Clinical Cases

Chirurgia (2013) 108: 719-724
No. 5, September - October

Liver Transplantation in a Patient with Unresectable Colorectal Liver Metastases – A Case Report

D. Hrehoreț[1*], S. Alexandrescu[1*], V. Brașoveanu[1], R. Grigorie[1], C. Zielinski[2] , I. Popescu[1]

[1]"Dan Setlacec" Center of General Surgery and Liver Transplantation of Fundeni Clinical Institute
Department of Surgery of University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania
[2]Clinical Division of Oncology of the General Hospital Vienna; Department of Medicine of Medical University Vienna, Austria

Rezumat

Transplant de ficat la un pacient cu metastaze hepatice colorectale nerezecabile. Pezentare de caz și recenzie a literaturii

Introducere: Datorită ratelor scăzute de supraviețuire înregistrate, în perioada inițială a transplantului hepatic, la pacienții cu metastaze hepatice colorectale, precum și datorită penuriei de organe, în ultimele două decade se consideră că metastazele hepatice colorectale reprezintă o contraindicație pentru transplantul de ficat. Totuși, numărul tot mai mare de donatori marginali, ca și progresele în ceea ce privește imunosupresia posttransplant, chimioterapia și modalitățile de decelare a metastazelor extrahepatice, au oferit perspectiva transplantului hepatic unor pacienți cu afecțiuni maligne (precum pacienți selectați cu hepatocarcinoame în afara criteriilor Milano, colangiocarcinoame sau metastaze hepatice ale unor tumori neuroendocrine). Întrucât la acești pacienți au fost înregistrate rezultate favorabile, în ultimii ani, unii autori au luat în considerare reanalizarea beneficiilor transplantului de ficat la anumiți pacienți cu metastaze hepatice colorectale nerezecabile. Astfel, în 2006, în Norvegia, a fost inițiat un studiu care a avut drept scop aprecierea rezultatelor transplantului hepatic la astfel de pacienți. Rezultatele acestui studiu pilot au fost favorabile, înregistrandu-se o supraviețuire globală la 5 ani de 60% și o calitate excelentă a vieții în primul an după transplant. Trebuie totuși amintit, că toți pacienții au prezentat recidivă neoplazică în primii doi ani posttransplant. În acest articol, prezentăm caracteristicile clinico-patologice, conduita terapeutică pre- și postoperatorie și rezultatele obținute în urma transplantului hepatic (cu grefă marginală) la un pacient cu metastaze hepatice colorectale nerezecabile care a dezvoltat insuficiență hepatică subacută datorită volumului hepatic funcțional insuficient și toxicității chimioterapiei. Considerăm utilă prezentarea unor astfel de observații, întrucât, prin colectarea și analizarea datelor raportate de diverse centre, ar putea fi identificat un grup de pacienți care să beneficieze de transplant hepatic.

Prezentare de caz: Un pacient de 42 de ani, a fost diagnosticat, în aprilie 2009, cu adenocarcinom de rect superior și multiple metastaze hepatice bilobare. S-a inițiat chimioterapie (în alt spital) și deoarece s-a constatat boală staționară după 7 cicluri de FOLFOX și Bevacizumab, pacientul a fost adresat serviciului de chirurgie (pentru o rezecție "în doi timpi"). În octombrie 2009 s-a efectuat rezecția tumorii primare asociată cu secționectomie laterală stângă și metastazectomie la nivelul segmentului 4. Deoarece, în noiembrie 2009, re-evaluarea tomografică a evidențiat progresia metastazelor hepatice, al doilea timp al rezecției hepatice a fost abandonat. Tratamentul ulterior a constat în radioembolizare, multiple linii de chimioterapie și anticorpi monoclonali. După mai mult de doi ani, metastazele

Corresponding author: Irinel Popescu, MD, PhD, FACS, FEBS
Professor of Surgery, Director
"Dan Setlacec" Center of General Surgery and Liver Transplantation
Fundeni Clinical Institute
Sos. Fundeni, no. 258, sector 2, Bucharest
Romania
E-mail: irinel.popescu220@gmail.com

*These authors contributed equally to this work

au progresat și pacientul a dezvoltat insuficiență hepatică subacută colestatică progresivă datorită parenchimului hepatic funcțional insuficient și toxicității chimioterapiei. În acest stadiu, pacientul a fost internat în centrul nostru, fiind dependent de proceduri de dializă hepatică și "plasma exchange". Datorită vârstei pacientului, faptului că tomografia computerizată a evidențiat absența metastazelor extrahepatice (după aproximativ 3 ani de evoluție a bolii) și întrucât acesta nu mai putea beneficia de niciun tratament oncologic datorită insuficienței hepatice subacute progresive, s-a luat în calcul transplantul hepatic cu o grefă marginală, acesta fiind efectuat în ianuarie 2012. Evoluția postoperatorie nu a fost grevată de complicații, iar calitatea vieții pacientului s-a ameliorat semnificativ (fiind reinserat social și professional). Tratamentul imunosupresor s-a bazat pe Sirolimus și Micophenolate mofetil, iar chimioterapia adjuvantă a început la două luni post-transplant. Totuși, pacientul a dezvoltat metastaze extrahepatice (pulmonare și retroperitoneale), dar în prezent, la mai mult de 20 de luni post-transplant, este în viață, într-o condiție clinică bună.
Concluzii: La pacienții cu metastaze hepatice colorectale nerezecabile, transplantul hepatic cu organe de la donatori marginali (care nu pot fi alocate unor receptori cu afecțiuni ce se încadrează în indicațiile unanim acceptate pentru transplantul hepatic) ameliorează supraviețuirea globală și calitatea vieții. Introducerea MDCT și a PET/CT, precum și utilizarea inhibitorilor m-TOR pot ameliora rezultatele transplantului hepatic la pacienții cu CLMs. Studii viitoare pot fi utile în încercarea de a identifica un anumit grup de pacienți, cu CLMs nerezecabile, care pot deveni candidați pentru transplantul hepatic.

Cuvinte cheie: metastaze hepatice colorectale, nerezecabile, transplant hepatic, insuficiență hepatică, donator marginal

Abstract
Background: Due to the lower survival rates achieved, in the early period of liver transplantation era, in patients with colorectal liver metastases, and because of the organ shortage, in the last two decades colorectal liver metastases are considered a contraindication for liver transplantation. However, the increasing number of marginal donors, and the improvements in posttransplant immunossuppresion, chemotherapy and methods to assess the extrahepatic dissemination of colorectal cancer, opened the perspective of liver transplantation to certain patients with malignancies (such as HCC beyond Milan criteria, and selected patients with cholangiocarcinoma or liver metastases from neuroendocrine tumors). Since some of these patients experienced favorable outcomes, in the last years, there were authors that considered a rationale revisitation of the benefits of liver transplantation in patients with unresectable colorectal liver metastases. Thus, in 2006, a Norwegian group started a study which aims to assess the results of liver transplantation in patients with unresectable colorectal liver metastases. Their results were unexpectedly favorable, revealing that 5-year overall survival rate was 60%, and the quality of life was excellent in the first year following transplantation. However, all the patients presented relapse of the disease in the first two years following transplantation. In the present paper we present the clinico-pathologic characteristics, the pre- and postoperative management and the outcome of a patient with unresectable colorectal liver metastases who underwent liver transplantation in a very advanced state of the disease (when he developed subacute liver failure due to insufficient functional liver parenchyma and toxicity of chemotherapy). We consider useful to present such observations, because collecting the data presented by different centers may be contributive to identification of a selected group of patients who could benefit from liver transplantation.
Case report: A 42-year old male patient, it was diagnosed with upper rectum cancer and multiple bilobar liver metastases in April 2009. Chemotherapy was started (in another hospital), and because the disease was stable after 7 cycles of FOLFOX and Bevacizumab, the patient was reffered to surgery (for a "two-stage" liver resection). In October 2009 it was performed primary tumor resection associated with left lateral sectionectomy and segment 4 metastasectomy. Because in November 2009 CT scan re-evaluation revealed progression of liver metastases, the second stage hepatectomy was precluded. Subsequent therapy consisted in radioembolization, multiple lines of chemotherapy, and targeted therapies. After more than 2 years, the liver metastases progressed and the patient developed progressive cholestatic subacute liver failure due to insufficient functional liver parenchyma and chemotherapy toxicity. In this state of the disease, he was admitted in our hospital, being dependant by liver dialysis and plasma exchange procedures. Due to the patients' age, and because the MDCT scan revealed the absence of extrahepatic disease (after almost three years of disease progression), and he could not benefited from any type of antineoplastic treatment due to progressive cholestatic subacute liver failure, liver transplantation with an organ from a marginal donor was considered and performed in January 2012. The postoperative course was uneventful, and the quality of his life improved (being fully reinserted social and professional). The immunosuppressive regimen consisted in Sirolimus and Mycophenolate mofetil, and the adjuvant chemotherapy started two months following liver transplantation. However, the patient developed extrahepatic relapse of the disease (lung metastases and retroperitoneal recurrence), but now, at more than 20 months following transplantation, he is still alive in a good clinical condition.
Conclusions: In patients with multiple unresectable liver only colorectal metastases, liver transplantation may improve overall survival and quality of life, by using marginal grafts which cannot be allocated to the patients with standard indications for liver transplantation. The advent of MDCT and PET/CT scan and the use of m-TOR inhibitors may improve the results achieved by liver transplantation in patients with CLMs. Further studies could be useful in an attempt to disclose whether a selected group of patients with unresectable liver only colorectal metastases could become acceptable candidates for liver transplantation.

Key words: colorectal liver metastases, unresectable, liver transplantation, liver failure, extended criteria donors

Introduction

Liver is the most frequent site of liver metastases location in patients with colorectal cancer (CRC) (1;2). In patients with liver only colorectal metastases, liver resection is the only potentially curative treatment, achieving 5-year overall survival rates ranging between 25% and 58% (3-7). Unfortunately, more than 75% of patients with colorectal liver metastases (CLMs) present with unresectable liver lesions at the time of their diagnosis (8). In the last decade, a certain number of onco-surgical strategies were used to render resectable such patients; these strategies include liver resection after portal vein embolization/ligation, "two-stage" hepatectomies, liver resection associated with radiofrequency ablation and liver resection after "down-sizing" of liver metastases following conversion chemotherapy (8-17). Even by applying these therapeutic strategies, more than 60% of patients with liver only metastases remain unsuitable for a complete liver metastases resection, the only treatment delivered to these patients being palliative chemotherapy (18). Palliative treatment, even by using the new chemotherapic drugs (such as Oxaliplatin and Irinotecan) and targeted therapies (Bevacizumab, Cetuximab, Panitumumab), achieves 5-year overall survival rates lower than 10%. Theoretically, for these patients with liver only unresectable CLMs, liver transplantation offers the chance of a complete removal of the tumor burden, giving the opportunity of an R0 resection. Although this concept guided many surgeons in the initial era of liver transplantation, unfortunately, the long-term results were disappointing, enabling 5-year overall survival rates less than 20% in the series published in the '80s (19). Due to the organ shortage and the lower survival rates than those achieved by patients undergoing liver transplantation for liver cirrhosis or HCC inside Milan criteria, it was considered that is not ethic to perform liver transplantation in patients with CLMs. Thus, in present, CLMs are considered a contraindication to liver transplantation in most centers.

In Norway, where is a fortunate situation due to a surplus of donor livers, it was conducted a study aiming to assess the results of liver transplantation for patients with unresectable CLMs (20). Recently, these results were published, revealing a 5-year overall survival rate of 60%, who may represent a starting point in reconsidering the current treatment paradigm in patients with unresectable CLMs (21). Although definitive conclusions could not be drawn based on this study, we consider that marginal organs, that are not suitable for patients which may benefit from liver transplantation for standard indications (e.g. liver cirrhosis, HCC inside Milan criteria, etc), may be offered to selected patients with unresectable CLMs.

In this paper we report the case of a patient with multiple unresectable liver only CLMs, who developed progressive cholestatic subacute liver failure, undergoing liver transplantation with a marginal graft. We present this observation to emphasize that liver transplantation could offer the chance of a prolonged survival, with a good quality of life, to a patient otherwise condemned to a rapid death. In our centre, this was the only patient undergoing liver transplantation for such an indication (out of 489 liver transplants). Although this case could not represent a plea for the acceptance of liver transplantation as a standard indication of treatment in patients with unresectable CLMs, it may be contributive, by corroboration with similar cases reported by other centers, to identify, in the future, a selected group of patients with unresectable CLMs who may really benefit from liver transplantation.

Case report

A 42 year-old male patient was diagnosed in April 2009 with rectal cancer and multiple bilobar CLMs (which did not spare any segment except for the caudate lobe). He was referred for systemic chemotherapy and he received 7 cycles of FOLFOX and Bevacizumab, with partial response of liver metastases. Subsequently, in another hospital, he was scheduled for a "two-stage" procedure associated with right portal vein embolization. In October 2009 he underwent a Dixon procedure with diverting ileostomy, combined with left lateral sectionectomy and a wedge resection of the metastasis from segment 4, thus ensuring the clearance of the left hemiliver. The staging of the disease, according to the pathologic examination, was pT3, pN0 (0/28), pM1a (hep). The CT scan before the second operation revealed disease progression (with development of new metastases in the remnant segment 4), thus the second stage of the procedure was postponed. The patient was referred for chemotherapy, receiving 3 cycles of FOLFOX and Bevacizumab and (on progression) 1 cycle of Capecitabine, Irinotecan and Bevacizumab. Due to the hepatic disease progression, in June 2010, the patient received radioembolization of the CLMs using Yttrium-90 microspheres, followed by 18 cycles of intraarterial chemotherapy with Irinotecan and systemic delivering of Cetuximab (since September 2010 until August 2011). In September 2011, hepatic disease progression was noted and the patient received 1 cycle of Capecitabine and Sutent, but due to the increased levels of liver function tests, the chemotherapy was aborted in October 2011. In November 2011, the patient was admitted in the Center of Digestive Diseases and Liver Transplantation of Fundeni Clinical Institute with jaundice, ascitis and splenomegaly. Laboratory findings revealed AST = 212 U/l, ALT = 59 U/l, Bilirubine = 12 mg/dl, Albumin = 2.5 g/dl. In spite of the medical treatment (Albumin, diuretics and amino-acids), the level of bilirubine increased steadily, without encephalopathy or coagulopathy, the patient developing progressive cholestatic subacute liver failure. Because the level of bilirubine increased to more than 23 mg/dl in December 2011, the patient underwent plasma exchange and hepatic dialysis (with Prometheus system) in order to reduce the bilirubine level. CT scan of the chest, abdomen and pelvis performed in December 2011 showed

innumerable CLMs ranging between 2.5 and 12 cm. in maximum diameter, without extrahepatic disease (Fig. 1), and the cytology of the ascitis did not revealed malignant cells. Because there was a young patient, who did not developed extrahepatic metastases during almost 3 years of disease progression, and his condition was stable except for the increasing level of bilirubin, it was decided, in January 2012, to perform an orthotopic liver transplantation (Fig. 2) with a whole graft from an extended criteria brain-dead donor (anti-HBc positive, prolonged hypotension, high doses of pressors).

The postoperative course was uneventful. Baziliximab was used for the induction of immunosuppression and maintenance immunosuppression regimen consisted in Sirolimus and Mycophenolate mofetil; the patient also received human hepatitis B immunoglobulin and Lamivudine.

The CEA and CA19-9 levels decreased from more than 1500 ng/ml and more than 1200 ng/ml, respectively (before operation), to 176 ng/ml and 21.15 ng/ml (six weeks after transplantation).

The clinical condition of the patient, as well as his quality of life, improved significantly, being reinserted social and professional.

Adjuvant chemotherapy started 6 weeks following liver transplantation, consisting in 6 cycles of Capecitabine and Oxaliplatin.

The CT scan performed in August 2012 revealed few nodules in both lungs (less than 1 cm each), considered as metastatic disease, and the patient continued chemotherapy, receiving 6 cycles of Irinotecan and Panitumumab. Under the chemotherapic treatment, the lung metastases are stable.

In January 2013, it was diagnosed a 5 cm retroperitoneal mass on the CT scan, and the chemotherapic regimen was changed to Irinotecan and Aflibercept. The abdominal CT scan performed in June 2013 revealed the progression of the retroperitoneal recurrence and the patient received, between July and August 2013, external radiation.

To date, at more than 20 months after liver transplantation, the patient is alive, under treatment with Aflibercept, and still enjoys a good quality of life.

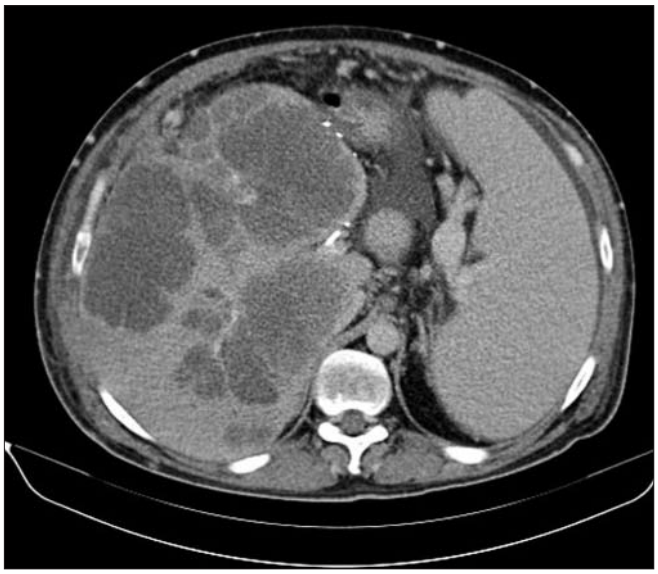

Figure 1. *Contrast-enhanced abdominal CT scan – innumerable (more than 20) CLMs ranging between 2.5 and 12 cm. in maximum diameter, and small volume of functional liver parenchyma*

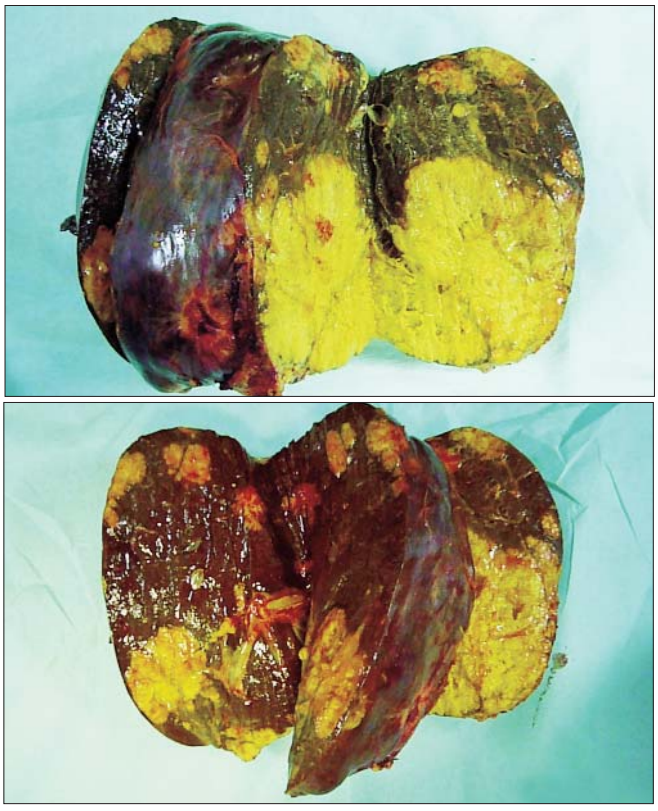

Figure 2. *Macroscopic view of the specimen (total hepatectomy) – innumerable CLMs*

Discussions

In the early period of liver transplantation, many centers performed this procedure in patients with CLMs. Because the survival rates were disappointing in comparison to those achieved in patients with liver cirrhosis (19) and due to the organ shortage, liver metastases from colorectal cancer became an absolute contraindication for liver transplantation. By this reason, the subject of liver transplantation in such patients was addressed in a limited number of papers in the last years (22).

Hence, in the last two decades, there were recorded several developments in the field of liver transplantation, as well as in diagnosis and management of patients with CLMs. Thus, by using the immunosuppressive agents as m-TOR inhibitors (that present antiangiogenic effects and inhibit tumor growth and proliferation), the recurrence rates following liver transplantation for malignant disease decreased (23,24). Moreover, the advent of the new radiologic techniques (MDCT, gadolinium-enhanced MRI, and PET/CT scan) and the use of genetic methods to detect lymph nodes metastases (25), may identify more reliably the patients without extrahepatic metastases. At least theoretically, these advances may

improve the survival rates following liver transplantation in patients with liver only colorectal metastases.

Furthermore, recent observations revealed favorable outcomes in selected patients undergoing liver transplantation for malignant diseases such as cholangiocarcinoma or liver metastases from neuroendocrine tumors (26-28). Recently, Uskudar et al. reported long term survival following liver transplantation due to the sclerosing cholangitis induced by intraarterial chemotherapy in two patients with resected CLMs (29).

For these reasons, certain authors proposed a rational revisitation of the concept of liver transplantation in patients with unresectable CLMs (20). Thus, in November 2006, in Norway, where the number of the available liver grafts is higher than the number of patients requiring liver transplantation, started a pilot study (SECA-study) aiming to assess the survival and quality of life in patients undergoing liver transplantation for unresectable CLMs. Unlike the patients presented by Uskudar et al. (29), the extent of metastatic disease was completely different in patients included in the Norwegian group study. According to the present criteria regarding resectability (30;31) based mainly on the volume of the future liver remnant, the patients enrolled in the Norwegian study had truly unresectable metastases.

The results of this study were published recently, revealing a 5-year overall survival rate of 60% (21) and an excellent quality of life at one year (32). Although definitive conclusions could not be drawn on the basis of the paper of Hagness et al. (21), it raises a curtain, unveiling a possible opportunity of treatment for certain patients otherwise condemned to a rapid death. In our perspective this paper should be a starting point for future trials, able to better clarify which patients with CLMs could really benefit from liver transplantation, and which is the optimal timing of this procedure in the setting of the multimodal approach of these patients.

The patient presented in our paper, was transplanted in a more advanced state of the disease, when all the available therapeutic options were no longer efficient. To our knowledge, this is the first patient reported in the literature undergoing liver transplantation for subacute liver failure due to the insufficient liver parenchyma because of the huge metastatic burden in the liver and chemotherapy toxicity.

In a country facing an important discrepancy between the number of donors and the need for liver transplantation, it is definitely unethical to use a good liver graft in such a patient. Hence, in the last years, we were faced up to an increasing number of marginal donors, whose organs could not be allocated to patients with liver cirrhosis or HCC inside Milan criteria. This was the reason why, we decided to use such a marginal graft in a young patient with subacute liver failure due to multiple unresectable liver metastases, who did not developed extrahepatic disease after almost three years of disease progression.

Undoubtedly, at the time of liver transplantation, the life expectancy of this patient, dependant by liver dialysis and plasma-exchange, would not exceed few weeks. Although transplantation could not offer him the chance of cure, it prolonged his life substantially, in a good clinical condition. This postoperative course is similar to those reported by Andersen et al. (32) who revealed that patients undergoing liver transplantation for liver only unresectable CLMs have good quality of life and have mostly minor symptoms during the first year after liver transplantation. Moreover, the patient already benefited for a survival longer than 20 months, which is superior to his life expectancy if he would not underwent liver transplantation.

Although the time to recurrence seems to be short in our patient, it has to be mentioned that in the Norwegian group experience, 19 out of 21 patients developed malignancy relapse after a median time of 6 months.

Furthermore, the type of disease recurrence was not uncommon, being similar to those presented by Hagness et al (21), who reported that the most frequent site of malignancy recurrence is in the lung (47% of their patients). Extrahepatic recurrence (altogether) was observed in 63% of patients in the Norwegian study.

So that, although our patient was transplanted in a more advanced state of the disease than the patients enrolled in SECA study, the time to recurrence and the type of recurrence were similar to those presented by Hagness et al (21).

It may be hypothesized that our patient could experienced even a better outcome if he would underwent liver transplantation during the period when the disease was controlled by chemotherapy. Meanwhile, Hagness et al revealed in their paper, that prognostic factors correlated with a better survival were the disease control under chemotherapy at the time of liver transplantation, maximum size of liver metastases less than 5.5 cm, disease-free interval between primary tumor resection and liver transplantation more than 2 years, and CEA levels $< 80 \mu g/L$ (21). Performing liver transplantation mainly in such patients with good prognostic factors, the results of liver transplantation could be further improved in the setting of a disease which is now still considered a contraindication for liver transplantation. Furthermore, if the liver transplantation is performed during the "window of opportunity", when the lesions do not progress under chemotherapy, the patients could experience even better survival rates, avoiding early disease recurrence.

Conclusions

In conclusion, our observation revealed that in patients with multiple unresectable CLMs and subacute liver failure (due to the insufficient functional liver parenchyma and chemotherapy toxicity), liver transplantation may improve overall survival and quality of life, by using marginal grafts which cannot be allocated to the patients with standard indications for liver transplantation. Because this type of organs are frequently allocated to the patients with HCC beyond Milan criteria, we consider that further studies should compare the survival rates achieved by patients undergoing liver transplantation for unresectable CLMs to those observed in patients undergoing transplantation for HCC beyond Milan criteria, cholangiocarcinoma, or liver

metastases from neuroendocrine tumors.

To the best of our knowledge, there are still liver transplant centers that do not use grafts from extended criteria donors due to the higher rates of primary non-function, post-transplant complications and death, especially among high-MELD recipients (33). However, these organs could be offered to selected patients with liver malignancies, improving their life expectancy and quality of life.

Further studies are needed to identify the favorable prognostic factors in order to select the most appropriate candidates for liver transplantation. The most suitable immunosuppressive and chemotherapic regimens should be identified in the future, in order to improve the disease-free and overall survival rates of the patients undergoing liver transplantation for CLMs.

Reference

1. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg. 2006;244(2):254-9.
2. McLoughlin JM, Jensen EH, Malafa M. Resection of colorectal liver metastases: current perspectives. Cancer Control. 2006; 13(1):32-41.
3. Aloia TA, Vauthey JN, Loyer EM, Ribero D, Pawlik TM, Wei SH, et al. Solitary colorectal liver metastasis: resection determines outcome. Arch Surg. 2006;141(5):460-6.
4. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg. 2005;241(5):715-22, discussion 722-4.
5. Popescu I, Ionescu M, Alexandrescu S, Ciurea S, Hrehoret D, Sarbu-Boeti P, et al. Tratamentul chirurgical al metastazelor hepatice ale cancerului colorectal. Chirurgia (Bucur). 2006; 101(1):13-24.
6. Portier G, Elias D, Bouche O, Rougier P, Bosset JF, Saric J, et al. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. J Clin Oncol. 2006;24(31): 4976-82.
7. Vigano L, Ferrero A, Lo TR, Capussotti L. Liver surgery for colorectal metastases: results after 10 years of follow-up. Long-term survivors, late recurrences, and prognostic role of morbidity. Ann Surg Oncol. 2008;15(9):2458-64.
8. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg. 2004;240(4):644-57.
9. Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. Ann Surg. 2000;232(6):777-85.
10. Adam R, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol. 2001;8(4):347-53.
11. Azoulay D, Castaing D, Smail A, Adam R, Cailliez V, Laurent A, et al. Resection of nonresectable liver metastases from colo-rectal cancer after percutaneous portal vein embolization. Ann Surg. 2000; 231(4):480-6.
12. Bismuth H, Adam R, Levi F, Farabos C, Waechter F, Castaing D, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg. 1996;224(4): 509-20.
13. Jaeck D, Bachellier P, Weber JC, Oussoultzoglou E, Greget M. Progrès dans la chirurgie d'exérèse des métastases hépatiques des cancers colorectaux. Bull Acad Natl Med. 2003;187(5): 863-76.
14. Jaeck D, Bachellier P, Nakano H, Oussoultzoglou E, Weber JC, Wolf P, et al. One or two-stage hepatectomy combined with portal vein embolization for initially nonresectable colorectal liver metastases. Am J Surg. 2003;185(3):221-9.
15. Pawlik TM, Izzo F, Cohen DS, Morris JS, Curley SA. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. Ann Surg Oncol. 2003; 10(9):1059-69.
16. Popescu I, David L, Brasoveanu V, Boros M, Hrehoret D. Two-stage hepatectomy: an analysis of a single center's experience. Magy Seb. 2006;59(3):184-9.
17. Popescu I, Alexandrescu S, Croitoru A, Boros M. Strategies to convert to resectability the initially unresectable colorectal liver metastases. Hepatogastroenterology. 2009;56(91-92):739-44.
18. Popescu I, Alexandrescu ST. Surgical options for initially unresectable colorectal liver metastases. HPB Surg. 2012;2012: 454026.
19. Muhlbacher F, Piza F. Orthotopic liver transplantation for secondary malignancies of the liver. Transplant Proc. 1987;19(1 Pt 3):2396-8.
20. Foss A, Adam R, Dueland S. Liver transplantation for colorectal liver metastases: revisiting the concept. Transpl Int. 2010;23(7): 679-85.
21. Hagness M, Foss A, Line PD, Scholz T, Jorgensen PF, Fosby B, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013;257(5):800-6.
22. Hoti E, Adam R. Liver transplantation for primary and metastatic liver cancers. Transpl Int. 2008;21(12):1107-17.
23. Fung J, Kelly D, Kadry Z, Patel-Tom K, Eghtesad B. Immunosuppression in liver transplantation: beyond calcineurin inhibitors. Liver Transpl. 2005;11(3):267-80.
24. Guba M, von BP, Steinbauer M, Koehl G, Flegel S, Hornung M, et al. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med. 2002;8(2):128-35.
25. Kappel S, Kandioler D, Steininger R, Langle F, Wrba F, Ploder M, et al. Genetic detection of lymph node micrometastases: a selection criterion for liver transplantation in patients with liver metastases after colorectal cancer. Transplantation. 2006;81(1):64-70.
26. Hrehoret D, Alexandrescu S, Grigorie R, Herlea V, Anghel R, Popescu I. Intrahepatic cholangiocarcinoma--a rare indication for liver transplantation. Case report and review of the literature. Chirurgia (Bucur). 2012;107(2):237-42.
27. Le Treut YP, Gregoire E, Klempnauer J, Belghiti J, Jouve E, Lerut J, et al. Liver transplantation for neuroendocrine tumors in Europe-results and trends in patient selection: a 213-case European liver transplant registry study. Ann Surg 2013;257(5): 807-15.
28. Rea DJ, Rosen CB, Nagorney DM, Heimbach JK, Gores GJ. Transplantation for cholangiocarcinoma: when and for whom? Surg Oncol Clin N Am. 2009;18(2):325-37, ix.
29. Uskudar O, Raja K, Schiano TD, Fiel MI, del Rio MJ, Chang C. Liver transplantation is possible in some patients with liver metastasis of colon cancer. Transplant Proc 2011;43(5):2070-4.
30. Minagawa M, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, et al. Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 2000 Apr;231(4):487-99.
31. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist. 2008;13(1): 51-64.
32. Andersen MH, Dueland S, Hagness M, Vidnes T, Finstad ED, Wahl AK, et al. Quality of life following liver transplantation in patients with liver metastases from colorectal carcinoma. Scand J Caring Sci. 2012;26(4):713-9.
33. Durand F, Renz JF, Alkofer B, Burra P, Clavien PA, Porte RJ, et al. Report of the Paris consensus meeting on expanded criteria donors in liver transplantation. Liver Transpl. 2008;14(12):1694-707.