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REVIEW

LIVER TRANSPLANTATION FOR UNRESECTABLE HEPATIC METASTASES FROM COLORECTAL CANCER: LITERATURE REVIEW

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Abstract

Colorectal cancer represents one of the most common malignancies reported worldwide, associated with an increased risk of hepatic metastases development. Historically, the development of liver metastases from colorectal cancer has been associated with extremely poor rates in terms of survival. Improvement of the surgical techniques, as well as of the perioperative outcomes, in association with the development of new chemotherapeutic agents lead to a better survival; however, in certain cases with unresectable liver metastases, association of chemotherapy and resection can be no longer feasible due to the extent of the disease. In such cases liver transplantation has been proposed with promising results. However, this therapeutic strategy is only indicated when the absence of extrahepatic disease is documented. This is a literature review of the largest studies which focused on the topic of liver transplantation for unresectable liver metastases from colorectal cancer.

Keywords: colorectal cancer, hepatic metastases, extrahepatic disease, liver transplant.

Résumé

Transplantation hépatique pour des métastases hépatiques non résécables d'un cancer colorectal – revue de la littérature

Le cancer colorectal est l'une des tumeurs malignes les plus répandues dans le monde, associée à un risque accru de développer des métastases au niveau du foie. D'un point de vue historique, le développement de métastases hépatiques colorectales a été associé à des taux de survie extrêmement médiocres. L'amélioration des techniques chirurgicales ainsi que la gestion périopératoire, associées au développement de nouveaux agents chimiothérapeutiques, ont permis d'améliorer la survie. Cependant, dans certains cas de métastases hépatiques inopérables, l'association de la chimiothérapie à la résection n'est plus possible en raison de l'étendue locale de la maladie. Dans de tels cas, la transplantation hépatique a été proposée avec des résultats prometteurs. Cependant, cette stratégie thérapeutique n'est indiquée que lorsque l'absence de maladie extrahépatique est documentée. Il s'agit d'une étude récapitulative des plus grandes études portant sur la transplantation du foie

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pour le traitement des métastases hépatiques inopérables du cancer colorectal.

Mots-clés: tumeur colorectale, métastases hépatiques, lésions extrahépatiques, transplantation du foie.

Introduction

Colorectal cancer represents one of the most commonly reported malignancies worldwide. Although this neoplastic process is rather facile to be diagnosed once the lower endoscopy has been widely performed, up to 25% of cases will be diagnosed in advanced stages of the disease, when liver metastases are already present. Moreover, up to half of the patients diagnosed with this malignancy will develop liver metastases at a certain point of the evolution of their disease. Once the distant metastases develop, the overall prognosis becomes extremely poor, the five years overall survival being of less than 10% in the absence of a radical therapeutic strategy. However, due to the improvement of the surgical techniques, as well as due to the improvement of the perioperative management of such cases, liver resection of the metastatic disease in association with systemic chemotherapy have been proposed with good results, the five years overall survival rate increasing at up to 45%. Unfortunately, not all the patients diagnosed with liver metastases from colorectal cancer can benefit from this therapeutic strategy, due to the fact that in certain cases, even after administration of systemic chemotherapy, the liver metastases remain unresectable[1-5].

Liver transplantation for unresectable colorectal metastases

Interestingly, two of the first seven reported liver transplantation procedures had been performed for unresectable liver metastases from colorectal cancer[6]; however, at that time the results were rather discouraging, the method not being considered as a viable strategy of treatment at that moment. For example, in the paper published by Graeme Poston in 2004, liver transplantation was considered as an inappropriate method of treatment for such cases due to the high rates of recurrence, mainly explained by the necessity of using a large amount of immunosuppressive drugs[7].

However, during the further period, the management of liver transplanted patients was submitted to permanent modifications, and the overall survival improved; the operative techniques have been well standardised while the pharmacokinetics of immunosuppressive treatment of choice has been better understood, rendering liver transplantation into a safer and more effective surgical therapeutic option[6,8-11]; for instance, the European Liver Transplantation Registry reported in 2007 an overall one year and five year survival rate of 85% and 74% respectively, demonstrating the safety as well as the efficacy of the method[12].

Therefore, later on the method was reanalysed and better results were reported in patients with unresectable colorectal liver metastases. Moreover, once the imagistic techniques improved, the rate of detection of the extrahepatic disease significantly improved, and therefore a better identification of the candidates for liver transplantation was feasible[13].

In consequence, the method has been reconsidered, being applied with encouraging results in certain cases presenting unresectable, but limited to the liver disease[3]. However, at this moment, the method is not recommended as a standard therapeutic strategy, not being included in the therapeutic guidelines. The lack of enthusiasm which has been demonstrated by certain liver transplantation centres when it comes to the introduction of this method as part of the standard treatment in patients with unresectable liver metastases from colorectal origin can be explained by the low number of donors that prohibits a wide use of the method in a patient in whom the oncological outcome cannot be presumed. Even if the patient presents at a certain moment of the evolution exclusively liver-related metastatic disease, the oncological outcomes after liver transplantation are hard to be anticipated, especially due to the fact that postoperatively he should be submitted to an aggressive immunosuppressive treatment which might favour the development of a systemic recurrence[14].

An interesting study which compared the results provided by chemotherapy as a single therapeutic option to those reported after neoadjuvant chemotherapy and liver transplantation for unresectable liver metastases with colorectal origin demonstrated a five years survival rate of 9% for the first group versus 56% in the second group, underlying the benefits of the surgical method. The study was a multicentric one, conducted in the Northern European countries and included 21 cases submitted to liver transplantation and 47 cases submitted to first line

chemotherapy; although the progression free survival interval was similar between the two groups (8 months versus 10 months), a dramatic difference in terms of the overall survival was demonstrated[15].

Studies reporting the feasibility and safety of liver transplantation for unresectable liver metastases from colorectal cancer

The first studies that took into consideration the idea of liver transplantation for unresectable, limited to liver colorectal cancer metastases came from Adam *et al.* and were published in 1995; at that moment the authors reported a series of 50 cases submitted to this therapy, with one year and five year survival rates of 62% and 18% respectively; at that moment the long-term results were considered rather poor and the method was abandoned[16]. Further on, the method was implemented in Vienna on a group of 25 patients, the authors reporting a significant benefit of survival, especially in patients who presented negative node disease at the time of surgery for the initial tumour[17]. Initially the Austrian authors proposed the method for 25 negative node patients and reported one year, three year and five year overall survival rates of 76%, 32% and 12%, respectively; later on, they found out that 15 out of these cases presented micro metastatic disease at the level of the lymph nodes and observed that this aspect significantly influenced the survival (the overall survival being of 118 months for patients with negative nodes and 28 months for patients presenting micro metastatic deposits, p=0.01)[17,18].

Liver transplantation for metastatic colorectal cancer was widely studied in the Northern European Countries due to the presence of a surplus of donor organs which was considered as an opportunity to explore the borderline indications for transplantation. In Norway for example the waiting list for liver transplantation is less than one month[19].

In May 2013, Hagness et al reported their preliminary experience with regard to the role of liver transplantation for liver limited colorectal metastases on a group of 21 patients[19]. The main criteria of inclusion in the present prospective study were represented by the absence of extrahepatic disease, resected primary tumour, and an interval higher than six weeks between the last cycle of chemotherapy and the liver transplantation procedure. After a median follow-up period of 27 months, 33% of cases presented no sign of recurrent disease, the most important prognostic factors after liver transplantation being related to the hepatic tumoral volume at the time of transplantation, to the time from resection of the primary tumour to liver transplantation, and to the response to chemotherapy, cases presenting progression under chemotherapy being associated with a poorer outcome. As for the pattern of recurrence, the authors mainly reported the development of pulmonary metastases which were frequently submitted to resection with curative intent. The overall survival of the entire group was of 95%, 68% and 60% respectively at one year, three years and five years follow-up, demonstrating similar results when compared to patients submitted to the classical liver resection of the metastatic disease. However, only 35% of cases remained free of disease at one-year follow-up, while at the three years follow-up all patients experienced recurrent disease. In terms of immunosuppressive therapy, in this study, mammalian target of rapamycin inhibitor was the option of choice and was associated with a rejection rate of the graft of 38%, this option remaining therefore questionable[19].

Currently, maybe the most encouraging data regarding the role of liver transplantation in this category of patients come from Toso et al and were published in 2017[20]. The authors reported the outcomes of 12 patients submitted to transplant between 1995 and 2015; initially, most often the tumour was staged as a T3 one, with a median number of invaded nodes of two. At the moment of liver transplantation, the median number of liver metastases was nine, most patients receiving a neoadjuvant treatment consisting of irinotecan and oxaliplation; however, none of these cases reported disease progression under chemotherapy. Liver transplant was performed at a median interval of 41 months after surgery for the primary tumour and was followed by the administration of mammalian target of rapamycin inhibitors. The overall post-transplant survival was of 83%, 62% and 50% at one year, three years and five years follow-up respectively, while the median follow-up period was of 26 months. During this period, there were six cases of recurrent disease developed at the level of lungs (in five cases), liver (in three cases) and peritoneum (in one case)[20].

Recently, a study conducted in Louvain, Belgium, demonstrated the feasibility of living related to liver transplant in patients with colorectal cancer and liver metastases; in the present study, the authors included 64 cases submitted to living related transplant between 1998 and 2016, two of them being submitted to liver transplantation for unresectable colorectal liver metastases. One case received a right hemi liver graft, while the second one received a left graft; the authors reported that the main complications encountered in the recipients were the biliary and vascular ones, while three patients developed a small for size syndrome; however, the morbidity was not correlated to the indication for liver transplantation[21].

Conclusions

Liver transplant seem to be a promising therapeutic strategy for patients presenting unresectable, confined to liver colorectal metastases. Improvement of the imaging techniques (in order to exclude the presence of extrahepatic disease), of the surgical techniques, as well as a better understanding of the pharmacokinetics and of the mechanisms of action of different types of immunosuppressive treatment were crucial in order to obtain better results in terms of survival. However, the method is not part of the standard therapeutic guidelines for the moment, probably due to the low number of donors. Further prospective studies are still needed in order to provide a better identification of the patients who could benefit most from this therapeutic approach.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

References

1. American Cancer Society. Cancer Facts & Figures 2017. Atlanta, Ga: American Cancer Society; 2017.
2. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. *J Clin Oncol.* 2005; 23(9):2038-2048.
3. Chakedis J, Squires MH, Beal EW, et al. Update on current problems in colorectal liver metastasis. *Curr Probl Surg.* 2017; 54(11):554-602.
4. Mohammad WM, Balaa FK. Surgical management of colorectal liver metastases. *Clin Colon Rectal Surg.* 2009; 22(4):225-232.
5. Nathan H, de Jong MC, Pulitano C, et al. Conditional survival after surgical resection of colorectal liver metastasis: an international multi-institutional analysis of 949 patients. *J Am Coll Surg.* 2010; 210(5):755-756.
6. Starzl TE. The saga of liver replacement, with particular reference to the reciprocal influence of liver and kidney transplantation (1955-1967). *J Am Coll Surg.* 2002; 195(5):587-610.
7. Poston GJ. Surgical strategies for colorectal liver metastases. *Surg Oncol.* 2004; 13(2-3):125-136.
8. Chan SC, Lo CM, Fan ST. Simplifying living donor liver transplantation. *Hepatobiliary Pancreat Dis Int.* 2010;9(1):9-14.
9. Chan SC, Fan ST, Lo CM, Liu CL, Wong J. Toward current standards of donor right hepatectomy for adult-to-adult live donor liver transplantation through the experience of 200 cases. *Ann Surg.* 2007;245(1):110-117.
10. Hwang S, Lee SG, Lee YJ, et al. Lessons learned from 1,000 living donor liver transplantations in a single center: how to make living donations safe. *Liver Transpl.* 2006;12(6):920-927.
11. Chan SC, Fan ST, Lo CM et al. A decade of right liver adult-to-adult living donor liver transplantation: the recipient mid-term outcomes. *Ann Surg.* 2008;248(3):411-419.
12. European Liver Transplant Registry: Data analysis booklet. Paris: 2007. Available at: http://www.eltr.org
13. Zhu JQ, He Q, Li XL. Liver transplantation benefits selected patients with hilar cholangiocarcinoma and colorectal liver metastases. *Hepatobiliary Pancreat Dis Int.* 2018;17(5):385-386.
14. Chan A. Liver transplantation for unresectable colorectal liver metastasis. *Hepatobiliary Surg Nutr.* 2013;2(3):162-164.
15. Dueland S, Guren TK, Hagness M et al. Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? *Ann Surg.* 2015;261(5):956-960.
16. Hoti E, Adam R. Liver transplantation for primary and metastatic liver cancers. *Transpl Int.* 2008;21(12):1107-1117.
17. Kappel S, Kandioler D, Steininger R, 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.
18. Muhlbacher F, Huk I, Steininger R, et al. Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? *Transplant Proc.* 1991;23(1 Pt 2):1567-1568.
19. Hagness M, Foss A, Line PD, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg.* 2013;257(5):800-806.
20. Toso C, Pinto MH, Andres A, et al. Liver transplantation for colorectal liver metastasis: Survival without recurrence can be achieved. *Liver Transpl.* 2017;23(8):1073-1076.
21. Iesari S, Inostroza Nunez ME, Rico Juri JM, et al. Adult-to-adult living-donor liver transplantation: The experience of the Universite catholique de Louvain. *Hepatobiliary Pancreat Dis Int.* 2019;18(2):132-142.