resection and to ensure adequate liver remnants, such as parenchyma-preserving techniques, portal vein embolization, two-stage liver resection (LR), and ALLPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy). Even with the use of these strategies, most patients with CRLM remain functionally or anatomically unresectable[20].

The justification for performing liver transplantation (LT) in patients with CRLM regards the increase in the number of resectable patients by performing a total hepatectomy. However, LT in patients with CRLM was considered an absolute contraindication before 1995, due to unacceptable results obtained at the time. The first experience was reported by the European Liver Transplant Registry (ELTR), presenting survival rate of 62% in 1 year and 18% in 5 years[5]. It is worth mentioning that both the perioperative results of LT and the chemotherapy drugs available for the treatment of CRC in the late 1980s and early 1990s justify these aforementioned negative results. The poor results associated with organ scarcity resulted in the discontinuation of LT for CRLM[8,12]. Based on the data currently available, the International Liver Transplant Society (ILTS) is recommended to perform LT with a specific protocol for CLRM[11].

Therefore, the aim of this study was to present a protocol proposal to guide the clinical use of LT in CRLM. This protocol needs to be validated in future studies.

METHODS

This protocol was performed by two high-volume centers of LT and LR in Brazil: University Hospital of the Medical School of the University of São Paulo (HCFMUSP) and Hospital Adventista Silvestre/Hospital São Lucas. The elaboration of the protocol was conducted in four stages.

In the first stage, a search in the literature was performed in order to obtain the main published studies regarding LT for CRLM to date. In the second stage, an outline of the protocol was designed by the first two authors and the last author, based on the SECA trials from the University of Oslo[4,9]. In the third stage, 10 experts elaborated the last version of the protocol, adapted to the Brazilian reality. The fourth stage consisted of the protocol submitted for approval in the National Transplant System (SNT—Sistema Nacional de Transplantes) of the Brazilian Ministry of Health.

Brazilian centers were selected for inclusion in the multicentric research project, and a total of 30 patients underwent transplantation according to the criteria of this protocol and were referred to these centers by the SNT. Preoperative, intraoperative, and postoperative data were prospectively recorded on the REDCap platform[10]. The following pretransplantation data were analyzed: age, gender, body mass index (BMI), clinical performance, comorbidities, laboratory examinations, staging examinations, size and number of tumors, previous chemotherapy, response to chemotherapy, anatomopathological analysis of the primary tumor, time between diagnosis of CRC and LT, and type of LT (deceased donor or living donor). The number of patients referred for the LT evaluation, as well as the number of patients who effectively met the criteria and were included for undergoing LT and those who were excluded before the LT (due to not meeting the criteria) were also assessed. After the LT, disease-free survival and overall survival rate in 1, 3, and 5 years, immunosuppression protocol, rejection episodes, and need for retransplantation were analyzed.

RESULTS

Figure 1 shows the LT protocol for CRLM proposed in this study by the authors. Figure 2 shows the document of SNT to be filled in to request a special situation for CRLM.

DISCUSSION

In the past two decades, there has been improvement in the survival rates after LT by 20–30% and improvement in the imaging examinations; there was also the introduction of immunosuppressants with antineoplastic action (mTOR inhibitors)[15,17]. This technical progress combined with the peculiar transplantation scenario in Norway, which has more organ donors than recipients on the list, provided the ideal scenario for performing LT in CRLM. In the SECA I study, conducted from 2006 to 2011 at the University of Oslo, 21 patients underwent LT for CRLM, whose main inclusion criteria at the time consisted of good clinical performance (ECOG 0 or 1), complete resection of the primary tumor, and a minimum of 6 weeks of chemotherapy. The authors obtained an overall survival rate of 60% in 5 years and identified four clinical variables associated with a worse prognosis (Oslo criteria): tumor diameter > 5.5 cm, CEA > 80 ng/ml, interval between resection and LT <2 years, and progression of the disease during chemotherapy[9].

The same group from Oslo continued the investigation of LT for CRLM through the SECA II study. From 2012 to 2016, 15 patients were transplanted with restrictive criteria in order to obtain a result similar to other causes of LT. Several criteria were included for the performance of LT, such as the Oslo criteria, the nonresectability due to partial hepatectomy, and the radiological tumor response after chemotherapy. The authors obtained an overall survival rate of 100% in 1 year, 83% in 3 years, and 83% in 5 years. Disease-free survival rate obtained was 53% in 1 year, 44% in 3 years, and 35% in 3 years. The main site of recurrence was pulmonary and most of them were fit for resection; therefore, the high rates of recurrence had less influence on the survival rate of patients[4].

Both the aforementioned Norwegian studies have major importance in the "Transplant Oncology," a term used to describe LT as a treatment option for hepatobiliopancreatic neoplasms. Recently, multiple centers in Europe and in the United States have started to perform LT for CRLM[11,19]. Fernandes et al. were pioneers in performing the first LT with a living donor in Latin America in a patient with CRLM, in agreement with the Oslo criteria[6].

The exclusion of transplantation in cases of right colon tumor and/or the presence of positive BRAF is a topic to be discussed. Mutation-positive BRAF is considered a risk factor and is associated with worse outcomes after transplantation. Tumors of the right colon also have a worse prognosis, precisely due to their higher frequency of positive BRAF[16]. Clinical studies

PROTOCOL FOR LIVER TRANSPLANTATION IN UNRESECTABLE COLORECTAL METASTASIS	
STEPS FOR LT IN CRLM	
LT centers	Specialized centers selected by SNT.
LT standardization	Performed based on a protocol under SNT supervision in order to evaluate outcomes.
LT approval	Approval in a multidisciplinary meeting at local institution with mandatory presence of radiologist, clinical oncologist, hepatopancreatobiliary surgeon, and transplantation surgeon.
LT notification	All cases must be referred to the SNT for evaluation and final approval.
LT INDICATION	
Patient selection	Synchronic or metachronic CRLM, restricted to the liver, unresectable, with a time interval superior to 12 or 24 months between the diagnosis of primary tumor and the date of listing for transplantation.
Official authorization	After SNT approval, patients will be included in the list for LT with a special MELD score (MELD 30).
LDLT	Follow the same inclusion and exclusion criteria of DDLT. They will only have coverage by the Brazilian Ministry of Health if meeting the established criteria.
Oslo criteria (to be fulfilled within 90 days before LT)	CEA level <80 ng/ml. The larger hepatic lesion must be <5.5 cm. Response to chemotherapy. Time interval superior to 12 or 24 months between the diagnosis of primary tumor and the date of listing for transplantation.
INCLUSION AND EXCLUSION CRITERIA	
Inclusion criteria (all the described criteria must be met for inclusion):	Histologically confirmed adenocarcinoma of the colon or rectum.
	Standard surgical procedure with adequate primary tumor resection margins, including circumferential resection margins (CRM) of at least ≥2 mm for patients with rectal cancer.
	Synchronic or metachronic CRLM, unresectable, restricted to the liver, not eligible for curative resection of the liver after compliance with the other described items.
	Previous treatment with first-line chemotherapy.
	Before starting first-line chemotherapy, no lesions should be >10 cm and the total number of lesions must be £20. If there are >20 nodules, the biggest lesion should have a maximum size of 5 cm.
	Response to chemotherapy (at least 10% response according to the RECIST criteria until third-line chemotherapy). Patients should be accepted for transplantation if there is no progression of the disease while undergoing chemotherapy.
	Absence of signs of extrahepatic metastatic disease or local recurrence of the primary tumor according to CT or MRI (chest, abdomen, and pelvis) within 4 weeks before the multidisciplinary meeting.
	Absence of signs of extrahepatic metastatic disease or local recurrence of the primary tumor according to full-body PET-CT within 3 months before the multidisciplinary meeting.
	Normal colonoscopy (no sign of local recurrence) in the previous 12 months before transplantation.
	Age ≥18 years old.
	Good clinical performance (ECOG 0 or 1).
	Satisfactory blood examinations Hb >10 g/dl, Bilirubin <2× upper limit of normality, AST, ALT <5× upper limit of normality, creatinine <1.25× upper limit of normality.
Exclusion criteria (meeting one criteria is enough for exclusion):	Weight loss >10% in the past 6 months.
	Previous extrahepatic metastatic disease or local recurrence of the primary tumor.
	Patients who did not receive standard preoperative, perioperative, or postoperative treatment for primary CRC.
	Palliative resection of the primary CRC (compromised margins and/or presence of <12 lymph nodes assessed in the surgical specimen).
	BMI > 35.
	Other malignant diseases in the past 5 years (except skin and cervical neoplasm, which will be analyzed by the pathologist).
	Hypersensitivity to the mammalian target of rapamycin (mTOR) inhibitors (everolimus and/or sirolimus).
	Pregnant or breastfeeding women.
	Recurrence of liver metastases after LT for CRLM.
POSTOPERATIVE AND FOLLOW-UP	
Clinical follow-up	Postoperative follow-up with outpatient appointments, CT (chest, abdomen, and pelvis), and CEA levels every 3 months in the first year.
	From the second year forward, perform the same postoperative follow-up every 6 months.
IMMUNOSUPPRESSION, TREATMENT OF REJECTION, AND RETRANSPLANTATION	
Immunosuppression	Immunosuppression will be performed according to the institutional protocol of each center.
	It is mandatory to use an mTOR inhibitor (everolimus or sirolimus) 1 month after the LT or as soon as possible after this period, depending on postoperative complications.
Rejection treatment	Performed according to the institutional protocol of each center.
Retransplantation for recurrent CRLM	Not allowed.
Retransplantation in other situations	Allowed on primary graft dysfunction, hepatic artery thrombosis, and chronic rejection.

LT=liver transplantation; DDLT=deceased-donor liver transplantation; LDLT=living-donor liver transplantation; CRLM=colorectal liver metastasis; CRC=colorectal cancer; SNT=national system of transplants; CT= computed tomography; MRI=magnetic resonance imaging; PET-CT=positron emission tomography; ECOG=performance status of Eastern Cooperative Oncology Group.

Figure 1 - Protocol created by the authors for liver transplantation in unresectable colorectal metastasis.

SNT NATIONAL SYSTEM OF TRANSPLANTS
SPECIAL SITUATION
UNRESECTABLE COLORECTAL METASTASIS

Patient: _____
RGCT: _____ (registration number at transplant center)
Center: _____
Hospital: _____

Special situation inclusion criteria: Synchronic or metachronic CRLM, restricted to the liver, unresectable, with a time interval superior to 12 or 24 months between the diagnosis of primary tumor and the date of listing for transplantation.

Diagnosis: ( ) Histologically confirmed adenocarcinoma of the colon or rectum Pathology: _____ Liver metastasis: ( ) Unresectable liver metastasis ( ) Synchronic metastasis ( ) Metachronic metastasis Size of the largest lesion* (cm): _____ Maximum number of lesions*: _____	Standard surgical procedure with adequate primary tumor resection margins, including circumferential resection margins (CRM) of at least ≥2 mm for patients with rectal cancer. CRLM synchronic or metachronic, unresectable, restricted to the liver, not eligible for curative resection. *Before starting first-line chemotherapy, no lesions should be >10 cm and the total number of lesions must be 20 or less. If there are >20 nodules, the biggest lesion should have a maximum size of 5 cm. Attach the medical and examination reports.
Clinical data and laboratory examinations: BMI: _____ ECOG: _____ Hb: Date: / / BT: BD: Date: / / AST: ALT: Date: / / Cr: Date: / / CEA: Date: / /	BMI ≤ 35 Good clinical performance (ECOG 0 or 1) Satisfactory blood examinations Hb >10 g/dl, Bilirubin <2× upper limit of normality, AST, ALT <5× upper limit of normality, creatinine <1.25× upper limit of normality. Attach the medical and examination reports.
Staging: CT (C/A/P) Date: / / MRI (abdomen) Date: / / PET-CT Date: / / Colonoscopy Date: / /	Staging of the disease performed by CT (chest, abdomen, and pelvis), MRI (abdomen), PET-CT, and colonoscopy. Absence of signs of extrahepatic metastatic disease or local recurrence of the primary tumor according to CT or MRI (chest, abdomen, and pelvis) within 4 weeks before the multidisciplinary meeting. Absence of signs of extrahepatic metastatic disease or local recurrence of the primary tumor according to full-body PET-CT within 3 months before the multidisciplinary meeting. Normal colonoscopy (no sign of local recurrence) in 12 months before transplantation. Attach the medical and examination reports.
Chemotherapy treatment: ( ) First-line chemotherapy QT: _____ Cycles: _____ ( ) Second-line chemotherapy: QT: _____ Cycles: _____ ( ) Third-line chemotherapy: QT: _____ Cycles: _____ Progression of the disease during chemotherapy: ( ) Yes ( ) No Details: _____ _____ _____	Previous treatment with first-line chemotherapy. Response to chemotherapy (at least 10% response according to the RECIST criteria until third-line chemotherapy). Patients should be accepted for transplantation if there is no progression of the disease while undergoing chemotherapy.
Oslo criteria: ( ) CEA level <80 ng/ml ( ) Larger hepatic lesion must be <5.5 cm ( ) Response to chemotherapy ( ) Time interval superior to 12 or 24 months between the diagnosis of primary tumor and the date of listing for transplantation	Mandatory to be fulfilled within 90 days before LT.
MD signature and stamp:	Date:

LT=liver transplantation; DDLT=deceased-donor liver transplantation; LDLT=living-donor liver transplantation; CRLM=colorectal liver metastasis; CRC=colorectal cancer; SNT=national system of transplants; CT= computed tomography; MRI=magnetic resonance imaging; PET-CT=positron emission tomography; ECOG=performance status of Eastern Cooperative Oncology Group.

Figure 2 - Document of SNT to be filled in to request a special situation for unresectable CRLM.

that are still in progress present heterogeneity regarding these items and, therefore, we chose to maintain them in our protocol until further studies. In Norway (NCT01479608, NCT02215889, and NCT03494946) and Germany (NCT03488953), the studies do not adopt these exclusion criteria, while in France (NCT02597348), Canada (NCT02864485), and Italy (NCT03803436), positive BRAF is the exclusion criteria[3,11].

The regulation of this protocol is in progress in the SNT for validation in the Brazilian national territory[2].

CONCLUSION

An LT protocol for colorectal unresectable metastasis was created to standardize the treatment and to enable a better evaluation of not only surgical results but also disease-free survival and overall survival of patients with CRLM.

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