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**Comparative analysis of outcomes after liver resection and liver transplantation
for early stages hepatocellular carcinoma in HIV-infected patients.**

An intention-to-treat analysis.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose.

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Abbreviations:

DFS: disease-free survival

ESLD: end stage liver disease

HAART: highly active antiretroviral therapy

HBV: hepatitis B virus

HCC: hepatocellular carcinoma

HCV: hepatitis C virus

HIV: human immunodeficiency virus

LR+: group of resected patients

LT+: group of transplanted patients

LT: liver transplantation

LTc: liver transplantation candidates

MELD: model for end-stage liver disease

OS: overall survival

POD: postoperative day

RFA: radiofrequency

SVR: sustained virological response

TACE: transarterial chemoembolization

TTR: time-to-recurrence

Key words: HCV; HIV; liver transplantation; hepatectomy, hepatocellular carcinoma.

Abstract: Objective: To address the results of resection for hepatocellular carcinoma (HCC) in human immunodeficiency virus (HIV)-carriers, and to compare them against survival after liver transplantation (LT).

Methods: All patients with HIV and HCC listed for LT (candidates = LTc+) or resection (LR+) between 2000 and 2017 in our centre were analysed and compared for overall survival (OS) and disease-free survival (DFS).

Results: The LTc+ group (n=43) presented with higher MELD scores and more advanced portal hypertension and HCC stages than LR+ group (n=15). One-, 3- and 5-year intention-to-treat survival rates were: 81%, 60% and 44%, versus 86%, 58% and 58% in the LTc+ and LR+ groups, respectively (p=0.746). Eleven LTc+ patients dropped out. After LT, OS was 81%, 68% and 59% (no difference with LR+ group; p=0.844). There tended to be better DFS after LT, reaching 78%, 68% and 56% versus 53%, 33% and 33% in the LR+ group (p=0.062).

Conclusion: This was the largest series of resections for HCC in HIV+ patients and the first intention-to-treat analysis. Although LT and resection do not always concern the same population, they enable equivalent survival. At the price of higher recurrence rate, resection could be integrated in the global armoury of liver surgeons.

INTRODUCTION

The use of combined antiretroviral therapy has enabled improved control of the human immunodeficiency virus (HIV) (1). However, a higher risk of mortality of HIV/hepatitis C (HCV) co-infected patients persists because of extra-hepatic conditions (2). Indeed, there is a close association between HIV, HCV and hepatitis B virus (HBV), and the presence of HIV used to shorten the time to the onset of fibrosis (3) so that liver transplantation (LT) is now a well validated indication in the event of end-stage liver disease (ESLD) in HIV+ patients (4-6). Nevertheless, the recent introduction of new direct-acting antiviral agents (DAA) means that ESLD as a major indication for LT is diminishing in this co-infected population (7).

Beyond the risk of ESLD, HIV+ patients are exposed to the other complications of chronic liver disease and particularly hepatocellular carcinoma (HCC). Classically, there was an increased incidence of HCC among HIV carriers, with HCC being diagnosed at an advanced stage and involving more infiltrative-type lesions and portal vein thrombosis (8,9), causing almost half of liver-related deaths (10). The risk of HCC has

been reported as being seven-fold higher in HIV+ patients than in the general population (11). However, thanks to the better efficacy and safety of DAA and highly active antiretroviral therapy (HAART), recent studies in the literature have suggested that this higher risk of HCC in co-infected populations no longer exists (2,12).

In HIV+ patients, HCC may have a more aggressive course (13), and little data has been published on resection in this setting. Conversely, the evolving role of LT for HCC in HIV+ patients has been widely reported. Most teams initially contraindicated LT (14,15) because of theoretically poorer outcomes due to the progression of HIV and HCV (16). More recently, numerous publications have demonstrated that LT is a safe procedure with outcomes comparable to those seen in the HIV- population (17-19), so that LT is becoming a standard of care in HIV+ patients (20,21). However, the high incidence of drop-outs remains a frequent issue and, even if there is no consensual recommendation regarding the management of HCC in HIV+ patients (22), one might wonder whether resection could also be a valuable option in highly selected HIV+ patients.

The aim of this study was therefore to consider the results of resection for HCC in HIV+ patients in a single tertiary centre and to compare the outcomes under intention-to-treat with those who were listed for transplantation. Our specific aim was to determine whether in HIV+ patients, BCLC stages 0-A HCC should be preferentially resected or transplanted.

PATIENTS AND METHODS

Study design and patients

The records of all patients with HIV and HCC listed for primary LT (liver transplant candidates = LTc+) or treated with liver resection (LR+) between January 2000 and December 2017 at the Centre Hepato-Biliaire, Paul Brousse Hospital (Villejuif, France) were evaluated retrospectively from our prospective database. Those listed for LT because of ESLD without HCC and those with incidental HCC (native liver) were not included in this analysis. The study population thus comprised 58 patients, of whom 32 were transplanted (LT+) and 15 were resected (LR+). The cut-off point for follow-up was June 2018.

The criteria used to indicate LT for HCC could be seen to change over the years: between 2000 and 2013, the Milan criteria were applied (23) but the AFP score was subsequently deployed (24).

The diagnosis of HCC was based on preoperative imaging and tumour marker levels; if necessary, biopsies of liver nodules were performed (22,25). Fibrosis was scored according to the METAVIR classification (26).

Before listing for any type of treatment, all patients had received HAART and both virological and immunological characteristics had been evaluated (21). HIV was staged according to the 1993 Centers for Disease Control and Prevention classification criteria (27). In all patients, antiviral therapies were administered according to current practices (28,29).

Before LT and during the waiting time on list, locoregional treatments for HCC were implemented if required: local destruction using radiofrequency ablation (RFA), and/or

transarterial chemoembolization (TACE). In the case of LT for an HCC recurrence after resection (performed during the study period in a curative intent), the patient was placed in the LR+ group (intention-to-treat analysis).

The first part of the study included an intention-to-treat analysis that evaluated all patients as from the time of listing for transplant (LTc+) or resection (LR+). We specifically focused on patients who had initially been either transplantable or resectable using current criteria (AFP score ≤ 2 , Model for End-Stage Liver Disease [MELD] < 12 , platelet level $> 100.10^9$ /L, without macrovascular invasion, age < 70), in order to compare the strategies in the event of BCLC stages 0-A HCC.

The second part compared survival rates in both groups (LT+ vs LR+) as from treatment in terms of overall survival (OS), time-to-recurrence (TTR) (30), disease-free survival (DFS) and their predictors.

Following their discharge, transplanted patients visited our outpatient clinic every 2 weeks for the first 2 months, and then once every 3 months, undergoing systematic Doppler sonography and AFP assays. A CT-scan was performed in the event of a rising AFP level or lower arterial index resistances and/or abnormal hepatic test findings. Resected patients underwent an initial CT-scan at postoperative day (POD) 30 and then once every 3 or 4 months (+AFP assay) during the first 2 years. Biological and imaging follow-up was subsequently scheduled every six months.

Statistical analysis

Continuous variables are described as medians and ranges, and categorical variables as a percentage. Categorical data were compared using the X² test or Fisher's exact test, whereas continuous variables were compared using a T-test or the Mann–Whitney U test, as appropriate.

Survival was analysed using the Kaplan-Meier method, and the results were compared using the log-rank test. Overall survival was calculated from the date of inclusion or surgery until death or the last follow-up examination. DFS was defined as the period between surgery and the first postoperative recurrence or death. Baseline and tumour characteristics, as peri- and post-surgery variables, were assessed as predictors of outcome using Cox proportional hazards models. Variables associated with a P value <0.10 under univariate analysis were considered for multivariate analysis. The hazard ratio (HR) estimates and associated 95% confidence intervals (CI) were calculated, and a P-value ≤ 0.05 in the Cox model was considered to be statistically significant.

Intention-to-treat survival was calculated from the day of inclusion on the waiting list (LTc+ group) or the indication of surgery (LR+ group). Death was considered as postoperative mortality in the case of events occurring during hospitalisation for the first surgery, or before POD 90.

RESULTS

General characteristics of HIV+ patients in our centre

During the study period, 714 HIV+ patients were evaluated, including 136 (19%) patients who suffered from HCC. Among these, 58 were listed for transplantation or resection and are described below while the 78 others were not candidates for surgery.

Characteristics of LTc+ and LR+ patients at diagnosis (Table 1)

Liver transplantation was indicated in 43 patients with HCC and resection was proposed to 15 others. Almost all the patients presented with controlled HIV infection. The LTc+ group presented poorer general status, but a lower tumour burden with a lower median AFP score (not significant) and a lower “outside-Milan” frequency (5% vs 27%, $p=0.04$). The “extra-criteria” LTc+ patients ($n=4$ according to the rules at that time) were nonetheless listed because of their Milan scores (before the era of AFP scores).

Early course after listing

In the LTc+ group, there were 11 (26%) drop-outs, with a median time before delisting of 159 days (range = 27–753 days). Among these patients, most were receiving RFA ($n=3$) and/or TACE ($n=9$) while waiting for LT. The principal reasons for drop-outs were tumour progression with the occurrence of macrovascular invasion ($n=4$), extrahepatic metastasis ($n=3$), multiple liver nodules out of the transplant criteria ($n=2$) and death from sepsis ($n=1$) or unknown causes ($n=1$).

In the LT+ group ($n=32$), treatments on the waiting list included surgical resection

(n=2), RFA (n=8) or TACE (n=19). The median waiting time before LT was 126 days (range = 24-990 days).

The only differences highlighted among LTc+ patients who dropped out versus those who did not were the initial AFP level (median: 37 [7-4000] vs 7 [2-1700], p=0.01), and the AFP score (median: 1 [0-3] vs 0 [0-4], p=0.06), higher in the drop-out group.

In the LR+ group, all listed patients were resected (no progression before surgery), the median waiting time being 24 days (range= 9-75 days). Two resected patients developed a recurrence after resection in curative-intent and then underwent salvage transplantation.

Under intention-to-treat, the survival rates at 1, 3 and 5 years after listing were (Fig. 1) 81%, 60% and 44% versus 86%, 58% and 58% in the LTc+ and LR+ groups, respectively (p=0.75).

Comparison of transplantable and resectable patients (intention-to-treat)

In order to compare the two strategies (transplantation vs resection) when both treatments were potentially applicable, we used intention-to-treat OS to compare patients with transplantable and resectable HCC. We thus compared nine patients in the LTc+ subgroup against nine patients in the LR+ subgroup. There were no differences regarding epidemiological and virological features between the two groups, and particularly no difference relative to HBV or HCV co-infection. As expected, liver function was poorer in the transplant group, with a median MELD score of 9.3 ± 1.5 vs 7.8 ± 1.5 (p=0.05). There was no significant difference regarding platelet levels (p=0.83), AFP levels (p=0.69), the median number of lesions (p=0.08) and maximal HCC size (p=0.45). No postoperative deaths occurred after resection and only one after

LT (cardiogenic shock at POD 70). The median OS values after listing in the transplant and resection subgroups were 66.8 months and 39.4 months, respectively. One-, 3- and 5- years survival rates were 89%, 78% and 67% vs 100%, 73% and 49% in the LTc+ and LR+ groups, respectively ($p=0.82$).

Characteristics of patients at transplantation or resection (Table 2)

There were no statistically significant differences between the groups regarding epidemiological features. The most prevalent cause of cirrhosis was HCV, involved in 81% and 87% of LT+ and LR+ cases, respectively. Among co-infected HIV/HCV patients, 15% and 38% of them had a history of co-infection with HBV in the LT+ and LR+ groups, respectively ($p=0.13$), but only three patients (LR+ group only) presented with a persistently positive HBV viral load at the time of surgery ($p=0.17$). Portal hypertension was more severe in the LT+ group, as evidenced by the platelets count, lower in this group (68 [15-240] vs 158 [57-239], $p=0.001$).

HIV infection was better controlled in the LR+ group, as reflected by higher levels of CD4 lymphocytes. Moreover, using the CDC classification, 50% of patients in group LT and 13% in group LR were classified as having AIDS-indicator conditions ($p=0.04$).

In the resected group, tumours were larger on preoperative imaging but all patients presented a single lesion, unlike the LT group where 11 patients (34%) had multiple lesions ($p=0.009$). In the resection group, tumours also displayed a more aggressive pattern; four of them (27%) were considered to have advanced tumours (BCLC C) because of macrovascular invasion. Twelve patients (80%) underwent minor hepatectomy (<3 segments).

Early postoperative outcomes in the LT+ and LR+ groups (Table 2)

In the transplant cohort, major complications (Dindo-Clavien III-IV) were recorded in 12 recipients (37.5%). Two developed primary non-function and were re-transplanted, but died during the post-transplant period from multiple septic complications. A third recipient died at POD 10 due to massive abdominal haemorrhage and one patient died after discharge from hospital, at POD 70 days due to unexpected cardiogenic shock. The other eight patients developed one or more of the following complications: sepsis (pulmonary origin [n=3], acute appendicitis [n=1]), abdominal bleeding (n=3), acute renal failure (n=3) biliary leak (n=1), haemorrhagic shock (n=1), and pulmonary embolism (n=1).

In the resected group, three major postoperative complications occurred (n=3; 20%): two patients required an urgent exploratory laparotomy for bleeding and biliary leak, and another developed post-hepatectomy liver failure (grade C), which was treated medically. There were no postoperative death.

Overall survival at six months reached 87.5% (four deaths) and 86% (two deaths) in the LT+ and LR+ groups, respectively.

Recurrence and survival after transplantation or resection (Fig. 1 and 2, Table 3)

The median follow-up after LT and resection was 45 [0-135] months and 22 [3-77] months, respectively. LR+ patients developed a higher recurrence rate than transplanted patients (n=8, 53% vs n=5, 16%; p=0.02), and earlier recurrence (4.2 months [2.3-32.4 months] vs 11.7 months [3.1-46.1 months], p=0.62). The OS at 1, 3 and 5 years reached 81%, 68% and 59% in the LT+ group versus 86%, 58% and 58% in the LR+ group (p=0.84). There was a trend towards longer DFS in the LT+ group as this reached 78%,

68% and 56% at 1, 3 and 5 years, versus 53%, 33% and 33% in the LR+ group ($p=0.06$). The mean time-to-recurrence was significantly shorter in the resected group (35 months vs 112 months, $p=0.001$).

In the LT+ group, there were three (60%) initial extrahepatic recurrences, one (20%) intra-hepatic recurrence only, and one (20%) both intra and extrahepatic localisation. The median survival after recurrence was 5.2 months and none of these patients were alive at the last follow-up. One recipient received RFA for post-LT recurrence.

At the end of follow-up, 17 patients (53%) in the LT+ group were alive without a recurrence and 15 recipients died (47%). Three of them clearly died from liver-associated complications (cirrhosis after reinfection from HCV, fibrosing cholestatic hepatitis, severe rejection after treatment with INF-based therapy for HCV reinfection).

All eight recurrences in the LR+ group were solely intrahepatic. Two patients were managed with a combination of TACE and salvage LT, and they were still alive (without a recurrence) 12 and 20 months later. One patient underwent a repeat resection and died from a recurrence after 17 months. Other patients received TACE ($n=4$) and best supportive care ($n=1$). The median survival after a recurrence was 8.3 months. At the last follow-up, 10 patients (67%) in the LR+ group were alive, six without disease and four with a recurrence; four patients died after a recurrence and one died from liver failure (after discharge).

In the LT+ group, mean survival was better in recipients who achieved SVR compared to those who did not, at respectively 123 and 36 months ($p<0.001$). In the LR+ group, there was no difference between groups as a function of SVR status (mean OS: 53 months if SVR+ vs 28 months if SVR-; $p=0.74$).

DISCUSSION

Statement of principal findings

This study reports on the largest cohort of HIV-carrier patients resected for HCC (n=15). We observed that hepatectomy for HCC procured the same OS as LT for HCC in HIV+ patients, when either inclusion at surgery or at diagnosis were considered. However, we observed a longer TTR survival in the LT+ group that could partly be explained by the more advanced stage of HCC in the LR+ group.

Even in the subgroup of patients who were potentially transplantable and resectable at diagnosis, the two strategies did not differ in terms of OS (p=0.82).

Our aim was not to demonstrate the superiority of a strategy, but rather to highlight the feasibility and reliability of hepatectomy in this context. Obviously, the LTc+ and LR+ groups were not strictly comparable, and only a few LTc+ patients could initially have been resected (9/43; 21%).

As previously reported, we confirm the high rate of drop-outs among LT candidates (11/43; 26%) (17,19). Interestingly, two patients who dropped-out had been resectable at diagnosis. We also confirmed the negative impact of high AFP level at diagnosis, and as a predictor of a higher risk of drop-out.

Strengths and weaknesses of the study

The main strength of this study was its sample size which, though limited, is the largest cohort of hepatic resections to have been reported in this setting. This series also reflects current management in a western, tertiary high-volume centre (>150 LT/year) with particular easy access to HAART and DAA. Indeed, most studies available in the

literature reported “historical” series without DAA and their transposition to current practices remains limited. Finally, the intention-to-treat design, completing the post-treatment analysis, strengthened the clinical relevance of the study.

The study was however affected by a series of limitations. The most important was its retrospective design which reduced the scope of its conclusions because of potential bias. Finally, the short follow-up period in the LR+ group prevented us from drawing definitive conclusions regarding long-term events in this group.

One important remark is that 75% of our transplanted cohort was managed before the era of new anti-HCV therapies. Although not statistically significant, the resected cohort was more recent. This is of great importance because it has now been clearly demonstrated that new DAA display considerable efficacy after LT, with high SVR rates and excellent tolerability (31,32), without causing a negative impact on the incidence of *de novo* HCC (as was initially suspected) (33-35). These good results have been confirmed in a recent multicentric study in HCV/HIV-coinfected patients (36). Using these drugs, we could expect even better long-term survival rates for HIV/HCV co-infected recipients than those demonstrated by our present series, and a comparison of survival versus resected patients could become more clearly in favour of LT.

Interpretation with reference to other studies

Rightly, the place for LT in HIV+ patients is now well established in a context of either ESLD or HCC. However, due to recent rises in the incidence of HCC in these patients and the shortage of liver grafts, alternatives to LT are now needed to avoid unacceptable waiting on the list or even higher rates of drop-outs (37).

Despite its consensual acceptance, LT for HCC in HIV-carriers raises many questions. First, Miro et al. recently updated the data, showing that survival in HCV/HIV co-infected patients was poorer than in HCV mono-infected patients (no long-term effects of DAA were reported) because of more aggressive HCV recurrences leading to graft loss and death (5-year survival: 50-55%) (21). In most series, as in ours, almost all HIV+ LT candidates are HCV-carriers so their expected survival is not as good as in the HIV- population. In the present series, 5-year survival in the LTc+ group under intention-to-treat only reached 44%.

Moreover, LT is a difficult procedure in this setting, as confirmed by intra- and post-operative data revealing more complex interventions than resections. After LT, there is also a high risk of opportunistic infections in HIV+ recipients. In a recent French series that included patients in whom adapted preventive measures had been implemented (vaccination, antibacterial/antiviral/antifungal prophylaxis), Teicher et al. reported up to 7% of post-LT deaths related to infection, and a MELD score >17 was associated with a 2-fold higher risk of developing infectious complications (38).

On the other hand, the role of liver resection in HIV+ patients needed to be specified because very few reports are available. To the best of our knowledge, only eight papers have been published on resection in HIV+ patients (36 cases; median number of cases/report = 3) (14,39-45). Regarding the two largest cohorts published by Berretta et al. (n=13) (41) and Yopp et al. (n=7) (45), they did not provide any data on the resection subgroup. D'Amico et al. detailed tumour characteristics (n=6): they resected more advanced tumours than our group (mean size: 4.45cm; mean preoperative AFP level: 117 ng/ml), which explains why their observed OS was lower than ours (1-, 3-, 5-year OS: 100%, 50%, 33%, respectively) (40).

More interesting is a comparison of our results in the LR+ group with data published in HIV- populations. Our 1-, 3- and 5-year OS and DFS rates after resection were 86%/58%/58% and 53%/33%/33%, respectively. In HCV+ HIV- populations, Hanazaki et al. reported 3- and 5-year OS of 63% and 52%, and DFS of 33% and 20%, rates that were lower than ours (46). Yeh et al. found 1-, 3-, and 5-year OS rates of 63%, 42%, and 32%, and their DFS were 51%, 34%, and 27%, once again lower than ours (47). These results, showing no additional mortality in HIV-infected patients, justify the place of HCC resection in HIV+ patients with results that are (at least) equivalent to those obtained in the general population.

Finally, although it is now accepted that LT can offer several advantages over resection under an intention-to-treat analysis in the general population (48,49), we probably need to apply the same decisional algorithm in both HIV+ and HIV- patients, in view of current graft shortages and the immediate availability of resection.

CONCLUSION

Liver transplantation and liver resection in HIV+ carriers procure comparable DFS and OS rates, either under intention-to-treat or after treatment, but targeting different populations. Indeed, in our study, the two groups differed quite markedly, with LTc+ patients displaying a more impaired liver function while LR+ patients were suffering from more advanced HCC. However, in rare situations when both treatments are potentially feasible at diagnosis, there is no clear argument in favour of LT because the DFS benefit seems to be counterbalanced by a higher drop-out rate. Whichever strategy is chosen, it should perhaps only be proposed to selected young patients, particularly those with a controlled viral load through the use of HAART and DAA in the event of HCV co-infection, and to ensure a strict monitoring after treatment.

REFERENCES

1. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. Okulicz JF, editor. PLoS ONE. Public Library of Science; 2013;8(12):e81355.
2. Salmon-Céron D, Nahon P, Layese R, Bourcier V, Sogni P, Bani-Sadr F, et al. HIV/HCV co-infected cirrhotic patients are no longer at higher risk for HCC or end-stage liver disease as compared to HCV mono-infected patients. *Hepatology*. John Wiley & Sons, Ltd; 2018 Dec 19;:1–25.
3. Massard J, Ratziu V, Thabut D, Moussalli J, Lebray P, Benhamou Y, et al. Natural history and predictors of disease severity in chronic hepatitis C. *J Hepatol*. 2006;44(1 Suppl):S19–24.
4. Duclos-Vallée J-C, Feray C, Sebah M, Teicher E, Roque-Afonso A-M, Roche B, et al. Survival and recurrence of hepatitis C after liver transplantation in patients coinfecting with human immunodeficiency virus and hepatitis C virus. *Hepatology*. 2008 Feb;47(2):407–17.
5. Tateo M, Roque-Afonso A-M, Antonini TM, Medja F, Lombes A, Jardel C, et al. Long-term follow-up of liver transplanted HIV/hepatitis B virus coinfecting patients: perfect control of hepatitis B virus replication and absence of mitochondrial toxicity. *AIDS*. 2009 Jun 1;23(9):1069–76.
6. Terrault NA, Berenguer M, Strasser SI, Gadano A, Lilly L, Samuel D, et al. International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Recipients. 2017. pp. 956–67.
7. Gadiparthi C, Cholankeril G, Perumpail BJ, Yoo ER, Satapathy SK, Nair S, et al. Use of direct-acting antiviral agents in hepatitis C virus-infected liver transplant candidates. *World J Gastroenterol*. 2018 Jan 21;24(3):315–22.
8. Lewin M, Gelu-Simeon M, Ostos M, Boufassa F, Sobesky R, Teicher E, et al. Imaging Features and Prognosis of Hepatocellular Carcinoma in Patients with Cirrhosis Who Are Coinfecting with Human Immunodeficiency Virus and Hepatitis C Virus. *Radiology*. 2015 Nov;277(2):443–53.
9. Gelu-Simeon M, Lewin M, Ostos M, Bayan T, Beso Delgado M, Teicher E, et al. Prognostic factors of survival in HIV/HCV co-infected patients with hepatocellular carcinoma: The CARCINOVIC Cohort. *Liver Int*. 2019 Jan;39(1):136–46.
10. Rosenthal E, Roussillon C, Salmon-Céron D, Georget A, Hénard S, Huleux T, et al. Liver-related deaths in HIV-infected patients between 1995 and 2010 in France: the Mortavic 2010 study in collaboration with the Agence Nationale de

- Recherche sur le SIDA (ANRS) EN 20 Mortalité 2010 survey. *HIV Med.* John Wiley & Sons, Ltd; 2015 Apr;16(4):230–9.
11. Berretta M, Martellotta F, Di Francia R, Spina M, Vaccher E, Balestreri L, et al. Clinical presentation and outcome of non-AIDS defining cancers, in HIV-infected patients in the ART-era: the Italian Cooperative Group on AIDS and tumors activity. *Eur Rev Med Pharmacol Sci.* 2015 Oct;19(19):3619–34.
 12. Vaziri A, Gimson A, Agarwal K, Aldersley M, Bathgate A, MacDonald D, et al. Liver transplant listing for hepatitis C-associated cirrhosis and hepatocellular carcinoma has fallen in the United Kingdom since the introduction of direct-acting antiviral therapy. *J Viral Hepat.* John Wiley & Sons, Ltd (10.1111); 2018 Oct 19;21(s1):5.
 13. Bourcier V, Winnock M, Ait Ahmed M, Sogni P, Pambrun E, Poizot-Martin I, et al. Primary liver cancer is more aggressive in HIV-HCV coinfection than in HCV infection. A prospective study (ANRS CO13 Hepavir and CO12 Cirvir). *Clin Res Hepatol Gastroenterol.* 2012 Jun;36(3):214–21.
 14. Puoti M, Bruno R, Soriano V, Donato F, Gaeta GB, Quinzan GP, et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *AIDS.* 2004 Nov 19;18(17):2285–93.
 15. García-Samaniego J, Rodriguez M, Berenguer J, Rodríguez-Rosado R, Carbó J, Asensi V, et al. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am J Gastroenterology.* Nature Publishing Group; 2001 Jan;96(1):179–83.
 16. Di Benedetto F, De Ruvo N, Berretta M, MASETTI M, Montalti R, Di Sandro S, et al. Hepatocellular carcinoma in HIV patients treated by liver transplantation. *Eur J Surg Oncol.* 2008 Apr;34(4):422–7.
 17. Vibert E, Duclos-Vallée J-C, Ghigna M-R, Hoti E, Salloum C, Guettier C, et al. Liver transplantation for hepatocellular carcinoma: the impact of human immunodeficiency virus infection. *Hepatology.* 2011 Feb;53(2):475–82.
 18. Agüero F, Forner A, Manzardo C, Valdivieso A, Blanes M, Bárcena R, et al. Human immunodeficiency virus infection does not worsen prognosis of liver transplantation for hepatocellular carcinoma. *Hepatology.* 2016 Feb;63(2):488–98.
 19. Di Benedetto F, Tarantino G, Ercolani G, Baccarani U, Montalti R, De Ruvo N, et al. Multicenter Italian experience in liver transplantation for hepatocellular carcinoma in HIV-infected patients. *Oncologist.* 2013;18(5):592–9.
 20. Baccarani U, Righi E, Adani GL, Lorenzin D, Pasqualucci A, Bassetti M, et al. Pros and cons of liver transplantation in human immunodeficiency virus infected recipients. *World J Gastroenterol.* 2014 May 14;20(18):5353–62.

21. Miro JM, Stock P, Teicher E, Duclos-Vallée J-C, Terrault N, Rimola A. Outcome and management of HCV/HIV coinfection pre- and post-liver transplantation. A 2015 update. *J Hepatol*. 2015 Mar;62(3):701–11.
22. European Association for the Study of the Liver., European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol*. 2018 Jul;69(1):182–236.
23. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996 Mar 14;334(11):693–9.
24. Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al. Liver transplantation for hepatocellular carcinoma: a model including α -fetoprotein improves the performance of Milan criteria. *Gastroenterology*. 2012 Oct;143(4):986–94.e3–quize14–5.
25. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Vol. 56, *JOURNAL OF HEPATOLOGY*. 2012. pp. 908–43.
26. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology*. 1996 Aug;24(2):289–93.
27. From the Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *JAMA*. 1993 Feb 10;269(6):729–30.
28. Coilly A, Roche B, Duclos-Vallée J-C, Samuel D. Optimum timing of treatment for hepatitis C infection relative to liver transplantation. *Lancet Gastroenterol Hepatol*. 2016 Oct;1(2):165–72.
29. Shaffer AA, Durand CM. Solid Organ Transplantation for HIV-Infected Individuals. *Curr Treat Options Infect Dis*. Springer US; 2018 Mar;10(1):107–20.
30. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst*. 2008 May 21;100(10):698–711.
31. Antonini TM, Coilly A, Rossignol E, Fougerou-Leurent C, Dumortier J, Leroy V, et al. Sofosbuvir-Based Regimens in HIV/HCV Coinfected Patients After Liver Transplantation: Results From the ANRS CO23 CUPILT Study. *Transplantation*. 2018 Jan;102(1):119–26.
32. Antonini TM, Furlan V, Teicher E, Haïm-Boukobza S, Sebah M, Coilly A, et al. Therapy with boceprevir or telaprevir in HIV/hepatitis C virus co-infected patients to treat recurrence of hepatitis C virus infection after liver transplantation. *AIDS*. 2015 Jan 2;29(1):53–8.

33. Nahon P, Layese R, Bourcier V, Cagnot C, Marcellin P, de Ledinghen V, et al. Incidence of Hepatocellular Carcinoma After Direct Antiviral Therapy for HCV in Patients With Cirrhosis Included in Surveillance Programs. *Gastroenterology*. 2018 Nov;155(5):1436–6.
34. Nishibatake Kinoshita M, Minami T, Tateishi R, Wake T, Nakagomi R, Fujiwara N, et al. Impact of direct-acting antivirals on early recurrence of HCV-related HCC: Comparison with interferon-based therapy. *J Hepatol*. 2019 Jan;70(1):78–86.
35. Waziry R, Hajarizadeh B, Grebely J, Amin J, Law M, Danta M, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. *J Hepatol*. 2017 Dec;67(6):1204–12.
36. Manzardo C, Londoño MC, Castells L, Testillano M, Luis Montero J, Peñafiel J, et al. Direct-acting antivirals are effective and safe in HCV/HIV-coinfected liver transplant recipients who experience recurrence of hepatitis C: A prospective nationwide cohort study. *Am J Transplant*. 2018 Oct;18(10):2513–22.
37. Pinato DJ, Dalla Pria A, Sharma R, Bower M. Hepatocellular carcinoma: an evolving challenge in viral hepatitis and HIV coinfection. *AIDS*. 2017 Mar 13;31(5):603–11.
38. Teicher E, Boufassa F, Vittecoq D, Antonini TM, Tateo MG, Coilly A, et al. Infectious complications after liver transplantation in human immunodeficiency virus-infected recipients. *Transpl Infect Dis*. 2015 Oct;17(5):662–70.
39. Bräu N, Fox RK, Xiao P, Marks K, Naqvi Z, Taylor LE, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. *J Hepatol*. 2007 Oct;47(4):527–37.
40. D'Amico G, Tarantino G, Ballarin R, Serra V, Pecchi AR, Guaraldi G, et al. Liver Resection for HCC in HIV-infected patients: A single center experience. *WCRJ*. 2015 Apr 2;2 (1) e490:1–6.
41. Berretta M, Garlassi E, Cacopardo B, Cappellani A, Guaraldi G, Cocchi S, et al. Hepatocellular carcinoma in HIV-infected patients: check early, treat hard. *Oncologist*. 2011;16(9):1258–69.
42. Lim C, Goutte N, Gervais A, Vullierme M-P, Valla DC, Degos F, et al. Standardized care management ensures similar survival rates in HIV-positive and HIV-negative patients with hepatocellular carcinoma. *J Acquir Immune Defic Syndr*. 2012 Dec 15;61(5):581–7.
43. Narushima Y, Ishiyama S, Kawashima K, Shimamura H, Yamaki T, Yamauchi H. Operated hepatocellular carcinoma in two HIV- and HCV-positive hemophilic patients. *J Hepatobiliary Pancreat Surg*. 2004;11(3):207–10.

44. Ettore GM, Vennarecci G, Boschetto A, Giovannelli L, Antonini M, Carboni F, et al. Resection and transplantation: evaluation of surgical perspectives in HIV positive patients affected by end-stage liver disease. *J Exp Clin Cancer Res*. 2003 Dec;22(4 Suppl):167–9.
45. Yopp AC, Subramanian M, Jain MK, Mansour JC, Schwarz RE, Balch GC, et al. Presentation, treatment, and clinical outcomes of patients with hepatocellular carcinoma, with and without human immunodeficiency virus infection. *Clin Gastroenterol Hepatol*. 2012 Nov;10(11):1284–90.
46. Hanazaki K, Kajikawa S, Shimozawa N, Shimada K, Hiraguri M, Koide N, et al. Hepatic resection for large hepatocellular carcinoma. *Am J Surg*. 2001 Apr;181(4):347–53.
47. Yeh C-N, Chen M-F, Lee W-C, Jeng L-B. Prognostic factors of hepatic resection for hepatocellular carcinoma with cirrhosis: univariate and multivariate analysis. *J Surg Oncol*. 2002 Dec;81(4):195–202.
48. Menahem B, Lubrano J, Duvoux C, Mulliri A, Alves A, Costentin C, et al. Liver transplantation versus liver resection for hepatocellular carcinoma in intention to treat: An attempt to perform an ideal meta-analysis. *Liver Transpl*. 2017 Jun;23(6):836–44.
49. Adam R, Bhangui P, Vibert E, Azoulay D, Pelletier G, Duclos-Vallée J-C, et al. Resection or transplantation for early hepatocellular carcinoma in a cirrhotic liver: does size define the best oncological strategy? *Ann Surg [Internet]*. 2012 Dec;256(6):883–

FIGURES LEGENDS**Fig 1**

Figure 1a: OS after listing for transplantation or resection (p=0.75)

Figure 1b: OS after transplantation or resection (p=0.84)

Fig 2: DFS after transplantation or resection (p=0.06)

Fig 3: Flow-chart of the study

Characteristics	Listed for LT (LTc) n=43	Listed for resection (LR) n=15	<i>p</i>-value
Male gender, n (%)	33 (77)	4 (73)	1
Age, years	49 (36-62)	53 (38-71)	0.06
Diabetes, n (%)	9 (21)	2 (13)	0.71
BMI	22 (15-37)	21 (16-35)	0.72
HIV viral load detectable	0 (0)	3 (20)	0.02
HBV infection, n (%)	12 (28)	7 (47)	0.21
HCV infection, n (%)	35 (81)	13 (87)	1
HCV genotype 1 (%)	14 (40)	5 (38)	1
Alcohol consumption, n (%)	13 (30)	6 (40)	0.53
CD4 cell count (/mm ³)	267 (50-840)	500 (50-950)	0.01
MELD score	12 (7-26)	8 (6-16)	0.0001
Child C, n (%)	6 (14)	0 (0)	0.32
Platelet count (10 ⁹ /L)	71 (15-252)	158 (57-239)	0.0003
Nodules, n	1 (1-3)	1 (1-1)	0.008
Max diameter, mm	20 (10-45)	28 (15-120)	0.05
AFP level, µg/L	11 (2-4000)	19 (2-1000)	0.52
AFP score (Duvoux)	0 (0-4)	1 (0-4)	0.22
AFP score >2, n (%)	4 (9)	4 (27)	0.18
Outside Milan criteria, (%)	2 (5)	4 (27)	0.04

Table 1. Characteristics of HIV patients at diagnosis as potential candidates for liver transplantation *versus* liver resection.

Quantitative variables are expressed as medians and ranges.

AFP: alpha-fetoprotein, BMI: body mass index

<i>Characteristics</i>	LT+ (n=32)	LR+ (n=15)	<i>p-value</i>
Preoperative data			
<i>Age, years</i>	50.4 (36.6 – 64.8)	53.6 (37.9 – 71.9)	0.24
<i>Male gender, n (%)</i>	23 (71.9)	11 (69.2)	>0.99
<i>Diabetes, n (%)</i>	8 (25.0)	2 (13.3)	0.46
<i>Alcohol consumption, n (%)</i>	9 (28.1)	6 (40.0)	0.51
<i>Liver disease</i>			
<i>HCV</i>	22 (68.8)	8 (53.3)	0.36
<i>HBV</i>	5 (15.6)	2 (13.3)	
<i>HCV + HBV</i>	4 (12.5)	5 (33.3)	
<i>Other</i>	1 (3.1)	0 (0.0)	
<i>HCV viral load (undetectable $\leq 1.6 \log$ 10/ml)</i>	11 (42.36)	8 (61.5)	0.43
<i>Presence of HCV SVR, n (%)</i>	14 (53.8)	10 (76.9)	0.29
<i>Prior treatment</i>			
<i>Surgery or RFA</i>	11 (34.4)	3 (20.0)	0.09
<i>TACE</i>	14 (43.8)	4 (26.7)	
<i>None</i>	7 (21.9)	8 (53.3)	
<i>MELD score, median (Min-Max)</i>	14.0 (7.0 – 40.0)	8.0 (6.0 – 16.0)	<0.001
<i>HCC within Milan criteria, n (%)</i>	30 (93.8)	11 (73.3)	0.07
<i>Child-Pugh A/B/C, n (%)</i>	15 (46.9) / 11 (34.4) / 6 (18.8)	13 (86.7) / 2 (13.3) / 0	0.03
<i>AFP score, median (Min-Max)</i>	0.0 (0.0 – 4.0)	1.0 (0.0 – 4.0)	0.15
<i>AFP level, $\mu\text{g/L}$, median (Min-Max)</i>	7.5 (1 – 1772)	19.2 (2.3 – 1000)	0.16
<i>Undetectable HIV ($\leq 1.6 \log$ 10/ml), n (%)</i>	31 (96.9)	12 (80.0)	0.09
<i>CD4 count, median (Min-Max)</i>	292 (54 – 840)	500 (231 – 950)	0.003
<i>BCLC stage 0/A/B/C, n (%)</i>	1 (3.1) / 29 (90.6) / 2 (6.3) / 0	2 (13.3) / 9 (60.0) / 0 / 4 (26.7)	0.006
<i>Number of lesions at imaging, median (Min-Max)</i>	1 (1 – 3)	1 (1 – 1)	0.01
<i>Lesion size at imaging (max diameter, cm), median (Min-Max)</i>	1.9 (1.0 – 7.0)	2.8 (1.5 – 12.0)	0.02
<i>Treatment before 2014, n (%)</i>	24 (75.0)	8 (53.3)	0.18

Intraoperative data			
<i>Surgery time (min), median (Min-Max)</i>	623.5 (258 – 843)	304.5 (181 – 480)	<0.001
<i>Bleeding (L), median (Min-Max)</i>	3 (1 – 14)	0.3 (0.15 – 1.6)	<0.001
<i>Blood transfusion, n (%)</i>	26 (81.3)	3 (20.0)	<0.001
<i>Complications Dindo-Clavien \geq III, n (%)</i>	12 (37.5)	3 (20.0)	0.32
<i>CCI, median (Min-Max)</i>	30.8 (0 - 100)	8.7 (0 - 52)	0.004
<i>Hospital stay (days), median (Min-Max)</i>	28.5 (9 – 189)	9.0 (5 – 36)	<0.001
<i>Postop. Mortality, n (%)</i>	4 (12.5)	0	0.38
Pathological analysis			
<i>Number of tumor nodules, median (Min-Max)</i>	1.0 (1 – 21.0)	1.0 (1.0 – 2.0)	0.02
<i>Single tumor nodule, n (%)</i>	19 (59.4)	14 (93.3)	0.02
<i>Max diameter (cm), median (Min-Max)</i>	2.0 (1.0 – 6.0)	2.5 (1.5 – 11.0)	0.09
<i>Cirrhosis (fibrosis F4), n (%)</i>	27 (84.4)	13 (86.7)	1.00
<i>Microvascular invasion*, n (%)</i>	10/25 (40)	12 (80)	0.03
<i>Macrovascular invasion*, n (%)</i>	2 (8.0)	4 (26.7)	0.25
<i>Differentiation grade 3-4*, n (%)</i>	13/25 (52)	11 (73.3)	0.32
<i>Presence of satellite lesions*, n (%)</i>	4/25 (16)	6 (40)	0.06
<i>Encapsulation*, n (%)</i>	12/25 (48)	6 (40)	0.87

Table 2. Perioperative and pathological data of transplanted and resected patients.

AFP: alpha-fetoprotein, AIDS: acquired immunodeficiency syndrome, CCI: Comprehensive Complication Index RFA: radiofrequency ablation, SVR: sustained virological response, TACE: transarterial chemoembolization

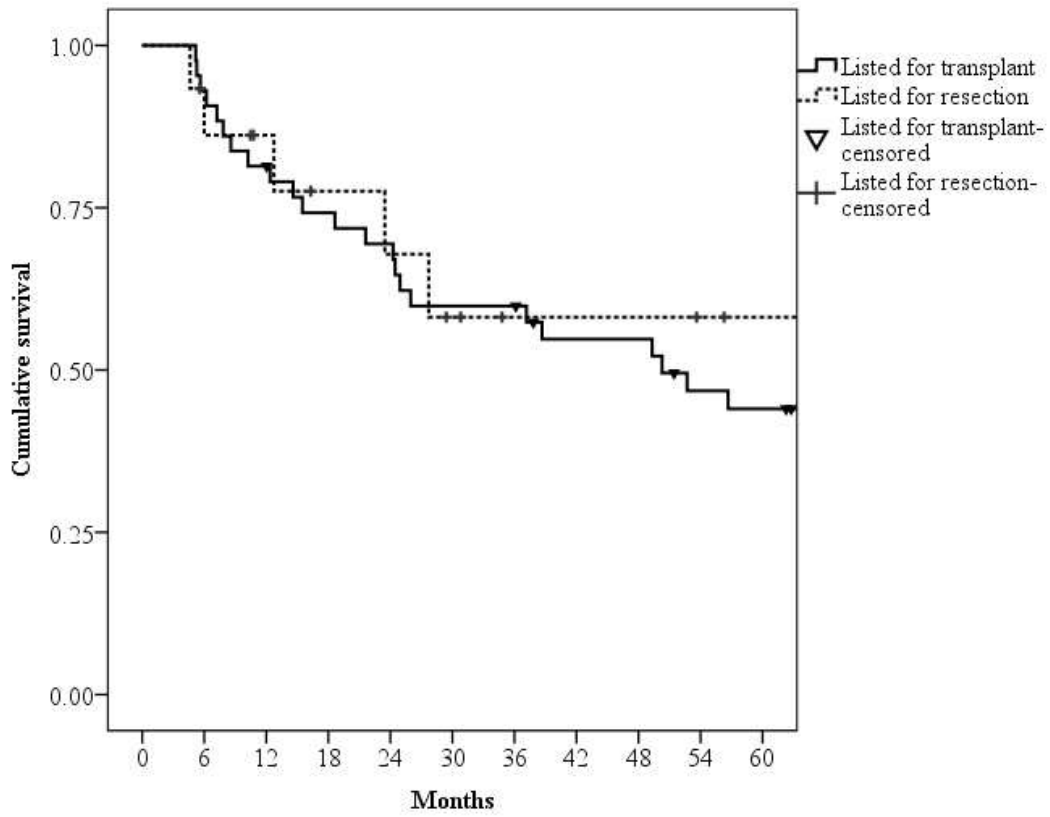
Variable	HR (95% CI)	Univariate <i>p</i> -value	HR (95% CI)	Multivariate <i>p</i> -value
OVERALL SURVIVAL				
Treatment				
Transplant	1	0.84	-	-
Resection	1.111 (0.39-3.18)			
AFP score	1.31 (0.99-1.75)	0.06	-	-
Blood transfusion	3.52 (1.03-12.05)	0.04	-	-
Complications ≥ III DC	3.05 (1.27-7.35)	0.01	-	-
CD4 level	1 (0.99-1.00)	0.75		
SVR for HCV	0.14 (0.04-0.44)	0.001	0.08 (0.02-0.32)	<0.001
Tumour Size				
≤3cm	1	0.03	-	-
>3cm	2.90 (1.13-7.48)			
Edmonson Grade	1	0.07	-	-
G1-G2	2.83 (0.91-8.78)			
G3-G4				
Milan Criteria				
No	1	0.05	1	0.05
Yes	0.33 (0.11-1.04)		0.18 (0.03-1.00)	
Macrovascular Invasion	17.70 (4.02-77.87)	<0.001	33.61 (3.61-313.28)	0.002
CCI score	1.03 (1.01-1.05)	0.001	1.03 (1.00-1.06)	0.01
Recurrence	3.68 (1.43-9.45)	0.007	-	-
DISEASE-FREE SURVIVAL				
Treatment				
Transplant	1	0.07	-	-
Resection	2.34 (0.94-5.28)			
Tumour Size				
≤3cm	1	0.01	-	-
>3cm	3.10 (1.32-7.26)			
Complications ≥ III DC	2.63 (1.17-5.88)	0.02	-	-
CD4 level	1.001 (0.99-1.00)	0.41		
HIV Viral Load				
Undetectable	1	0.02	-	-
Detectable	3.52 (1.17-			

		10.58)			
Histological Grading	G1-G2			-	-
	G3-G4	1			
		2.96 (1.07-8.18)	0.04		
Macrovascular Invasion		22.02 (5.26-92.23)	<0.001	46.32 (6.96-308.46)	<0.001
SVR for HCV		0.19 (0.07-0.49)	0.001	0.17 (0.06-0.49)	<0.001
AFP Score		1.32 (1.02-1.70)	0.03	-	-
CCI score		1.02 (1.00-1.03)	0.02	-	-

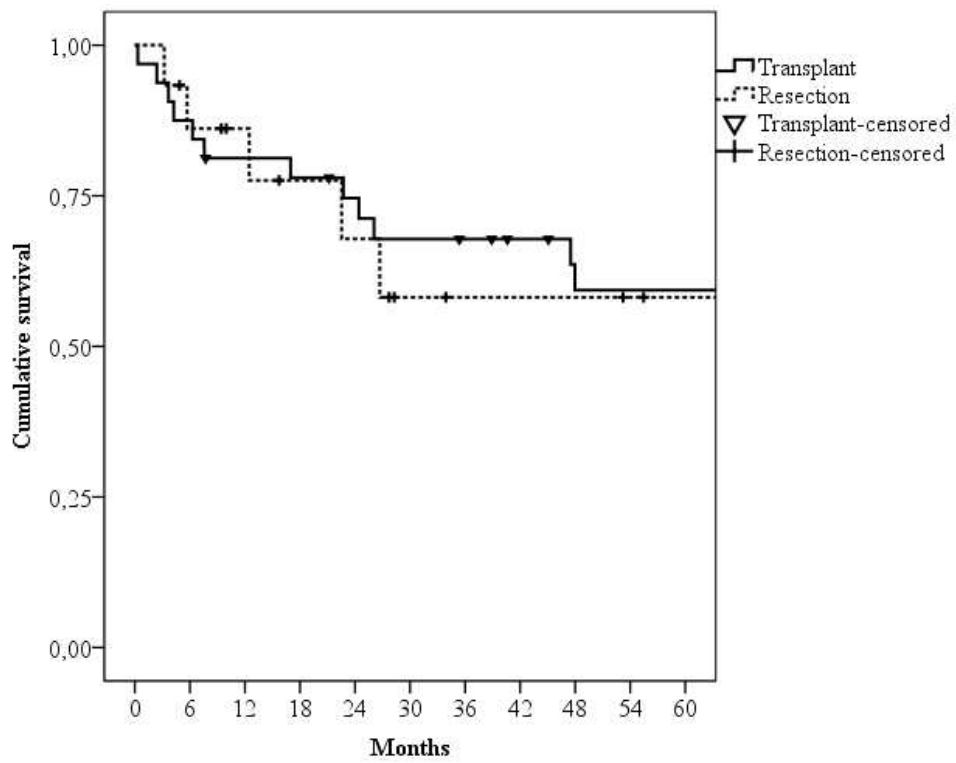
Table 3. Prognostic factors associated with overall and disease-free survivals under univariate and multivariate analysis (transplanted and resected patients).

CCI : Comprehensive Complication Index ; DC: Dindo Clavien; SVR: sustained virologic response

Figure 1a. OS after listing for transplantation and resection (p=0.75)

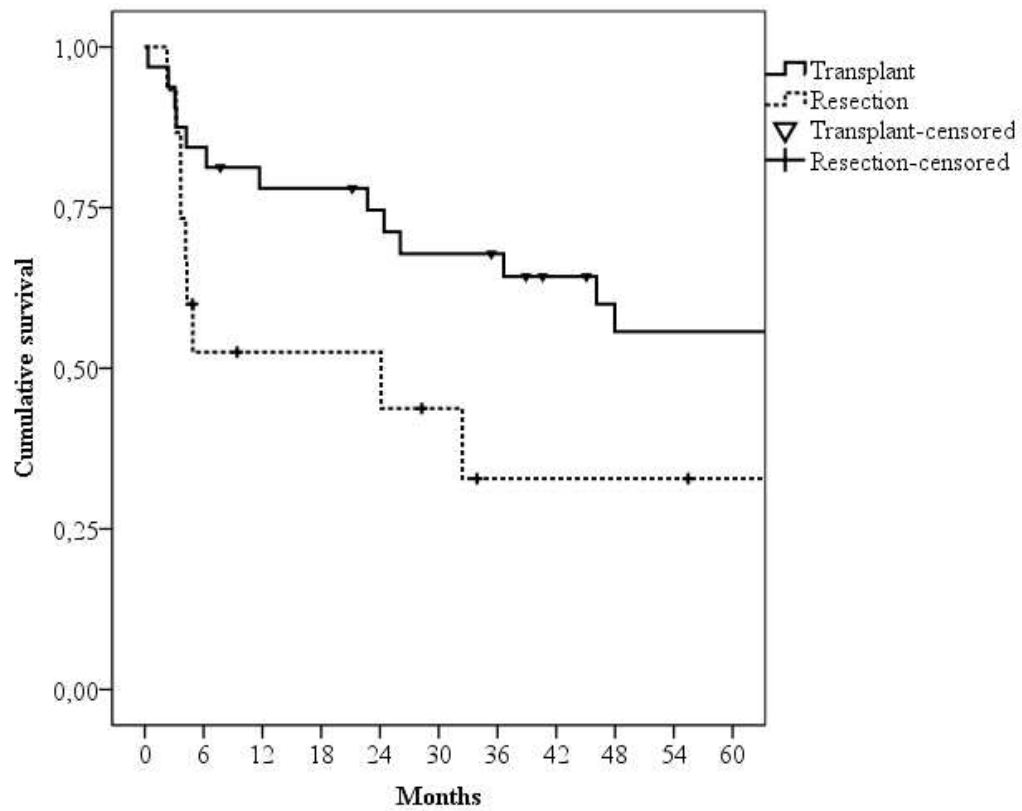


Patients at risk	Total	12m	24m	36m	48m	60m
Listed for LT	43	35	29	25	21	16
Listed for resection	15	10	7	3	3	1

Figure 1b. OS after transplantation or resection ($p=0.84$)

Patients at risk	Total	12m	24m	36m	48m	60m
Transplant	32	25	22	19	14	14
Resection	15	10	7	3	3	1

Figure 2. DFS after transplantation or resection (p=0.06)



Patients at risk	Total	12m	24m	36m	48m	60m
Transplant	32	24	22	19	13	13
Resection	15	6	6	2	2	1

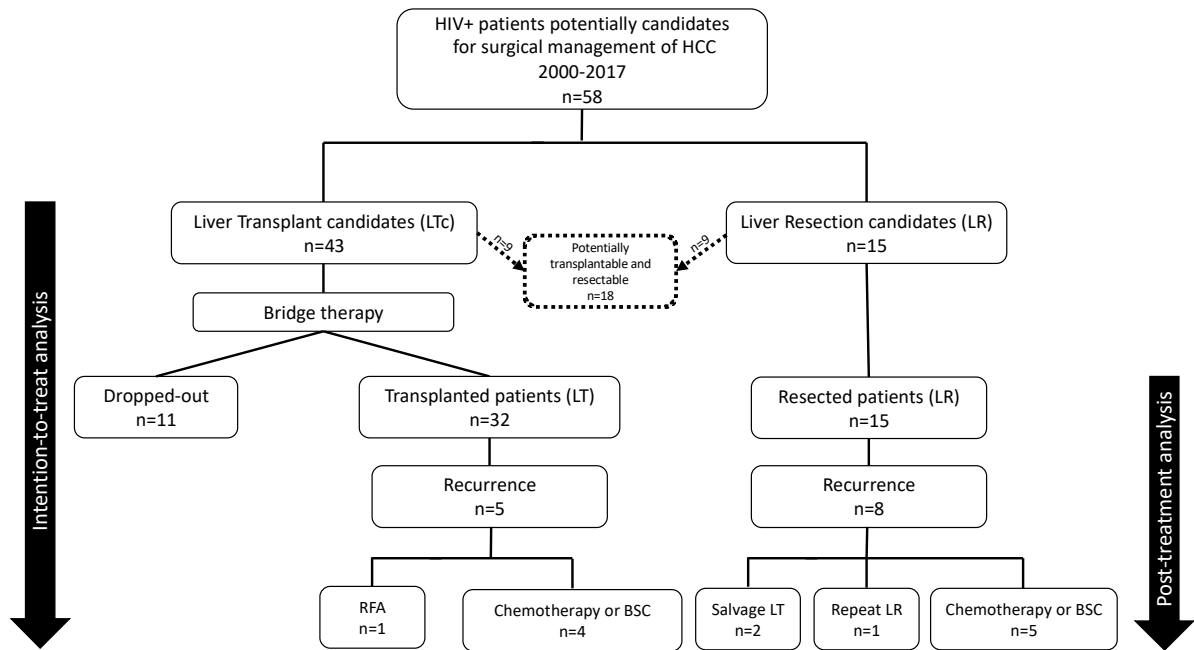


Fig 3 : Flow-Chart