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Review Article

A review of the role of liver resection in the treatment of human immuno-deficiency virus-positive patients with hepatocellular carcinoma

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ABSTRACT

Background: Patients with human immune-deficiency virus (HIV) have increased risk of developing hepatocellular carcinoma (HCC); this neoplasm apparently behaves more aggressively in this population, leading to worse outcomes. Questions remain regarding the best treatment of HCC in these patients, mainly related to the role of surgical resection. Some studies show that, after transplantation, this group of patients has an overall survival rate comparable to that of uninfected patients. This integrative review assesses and summarize the survival outcome of resection in the treatment of HIV-positive patients with HCC.
Methods: Integrative review of articles published in English, in PubMed and Scielo databases until October 2021, using the terms: HIV, HCC, and resection.
Results: Four publications were analyzed in relation to their content and relevance to the research question. We identified 54 patients who underwent surgical resection, with great variability in overall survival between studies (median between 18 and 72 months); only one study demonstrated disease-free survival. There was also great variability in morbidity and mortality rates after the procedure. All studies were non-comparable.
Conclusions: Data regarding the impact of surgical resection on survival in HIV-positive patients with HCC are scarce, and questions remain about the best treatment options with curative intent. Further studies on the topic are needed, given the practical implications for decision-making. Therefore, we suggest that the treatment of these patients should still be conducted similarly to that indicated by the main guidelines on the treatment of patients with HCC, without distinction to HIV serology.

Keywords: Hepatocellular carcinoma, Liver resection, HIV-positive, Outcomes

INTRODUCTION

According to the International Agency for Research on Cancer, recent data suggests liver cancer incidence has stabilized after decades of incline but is the 5th and 7th most lethal cancer in men and women, respectively.[1] Data from the Brazilian National Cancer Institute (INCA) shows that primary liver cancer was the 10th most common cancer in men (excluding non-melanoma skin cancer) in 2022 with 6.390 new cases recorded, representing 2.7% of all cancers, and accounting for 6.093 deaths (5.2%) in the year of 2020.[2] Hepatocellular Carcinoma (HCC) accounts for approximately 80% of primary liver malignancies, and despite its low incidence, it is a serious public health issue, therefore the emphasis on the importance of correct evaluation and treatment of patients diagnosed with this

neoplasm, since their overall survival is 10-15% in 5 years, largely due to late diagnosis.[3-5]

Furthermore, the human immunodeficiency virus (HIV) has a high prevalence in Brazil. Data from the Brazilian Ministry of Health shows that, between 1980 and 2022, 1.088.536 cases of acquired immunodeficiency syndrome (AIDS) were recorded, with an incidence of 16.5/100.000 in 2021.[6] About 1/3 of HIV-infected patients have non-alcoholic fatty liver disease (NAFLD) due to risk factors related to HIV: increased BMI, use of antiretroviral drugs, and related comorbidities.[7] Because of the similar routes of contamination, it is believed that around 6% of the HIV-infected population worldwide is co-infected with hepatitis C (HBV), and 26% co-infected with the C virus (HCV) and eventually co-infected with both viruses.[8] A reflection of this is the identification of liver diseases as the main causes of mortality not AIDS-related in this group of patients.[7] As such, an increasing incidence of hepatocellular carcinoma in the population with HIV has been identified, as well as up to 4-fold increased risk of developing this neoplasm compared to uninfected individuals.[8-10]

The increased survival of patients with hepatocellular carcinoma is directly related to the use of potentially curative procedures: ablation therapies (radiofrequency, microwave ablation), liver resection and liver transplantation.[11] Some studies show that the group of HIV patients experience more aggressive neoplasms – occurring in younger patients, with higher rates of vascular invasion and multinodular disease – and, therefore, a worse overall survival compared to patients without HIV infection.[8,11-13] In light of this, publications demonstrating the results of surgical resection in HIV positive patients are rare, a fact possibly related to the theoretical risk of worse outcomes of this therapy. Nevertheless, there are studies showing that, after transplantation, this group of patients have an overall survival rate comparable to that of uninfected patients.[14,15] In this scenario of uncertainty, when analyzing international guidelines, such as the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of Liver (EASL) and the National Comprehensive Cancer Network (NCCN), regarding the treatment of patients with HCC and HIV, none of them cites a possible different approach for this group of patients.[16-18] This study aimed to perform a review of the topic of curative resection of hepatocarcinoma in HIV patients, especially in respect to outcomes, and if the outcomes are comparable to those identified in non-HIV patients.

METHODS

An integrative review of articles published in the English language was conducted using PubMed and Scielo databases, up to October 2021, using the terms: HIV, HCC, and resection (associated with their MeSh terms) in combination with the Boolean operators "or" and "and". Exclusion criteria included review articles, case reports, editorials, HIV-negative patients or patients with non-HCC pathology, and studies that did not demonstrate the specific results of resection in the study population (overall survival and/or disease-free survival after intervention).

Initially, a total of 593 articles were identified, of which 3 were selected after the elimination of papers that met the exclusion criteria. After analyzing the bibliography of the articles listed, 1 additional article was included. Thus, 4 articles were assessed regarding their content and relevance to the research question.

The articles were evaluated for their methodological quality and the presence of possible biases using the checklist provided by the Joanna Briggs Institute (JBI), which uses 11 aspects considered important in the analysis of cohort studies.[19] No studies were excluded based on this assessment. They were also classified according to the journal in which they were published, using the Qualis Periodicals instrument - a set of procedures used in the assessment of scientific journals that consists of a descending scale, according to the impact factor: A1, A2, B1, B2, B3, B4, B5 and C. The data from the selected papers were extracted and organized in a synthesis matrix, as described by Garrad (Table 1), while the analysis and synthesis of the results were conducted descriptively (not by meta-analysis) since there is no homogeneity in the results of the trials included in this study, as cited by De-La-Torre-Ugarte-Guanillo et al.[20,21]

RESULTS

All 4 selected studies were defined as retrospective cohort studies, as proposed by Dekkers et al, and all of them included patients from a single hospital center.[22] The number of patients undergoing intervention ranged from 6 to 26, totaling 54 resected individuals included in this review; all were recruited after the year 2000. As for the methodological quality of the studies, using the JIB checklist, they received scores ranging from 6 to 11, denoting some variability in the critical appraisal of the studies. Three studies were published in journals with Qualis ratings of at least B. The World Cancer Research Journal in which the work by D'Amico et al was published was not found in this classification.[23] Finally, three publications included patients treated in hospitals located in the West, while the publication by Zhao et al includes patients from the East.[24] The limitations and strengths of each study were grouped and are shown in the summary matrix (Table 1).

Survival analyses after resection

In all articles, overall survival (OS), considered in this study the period from surgery to date of death or loss to follow up, ranged from 65.4% to 90% at 1 year after hepatectomies. Three studies assessed OS at 3 years as ranging from 29.9% to 58%, and two demonstrated OS at 5 years ranging from 33% to 58%, thus showing an apparent wide variability in this outcome. The median

overall survival of these patients ranged from 18 to 72 months.

Only the article published by Golse et al demonstrated the analysis of disease-free survival (DFS) at 1, 3, and 5 years: 86%, 58%, and 58%, respectively.[25] It was also the only study to demonstrate the relapse rate after the intervention, which was 53%.

In the analysis of factors related to worse outcomes in terms of survival, two publications analyzed seropositivity as a possibly related factor.[24,26] Only in the publication by Zhao et al was the presence of HIV a factor independently related to worse overall survival, with a hazard ratio of 3,869.[24]

Survival analysis with comparative groups

No analyses comparing hepatectomies with ablative therapies were identified in this review. The publication by Zhao et al, comparing outcomes after surgery between patients with and without HIV, demonstrates a higher overall survival in seronegative patients (3-year OS of 29.9% versus 79.1%). It is noticeable that the text clearly states that the groups were not comparable across key factors related to prognosis: HIV-positive patients had higher alpha fetoprotein (AFP) rates (225.4 ng/ml versus 16.5 ng/ml), larger nodules (3.85 cm versus 3 cm), and higher microvascular invasion (MVI) rates (69.2% versus 38.6%).[24]

Table 1: Review matrix for integrative reviews.

Parameters	Zhao et al (2021)	Golse et al (2020)	D'Amico et al (2015)	Yopp et al (2012)
Qualis score	A2	B1	N/A	A1
JBI score	9/11	11/11	6/11	9/11
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort
Period	2013-2019	2000-2017	2003 - 2014	2005 - 2010
Objective	Compare outcomes post resection between seropositive and seronegative patients	Compare outcomes in seropositive patients undergoing either resection or transplantation	Analyze outcomes in seropositive patients post resection	Compare seronegative and seropositive patient presentation, treatment and outcomes
Sample (n)	26 seropositive and 75 seronegative	15 resected and 32 transplanted	6	7 (seropositive) and 6 (seronegative) underwent resection
OS/DSF	1-, 3-year OS in HIV+ = 65.4% and 29.9% Median OS of 18 months	Resected 1-, 3- and 5-year OS = 86%, 58% e 58% 1-, 3- and 5-year DFS = 53%, 33% and 33% Median OS of 72 months	1-, 3- and 5-year OS = 100%, 50% and 33%. Median OS of 35 months	OS in 1 year = 90%
Comparison between groups	1-, 3-year OS in HIV- = 93.3% and 79.1% (p=0.000)	Transplanted 1-, 3- and 5-year OS = 81%, 68% and 59% (p=0.84). 1-, 3- and 5-year DFS = 78%, 68% and 56% (p=0.06)	N/A	Median survival not reached in either group; 90% versus 86% one-year survival (p=0.32)

JBI=Joanna Briggs Institute critical appraisal checklist for cohort studies, OS=overall survival; DFS=disease free survival; HIV=human immunodeficiency virus

The publication by Golse et al was the only study that compared resection and transplantation using analysis from exposure and intention-to-treat. Both OS and DFS were comparable and statistically significantly, although the patient groups in both analyses were not comparable as patients undergoing liver transplantation had greater severity from a liver function standpoint, while those resected had more advanced tumors. When the recurrence rate after the procedures was analyzed, a higher number of tumors recurred in the group of patients who underwent hepatectomy (53% versus 16%, p=0.02). The 1-, 3- and 5-year OS were 89%, 78%, and 67% versus 100%, 73%, and 49% in the transplant and resection groups, respectively (p=0.82).[25]

Postoperative morbidity and mortality

The publication by Golse et al was also the only one to clearly define postoperative mortality (those occurring within 90 days) and morbidity using the Clavien-Dindo classification tools and the comprehensive complication index, CCI score.[27,28] No deaths occurred as a result of the resection, and only 20% of these patients had major

complications. Specifically, on postoperative morbidity, when compared to therapies and using the CCI, transplants were associated with a higher complication rate (score of 30.8 versus 8.7, p=0.004).

Regarding the remaining studies, Yopp et al did not present data on these outcomes, and D'Amico et al reported that there were no postoperative complications and mortality, however, they do not describe in their methodology how these outcomes were evaluated.[23,29] Finally, Zhao et al identified higher mortality related to tumor recurrence and postoperative liver failure in the HIV-positive group compared with seronegative patients (respectively, 42.3% versus 17.3%, p=0.016; 19.2% versus 2.7%, p=0.012).[24]

DISCUSSION

One of the aims of an integrative review, as described by Whittemore and Knalf, is to synthesize results of primary and/or secondary studies to reduce uncertainty about practices, better understand a phenomenon of concern and facilitate the decision-making process.[30] This integrative review was formulated to identify and analyze the outcomes, especially in terms of survival, of liver resection in HIV-positive patients with hepatocellular carcinoma.

All articles included were retrospective, single-center cohort studies, with a total of 54 patients undergoing therapy. Overall survival after hepatectomy ranged from 65% to 90% at 1 year, and from 33% to 58% at 5 years; median OS was between 18 and 72 months. Disease-free survival at 1 and 5 years was 86% and 58%, demonstrated in only one publication. The large variability in OS results is probably due to the different characteristics of the patients included in the studies. For example, in the article by Zhao et al which showed the worst survival amongst all those listed in this review, the median serum AFP values were 225 ng/ml and the maximum nodule diameter (median) was 3.85 cm, while in the publication by Golse et al with the best survival, these values were 19. 2 ng/ml and 2.5 cm - factors known to be related to worse outcomes after resection in patients with HCC.[24-26,31] It is important to mention that the publication by Yopp et al despite reporting the OS of patients undergoing the cited therapy, did not list the baseline characteristics of this group of patients, making further analysis not possible.[29] Zhao et al showed that HIV seropositivity was an independent risk factor for worse survival after resection in patients with HCC; however, after evaluation of some factors included in the multivariate analysis of the study, there are arbitrary values of AFP>400 and larger tumor diameter (>5 cm), which could account for potential selection bias.[24]

The publication by Golse et al was the only one to perform a survival analysis comparing different types of treatment-in this case, transplantation and resection - demonstrating, regardless of the methodology employed, comparable results of overall survival and disease-free survival.[25] It was the publication that obtained the best evaluation in terms of methodological quality. Only two publications demonstrated results concerning postoperative mortality and morbidity.[24,25] However, Zhao et al does not demonstrate the definition of the postoperative mortality and morbidity classification. Nevertheless, higher mortality related to tumor recurrence and postoperative liver failure is cited in the group of HIV-positive patients compared to seronegative patients and, in addition, a possible mortality rate of 23%. In comparison, Golse et al showed no deaths after hepatectomy and lower postoperative morbidity when compared to transplantation.

Regardless of the presence of HIV infection, there is a consensus that treatment of HCC with curative therapies is associated with better survival outcomes.[16,17] There are many publications comparatively evaluating the outcomes of these treatments in populations in which HIV infection is not the subject of study, with conflicting results. However, there are reviews with a high level of evidence that may help the practitioner's decision-making process. A systematic review and meta-analysis published by Proneth et al on cases potentially treatable by surgical resection and liver transplantation, comparable overall survival was identified between the therapies, with a total of 1572 patients included.[32]

When searching for studies evaluating the outcomes of potentially curative treatments in HIV-infected patients, these are found in a smaller proportion. The data on liver transplantation in this patient group are specifically promising - some publications demonstrate that after the procedure, survival analyses are comparable between infected and uninfected groups.[33,34] However, as identified by Vibert et al, the analysis of these results from the time of inclusion on the transplantation list showed a high drop-out rate in the subgroup of patients with HIV (23% versus 10%).[34] This shows that HCC possibly behaves differently in HIV-positive patients, a fact corroborated by studies demonstrating both a more aggressive behavior of the neoplasm in these patients and a faster progression to end-stage liver disease.[12,13,35] Unfortunately, there is a lack of data on the outcome of therapies other than liver transplantation. Some possible explanations include: teams have a greater tendency to indicate transplantation, given the aforementioned greater tumor aggressiveness, and avoid a possible increased risk of recurrence; and the fact that, given its aggressive behavior, patients tend to present with advanced stage of the disease (greater number of nodules, larger lesions), turning surgical resection or ablative therapies impossible.

The limitations of the present study, besides the aforementioned small number of publications and the small number of patients undergoing resection, can be listed as follows: all studies are retrospective which, as is known, are subject to selection biases and loss of data from medical records, only articles in English were analyzed, and a single reviewer performed the critical evaluation of the studies. Furthermore, the publications included

reported the results of patients from different regions of the world, where the prevalence of risk factors for chronic liver disease are different, with practical implications in terms of survival.[36] Zhao et al included patients treated in a hospital located in China, where hepatitis B virus infection is more prevalent, while in the publication by Golse et al patients were treated in a French service, where C virus infection is more prevalent.[17]

CONCLUSION

The present review synthesized quantitative and qualitative data from primary studies on the outcomes of liver resection in the treatment of patients with hepatocarcinoma and HIV.

As a result, major questions remain about the best treatment options with curative intent in these patients, especially those in whom more than one therapeutic option can be used. The great virtue of this study was to demonstrate a gap in this area of interest and the need for further studies on the subject since it has practical implications for the decision-making of teams that perform both resection and transplantation in patients with HCC.

We believe that liver transplantation should not be favored over other therapies with curative potential because there is no robust evidence for doing so. Thus, we suggest that the treatment of patients with HCC and HIV infection should follow main guidelines on the treatment of HCC.

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