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Research Article

Hepatocellular Carcinoma after Liver Transplantation: Surgical Management

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Abstract

Background: Hepatocellular carcinoma (HCC) is a serious disease with an increasing incidence in the last decade and it's the third cause of cancer death in the world. Orthotopic liver transplantation (OLT) is the best treatment for early HCC in selected patients but recurrence of the tumor in the transplanted liver reaches up to 20%. Because of this, there has been an increasing interest in finding factors that predict recurrence but actually the level of evidence is poor and more research on this issue is needed.

Material and Methods: An extensive electronic search of the relevant literature was carried out using PubMed (Medline), EmBase, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Plus databases from May 2000 to May 2017. All descriptive studies reporting an assessment of surgical treatment of the liver graft for recurrent HCC and published in a peer-reviewed journal with available full-text were considered for a qualitative analysis. In the same way retrospective descriptive study of HCC transplanted patients of our geographical area of health was implemented.

Results: We included 30 studies pertaining to the surgical treatment of HCC in liver grafts. Of these, 21 studies were qualitatively analysed. Since 1996 485 liver transplants have been performed in our area, including 140 (28%) for HCC. Twenty of these patients have had a liver recurrence, but just one of them has been resected (0.71%).

Conclusion: HCC recurrence is the main drawback after liver transplantation for HCC and threatening their survival. Literature showed that survival and recurrence rates depend on the criteria used to select patients for transplant. The main reason why there are few studies on the local treatment of liver recurrences of HCC is that it is considered a systemic disease. Our conclusion is that we need more reports and a greater number of patients to be able to set clear indications about the treatment of these patients.

Keywords: *Hepatocellular Carcinoma; Liver Transplantation; Cochrane Plus*

Introduction

Hepatocellular carcinoma (HCC) is a serious disease with high mortality rates and with an increasing incidence in the last decade due to viral hepatitis C (VHC) and B (VHB) [1,2]. Eighty per cent of the cases of HC appears in patients affected with VHC, VHB, alcoholic cirrhosis, non-alcoholic fatty liver disease (NAFLD) and metabolic disorders such as hemochromatosis. For some authors, HCC develops in cirrhotic patients with an incidence between 3% and 5% per year [3]. In USA, Europe and Japan more than half of the cases are caused by

chronic hepatitis and cirrhosis due to VHC, with a latent period of 20 to 40 years between the viral infection and the diagnosis of the tumor [3]. Within the next 10 years an increase of incidence of HCC is expected in Western Europe because of epidemic VHC and NAFLD [4,5].

HCC is the fifth more frequent cancer (500,000 - 750,000 new cases diagnosed every year) and the third cause of cancer death in the world. Therefore, HCC is considered a worldwide health problem [4-7].

Surgical treatment of patients with HCC includes liver resection, ablation and orthotopic liver transplantation (OLT). The last one is the best treatment for early HCC in selected patients, mainly for those with unresectable tumors owing to their anatomical location or with limited functional liver remnant (Child-Pugh B and C) [3,4,6]. At the same time, HCC is the main indication of OLT, since this procedure treat both the tumor and the underlying liver disease [1,3,5].

However, even after OLT done adopting the Milan criteria proposed by Mazzaferro in 1996 (single tumors ≤ 5 cm in diameter or no more than three tumors ≤ 3 cm in diameter and without macroscopic vascular invasion), recurrence of HCC in the transplanted liver varies from 8% to 20% [8-10]. Although there is a lower recurrence of OLT following these criteria, many groups use expanded indications to encompass a greater number of patients [9-12]. These groups have shown that factors other than number and size such as tumor grade or tumor microinvasion, affect the prognosis of these patients and should be included in the selection criteria for transplantation [9]. For patients grafted under strict Milan criteria, long-term survival is similar to that achieved by transplanted patients without HCC [4,6]. The main limitation in survival in those patients with HCC is the recurrence due to circulating cancer cells and/or missed micrometastasis, which can be found in 10% to 60% of the patients, depending on the more or less stringent criteria used in their selection for OLT [2-5,8,12-16]. Time interval until recurrence is between 1 and 2 years after OLT. Few data exist regarding liver relapse after 2 years; in these cases the new tumor is considered as a *de novo* lesion [2]. There is also a close relationship between a shorter interval until recurrence and a poorer survival, with a mean survival time after diagnosis of less than 12 months [6,8].

Recently, there has been an increasing interest in finding factors that predict recurrence [4,12] such as tumor grade, tumor burden, vascular invasion or serum level of alpha-fetoprotein and in adding them to the classical criteria of size and number [4,11,17]. However, there is scarce information about the treatment of this liver recurrence and the papers covering this issue have important limitations [4,10]. Liver relapse is considered a metastatic disease (although most of the cases of recurrence are extrahepatic), rarely thought as curable, without any adjuvant therapy to prevent it. Thus, the only treatment is palliative (transarterial chemoembolization [TACE], immunosuppression or sorafenib) for those patients who cannot be operated [6,13,18]. Treatment choice must be individualized [4,5,11,19] taking into account that the longer the interval until recurrence, the better the survival after liver resection [6,10].

At present, the level of evidence in this controversial topic is low and more research on this issue is needed, even more when a greater number of recurrences are expected in the near future following the expanded indications of OLT [4,14].

The aim of this review of the surgical treatment of the liver recurrence of HCC after OLT is to set a basic notion as starting point to improve our results.

Materials and Methods

An extensive electronic search of the relevant literature with language restrictions (Spanish and English) was carried out using PubMed (Medline), EmBase, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Plus databases from May 2000 to May 2017. All descriptive studies reporting an assessment of surgical treatment of the liver graft for recurrent HCC and published in a peer-reviewed journal with available full-text were considered for a qualitative analysis, since they were not suitable for statistical combination.

Likewise, a retrospective descriptive study of HCC transplanted patients of our geographical area of health was implemented, looking for those with HCC relapse and those operated because of it.

Results

We included 30 studies pertaining to the surgical treatment of HCC in liver grafts. Of these, 21 studies with levels of evidence 2 to 4 (non-randomized controlled trials, prospective or retrospective case series and literature reviews) were qualitatively analysed. We did not find any randomized controlled trial (level of evidence 1).

The first liver transplantation in our area was done in 1996. Since then, 485 liver transplants have been performed, including 140 (28%) for HCC. Twenty of these patients have had a liver recurrence, but just one of them has been resected (0.71%). This patient is free of disease 3 years later. Time interval for recurrences was from 5 to 26 months.

Discussion and Conclusion

HCC recurrence is the main drawback after liver transplantation for HCC, appearing in 16% of the patients [4] and threatening their survival. Valdivieso., *et al*. [8] showed a survival rate of 83.5% at 5 years for disease-free patients, but only of 43% for those who relapsed. Clavien., *et al*. [1] and Valdivieso., *et al*. [8] showed that survival and recurrence rates depend on the criteria used to select patients for transplant. Within Milan criteria, 5-year survival rates are over 70% and the recurrence rate varies between 8% and 20%; when expanded criteria for transplant are used, numbers are 43.2% and 45.4%, respectively [9]. Our results showed a recurrence rate of 14.3%, which is in line with what was published.

Most of the papers displayed that the time elapsed between the grafting and the recurrence is an important predictor of survival, with a worse prognosis for those patients who relapse in less than 2 years. Valdivieso., *et al*. [8] said that recurrences appeared within the first 2 years are associated with survival rates shorter than 12 months. Recent interest in systemic treatments are showed in Toso., *et al*. [12] paper, which displayed a better survival with mTOR inhibitors treatment after liver transplant, or in Clavien., *et al*. [1] and Davis., *et al*. [17] publications, which proposed treatment with sorafenib, alone or combined with mTOR inhibitors, when local treatment (for the recurrence) is not possible.

The main reason why there are few studies on the local treatment of liver recurrences of HCC is that it is considered a systemic disease, frequently with multiple hepatic and extrahepatic metastases. De'Angelis., *et al*. [4] in their systematic review on this subject found 1021 patients with liver recurrence, 67% of them with extrahepatic disease in lungs, bones, adrenals, brain or peritoneum at the time of diagnosis.

Few papers address the surgical treatment of the liver recurrence of HCC (Table 1). Taketomi., *et al*. [11] concluded that liver resection increases survival, with a better prognosis for solitary tumors, showing 1, 3 and 5-year survival rates of 100%, 87.7% and 87.5% compared with those of 50%, 12.5% and 0% in inoperable patients. Kornberg., *et al*. [9] multivariate analysis on 60 patients showed that liver resection is an independent predictor of survival. Similar results are reported by Pfiffer., *et al.* [10] on 24 patients with recurrence out of 139 with OLT. De'Angelis., *et al*. [4] concluded that the best treatment for isolated recurrences, both hepatic and extrahepatic, is surgical resection. They showed that operated patients usually present a better performance status, later recurrences and fair locations of their tumors than non-operated ones, which contributes to improve their survival, as supported by Valdivieso., *et al* [8]. Welkner., *et al*. [5] systematic review reaches the same conclusions and showed significant differences between the median survival of 32.3 ± 21.5 months in patients undergoing surgery compared to 11.9 ± 6.9 months in those who did not. These numbers are similar to those reported by Valdivieso., *et al*. [8]. Nevertheless, they found that 50% of the surgically rescued patients developed a second recurrence, as Regalia., *et al*. [15] in 1998 and Roayaie., *et al*. [16] in 2004 have published. Sommacale., *et al*. [20] sustain that surgery was a feasible and safe treatment for the HCC liver recurrence in their 8 patients, which account for the 0.66% of their grafted patients. HCC recurrence rate is low among patients transplanted within the Milan criteria (12.6%) but has a significant impact on survival. Therapeutic options for this

complication are limited, but patients with recurrences amenable to surgery should be resected. Although there is an obvious selection bias, surgery seemed to prolong survival even when it was not curative (64% re-recurrence). There is a rationale for the use of sorafenib _mTOR-based immunosuppression [8].

Ref.	Year	No. of Transplants	Recurrence %	Liver Resection	Journal
Regalia., *et al.* [15]	1998	132	15,90%	2	*J Hepatobiliary Pancreat Surg*
Roayaie., *et al.* [16]	2004	311	18,30%	5	*Liver Transpl*
Kornberg., *et al.* [9]	2010	60	26,66%	2	*Eur J Surg Oncol*
Valdivieso., *et al.* [8]	2010	182	12,60%	2	*Transplant Proc*
Taketomi., *et al.* [11]	2010	101	16,70%	6	*Ann Surg Oncol*
Pfiffer., *et al.* [10]	2011	139	17,30%	1	*Tumori*
Chok., *et al.* [2]	2011	139	17,20%	2	*World J Surg*
Roh., *et al.* [14]	2014	458	16,00%	4	*Clin Transplant*
Sommacale., *et al.* [20]	2013	8	37,50%	3	*Transplant Proc*
Toso., *et al.* [12]	2013	234	12,80%	1	*J Hepatobiliary Pancreat Sci*
Sapisochin., *et al.* [21]	2015	780	15,50%	NR*	*Ann Surg Oncol*
Sahakyan., *et al.* [6]	2016	89	20,20%	2	*Case Reports in Oncological Medicine*

Table 1: *Liver surgical treatment for recurrent hepatocellular carcinoma in liver transplantation patients.*

**NR: No Referred*

Our conclusion, after analysing these reports on the surgical treatment of the recurrent HCC in the transplanted liver, is that we need more reports and a greater number of patients to be able to set clear indications about the treatment of these patients.

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