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ORIGINAL ARTICLE

Is there increased risk of hepatocellular carcinoma recurrence in liver transplant patients with direct-acting antiviral therapy?

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Abstract

Background Recently, a controversy has emerged: is the rate of recurrence of hepatocellular carcinoma (HCC) higher following treatment of hepatitis C virus (HCV) with direct-acting antiviral (DAA) therapy? However, the risk of HCC recurrence has not been studied in liver transplant (LTx) recipients who received DAA therapy. The aim of the present study is to compare the rate of HCC recurrence in LTx recipients who did or did not receive DAA therapy.

Patients and methods Sixty-three patients received LTx with HCC. Twenty-seven (42.9%) with HCV received DAA therapy (Group A), 20 (31.7%) with HCV did not receive DAA therapy (Group B), and 16 (25.4%) did not have HCV (Group C).

Results In group A, three (11%), in group B, one (5%), and in group C, none had recurrence of HCC. Actuarial 4-year recurrence-free survival was 88.9, 95, and 100% in group A, B, and C, respectively ($p=0.37$). Group A was subdivided into two groups for comparison with Group B: A1 included five patients who had end of treatment response (ETR) without sustained virological response (SVR), and A2 included 20 patients who achieved SVR. Three patients from A1 had HCC recurrence and no patients from A2 had HCC recurrence. ($p=0.0038$; group A1, A2, and B).

Conclusions The rate of HCC recurrence in LTx patients with DAA therapy was significantly higher with ETR, without SVR, after DAA therapy compared to patients with SVR or patients who did not receive DAA therapy. LTx recipients with HCC receiving DAA therapy requires further studies.

Keywords Immunosuppression · Metastatic disease · Chemoembolization · Hepatitis C

Background

Liver transplantation (LTx) is the preferred modality of therapy for unresectable hepatocellular carcinoma (HCC) within Milan criteria. This provides recurrence-free survival of up to 84% at 4 years [1].

HCC is often associated with hepatitis C viral (HCV) infection. HCV is known to recur post-LTx at a much faster rate with a significant amount of damage to the transplanted liver [2–4]. Newly developed first- and second-generation direct-acting antiviral (DAA) therapies are effective in the eradication of HCV in more than 90% of pre- and post-LTx patients [5–7]. In the pre-LTx population, a controversy has emerged over whether the incidence and recurrence of HCC are higher after the use of DAA therapy to treat HCV-related cirrhosis [1, 2, 8–11]. However, risk of HCC recurrence after DAA therapy has not been studied in post-LTx patients.

The aim of the present study is to compare the rate of recurrence of HCC in post-LTx recipients who received

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DAA therapy to those who did not receive DAA therapy and to examine factors which could have an impact on the recurrence of HCC.

Patients and methods

All patients with HCC within Milan criteria who received LTx between March 2010 and December 2016 were retrospectively studied after institutional review board approval. The subjects were divided into three groups: HCC LTx recipients with HCV who received DAA therapy (group A), HCC LTx recipients who did not receive DAA therapy (group B), and HCC LTx recipients without HCV infection (group C). Basic patient demographics, pre- and post-LTx clinical course, and follow-up for recurrence of HCC were examined carefully. There were 63 patients who received LTx with HCC within Milan criteria. The mean age at the time of LTx for all patients was 60.1 ± 5.8 (median 59.8, range 45.9–72.0) years. All pre-LTx contrast computed tomography (CT) and/or magnetic resonance imaging (MRI) studies were examined for HCC tumor count, size, and characteristics based on Liver Imaging Reporting and Data System (LI-RADS) categorization [12]. The number of loco-regional therapies, consisting of highly selective transarterial chemoembolization (TACE) with doxorubicin/cisplatin or mitomycin with or without lipiodol [13], to treat HCC was cataloged for each patient. Intraoperative findings and postoperative pathology results of the explanted liver were recorded, including tumor counts, the viability of each tumor, tumor size, histologic grade, and macro- or microvascular invasion. Tumor size and count were confirmed, postoperatively, to be within Milan criteria. All post-LTx patients underwent a contrast-enhanced chest, abdomen, and pelvis CT scan or MRI scan every 3 months for the 1 year, then every 6 months for 3 years, and yearly after that, as per our protocol. Additional radiological studies were obtained if clinically indicated.

Statistical analysis

Quantitative values were presented as the mean and standard deviation. Categorical values were presented as count number and proportions. For categorical values, Chi-squared analyses were performed using Microsoft Excel Professional Plus 2016 (version 1706). Kaplan–Meier recurrence-free survival was calculated using SPSS statistical package version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) A log-rank statistical formula was used to compare the survival differences. A p value of less than 0.05 was considered statistically significant.

Results

Between March 2010 and June 2017, 63 patients with HCC within Milan criteria received LTx at our transplant center. Twenty-seven patients (42.8%) were HCV-positive and received DAA therapy (group A). Seven patients (25.9%) received DAA therapy 13.3 ± 5.6 months before LTx, and 20 patients (74.1%) received DAA therapy 23.9 ± 16.9 months after LTx. The baseline characteristics of each patient in both study groups are described in Table 1. Twenty patients (31.7%) did not receive DAA therapy (group B). Sixteen patients (25.4%) were HCV-negative (group C). The mean age in group A was 60.1 ± 4.7 years at the time of LTx, and 23 (85.0%) were male. In group B, the mean age was 59.4 ± 5.7 years, and 14 (70%) were male. In group C, the mean age was 61.9 ± 7.2 years and 11 (69%) were male. The mean post-LTx follow-up was 50.5 ± 25.4 months in group A, 71.2 ± 23.8 months in group B, and 61.5 ± 30.4 months in group C The only difference of statistical significance among the groups was that the follow-up in groups B and C was longer than in group A, which was only 50.5 months ($p \leq 0.05$). In the explanted liver, tumor burden with count and size were confirmed to be within Milan criteria in all cases. However, microvascular invasion was detected in the explanted hepatic specimen in six cases (four in group A and one each in groups B and C). The patient characteristics of groups A, B, and C are compared in Table 2.

In group A, sustained virological response (SVR) from DAA therapy was achieved in 20 (74%) cases, and 2 (5.4%) did not respond (NR). Five patients achieved end-of-treatment response (ETR) with an initial 12–24-week DAA therapy regimen but failed to maintain SVR. One of them eventually achieved SVR after extending the course of DAA by 24 weeks with the addition of simeprevir (case #2, described below). Group A was subdivided into the five patients who achieved only ETR (subgroup A1) and the 20 patients who achieved SVR (subgroup A2), for comparison with HCV-positive patients who did not receive DAA at all (group B).

The rate of HCC recurrence

In group A, three patients (11.10%) developed HCC recurrence with metastatic spread, post-LTx. In group B, one patient (5.0%) developed HCC recurrence with metastatic

Table 1 Demographic details; HCC with HCV and DAA therapy HCC characteristics (group A)

Subject no.	Age at LTx (years)	Gender (M = male, F = female)	Follow-up in months	HCV genotype	DAA start months before (-)/after LTx	DAA agents	NR, ETR, SVR	Number of locoregional therapy	Size of HCC (cm) on explant	Histologic HCC differentiation	Microvascular invasion	HCC recurrence
1	54.9	M	51.9	2	30.0	SOF + RIB	SVR	1	2.8 × 1.8 × 1, 1.3 × 1.3 × 1.0	Moderate	No	No
2	72.0	M	48.7	1a	27.7	SOF + then + RIB, then + SIM	ETR/SVR	4	2.5 × 2.5 × 1.4	Moderate	No	Yes
3	58.4	M	50.5	1a	28.7	SOF + LDV	SVR	2	2.5 × 2.0 × 1.5	WD	No	No
4	57.1	M	46.9	1a	4.2	SOF + LDV	SVR	1	1.0 × 1.0 × 1.0	Necrotic	No	No
5	58.1	M	44.2	1	15.2	SOF + LDV	SVR	2	1.5 × 1.5 × 1.0	Poor	No	No
6	55.3	M	13.4	1b	3.1	SOF + SIM	NR	4	3.5 × 3 × 3	Moderate	yes	No
7	52.7	F	32.9	1a	1.7	SOF + LDV	SVR	1	1.2 × 1.0 × 1.0	WD	No	No
8	66.1	M	29.2	1b	− 5.8	SOF + LDV	SVR	1	2.7 × 2.7 × 2.5	Necrotic	No	No
9	61.5	M	28.0	3a	− 20.0	SOF + RIB	ETR	3	2.8 × 1.8 × 2.2	Necrotic	No	No
10	58.7	M	13.9	1a	11.7	SOF + LDV	SVR	1	2.0 × 2.0 × 1.5	Necrotic	No	No
11	66.3	M	26.8	1	20.5	SOF + LDV + RIB	SVR	2	1.2	WD	No	No
12	62.8	M	26.8	1b	− 12.2	SOF + RIB	ETR	4	1.5 × 0.8 × 0.8, 2.2 × 0.7	WD	No	No
13	58.1	M	10.9	3a	− 13.0	SOF + RIB	ETR	3	2.5 × 1.5 × 1.2, 1 × 0.5 × 0.5	Moderate	No	Yes
14	61.6	M	21.5	2b	− 26.3	SOF + RIB	ETR	1	2.0 × 1.0 × 0.8, 2.0 × 1.5 × 1.0	Moderate	Yes	Yes
15	67.3	M	18.6	1a	− 18.9	SOF + LDV	SVR	1	No viable tumor	Necrotic		No
16	65.5	M	8.8	1a	− 24.2	SOF + LDV	SVR	1	2.7 × 2.4 × 2.3	Necrotic	No	No
17	53.9	M	58.6	1a	22.2	SOF + SIM	SVR	1	1.9 × 1.8 × 1.4, 1.2 × 1.2 × 1.1	WD	No	No

Table 1 (continued)

Subject no.	Age at LTx (years)	Gender (M = male, F = female)	Follow-up in months	HCV genotype	DAA start months before (-)/after LTx	DAA agents	NR, ETR, SVR	Number of locoregional therapy	Size of HCC (cm) on explant	Histologic HCC differentiation	Microvascular invasion	HCC recurrence
18	58.9	M	62.8	1b	39.9	SOF + LDV	SVR	3	2.5 × 1.7 × 1.0, 1.0 × 0.7 × 0.7, 0.9 × 0.8 × 0.6	Moderate	Yes	No
19	57.9	F	62.1	1b	48.7	SOF + LDV	SVR	2	2.0 × 1.8 × 1.5, 0.5 × 0.5 × 0.5	Necrotic	No	No
20	59.4	F	64.0	1a	40.7	SOF + LDV	SVR	2	2.0 × 1.0 × 0.5 cm	Necrotic	No	No
21	59.7	F	80.6	1a	52.8	SOF + SIM	SVR	1	2.5 × 2.5 × 1.5 cm	WD	No	No
22	58.4	M	84.2	1b	78.3	SOF + LDV + RIB	SVR	1	1.8 × 1.5 × 1.4, 1.2 × 1.0 × 0.7	WD	No	No
23	63.0	M	84.7	1	66.2	SOF + LDV	SVR	1	4.0 × 3.5 × 3.5	Moderate	No	No
24	55.5	M	57.7	1a	17.7	SOF + SIM	SVR	1	2.0 × 1.8 × 1.5	Moderate	Yes	No
25	53.9	M	71.0	1a	48.8	SOF + LDV	SVR	1	1.8 × 1.7 × 1.5	Necrotic	No	No
26	60.1	M	60.1	1	− 20.89	SOF + LDV + RIB	SVR	1	2.2 × 1.5 × 1.3	Poor	No	No
27	50.4	M	50.4	3a	− 36.39	SIM then SOF + LDV	NR	4	Multifocal	Moderate	No	No
Mean	59.9		43.9									
SD	4.8		23.7									

NR non responder, *ETR* end of treatment response, *SVR* sustained virological response, *WD* well-differentiated, *SOF* sofosbuvir, *RIB* ribavirin, *SIM* simeprevir, *LDV* ledipasvir

Table 2 Characteristics of patients with HCC

	Group A HCV + DAA	Group B HCV, No DAA	Group C No HCV	*p* value
Number of cases	27	20	16	0.83
Male, *n* (%)	23 (85)	14 (70)	11 (69)	0.43
Age (years), mean ± SD	60.1 ± 4.7	59.4 ± 5.7	61.9 ± 7.2	0.98
Months follow-up post-LTx, mean ± SD	50.5 ± 25.4	71.2 ± 23.8	61.5 ± 30.4	< 0.05
Microvascular invasion, *n* (%)	3 (12)	1 (5)	1 (6)	0.98
Tumor differentiation				
Well differentiated, *n* (%)	7 (26)	8 (40)	9 (56)	8.85
Moderate, *n* (%)	8 (30)	6 (30)	4 (25)	
Poor, *n* (%)	3 (11)	1 (5)	2 (13)	
Necrotic, *n* (%)	9 (33)	4 (20)	1 (6)	0.54
HCC recurrence, *n* (%)	3 (11)	1 (5)	0 (0)	0.8
HCC-recurrence-free 4-year (actuarial) survival	88.90%	95%	100%	0.374
	Group A1 No SVR after initial ETR from DAA	Group A2 SVR from DAA	Group B No DAA	*p* value
Subgroup analysis—HCV-positive				
Number of cases	5	20	20	
Recurrent HCC (%)	3 (60.0)	0 (0)	1 (5.0)	0.0038

HCC hepatocellular carcinoma, *HCV* hepatitis C viral, *DAA* direct-acting antiviral, *LTx* liver transplant, *SVR* sustained virological response, and *ETR* end of treatment response

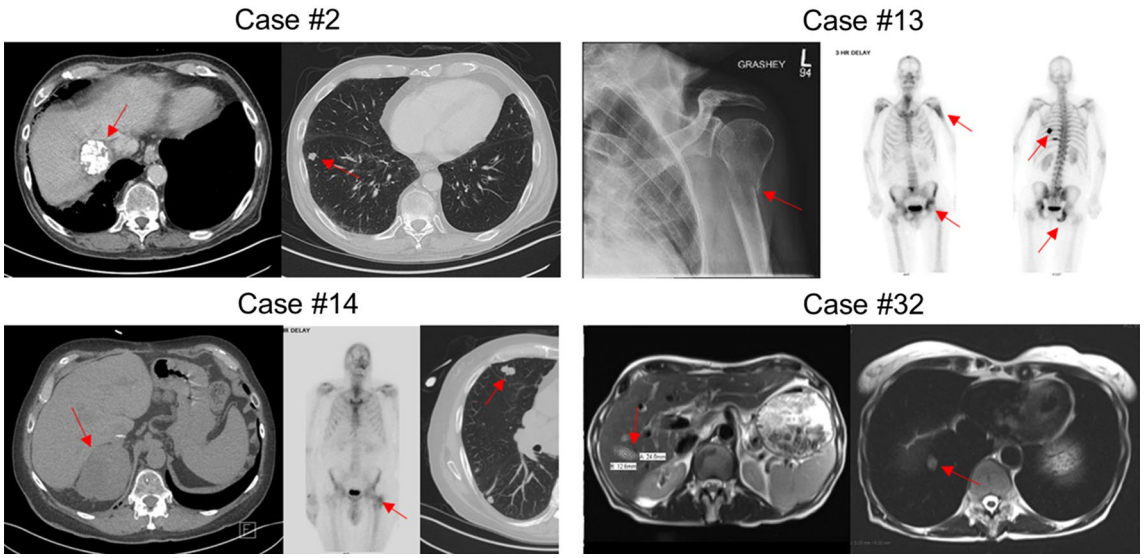

Fig. 1 Case #2 (left) HCC recurrence in liver: segment VII, 5.2 × 4.5 cm, (right) metastatic disease in lung: 1.1 cm. Case #13 (left) pathological fracture of neck of left humerus, (right) multiple bony metastases: L5 vertebral body, left posterior eighth rib, posterior left acetabulum, right inferior pubic ramus Case #14 (left) metastatic disease in right adrenal: 7.5 × 6.0 cm, (middle) multiple bony metastases: 3.3 cm, lytic destruction involving lesser trochanter of left femur, metastatic disease in right lung: 2.3 cm. Case #32 (left) HCC recurrence in liver: segment VI, 4.0 × 1.2 cm,(right) metastatic disease in lung: 0.9 cm

spread to the lung (Fig. 1) and in group C, HCC recurrence was not observed (0%).

The pre- and postoperative clinical course, with respect to HCC and its recurrence, in these four cases is briefly described below.

Group A

Case #2: 72-year-old man received deceased donor LTx for HCC with HCV genotype 1a. Before LTx, he received four treatments of TACE using doxorubicin ± mitomycin for two hepatic lesions: 2.7 × 2.0 and 2.6 × 2.3 cm in diameter. The explanted liver showed a single lesion of moderately differentiated HCC: 2.5 × 2.5 × 1.4 cm in diameter without microvascular invasion. Twenty-nine months post-LTx he received sofosbuvir and ledipasvir for 8 weeks to which he did not respond. Hence, ribavirin was added to the DAA therapy for another 8 weeks. Following that, he achieved ETR, but subsequently relapsed. He received simeprevir, sofosbuvir, and ribavirin for another 24 weeks, with achievement of SVR. Six months after the start of DAA therapy was found to have recurrence of HCC in segment VII of the liver measuring 1.9 × 1.5 cm. He was recurrence-free prior to start of DAA therapy. This recurrent tumor rapidly increased in size to 5.2 × 4.5 cm over 5 months. He was also found to have a pulmonary lesion 1.1 cm in diameter (Fig. 1, top left). He received sorafenib and two series of TACE. He died 2 years after the recurrence of HCC.

Case #13: 58-year-old man with HCV genotype 3a who commenced a 24-week course of sofosbuvir and ribavirin, 13 months before LTx. He achieved ETR without SVR. He was known to have HCC within Milan criteria prior to the initiation of DAA therapy for which he received three series of TACE using doxorubicin ± mitomycin. The explanted liver showed two lesions: 1) 2.0 × 1.5 × 1.2 cm, 90% necrotic and 2) 1.0 × 0.5 × 0.5 cm, 70% necrotic. Both lesions were confirmed to be moderately differentiated HCC, without microvascular invasion. Eight months post-LTx he presented with a pathological fracture of the left humerus as a result of biopsy-proven metastatic HCC (Fig. 1, top right). He also had metastatic lesions in the L5 lumbar vertebra, pubic ramus, acetabulum, and ribs. He died 10 months after LTx.

Case #14: 61-year-old man with HCV genotype 2b received a 12-week course of sofosbuvir and ribavirin 26 months before LTx. He achieved ETR without SVR. He was treated with one TACE using doxorubicin and mitomycin. The explanted liver revealed two HCC lesions: 2.0 × 1.5 and 2.0 × 1.0 cm, moderately differentiated HCC with microvascular invasion. Fifteen months post-LTx, he presented with metastatic disease in the adrenal gland, 7.5 × 6.0 cm, a 2.3-cm lesion in the lung, and a 3.3-cm lesion in the lesser trochanter of the left femur. Before LTx, his metastatic work up for HCC was negative. He also developed multiple pulmonary lesions up to 2.3 cm in diameter (Fig. 1, bottom left).

Group B

Case #32: 61-year-old female with HCV genotype 1a presented with a single lesion of HCC: 3.8 × 2.1 cm. Before LTx, she was treated with two series of TACE containing cisplatin, doxorubicin, and mitomycin. She did not receive DAA therapy. The explanted liver showed a single lesion: 3.2 × 2.8 × 1.9 cm, the majority of which was necrotic; hence, presence of microvascular invasion could not be determined. Ten months post-LTx, she developed recurrent HCC: 2.4.0 × 1.2 cm, in segment VI of the liver. Subsequently, a 0.9-cm lesion was found in the lung (Fig. 1, bottom right). She died 15 months post-LTx.

Recurrence-free survival

Recurrence-free survival was calculated using Kaplan–Meier estimation. Patients who died without recurrence of HCC were considered to be recurrence-free until death. Recurrence-free survival at 1, 2, 3, and 4 years for group A was 96.1, 92.1, 87.7, and 87.7%, respectively. For group B, HCC recurrence-free survival was 94.1% for up to 4 years. For group C, there were no HCC recurrences; hence, recurrence-free survival was 100% for one to 4 years follow-up. These differences in recurrence-free survival were not statistically significant ($p = 0.374$), (Fig. 2, top). Subgroup analysis was then performed for patients in group A depending on the response rate to DAA. Comparing those who had ETR after initial DAA therapy (group A1) to those who achieved SVR (group A2) and to those who did not receive DAA therapy (group B), a statistically significant difference was observed. Recurrence-free survival at 1, 2, 3, and 4 years was 80, 60, 40, and 40%, respectively, for group A1, 100% at 1–4 years follow-up for group A2, and 94.1% at 1–4 years follow-up for group B (log rank, $p < 0.0001$), (Fig. 2, bottom).

Discussion

Mazzaferro et al. have shown that LTx for small unresectable HCC (stage I and II) provides 84% recurrence-free survival at 4 years [1]. Since then, this has become an acceptable treatment option. Realizing the need of timely LTx before HCC exceeds the Milan criteria, UNOS (United Nation Organization of Organ Sharing) implemented a policy to award exceptional MELD (Model for End-Stage Liver Disease) points for this group of patients [14, 15]. HCV infection is prevalent worldwide, and chronic HCV infection is a risk factor for HCC. Currently, a significant number of liver transplants are performed for HCV with HCC within Milan criteria [4]. However, after successful LTx, biochemical and histological recurrence of HCV is universal. Furthermore, recurrence of HCV could result in allograft failure,

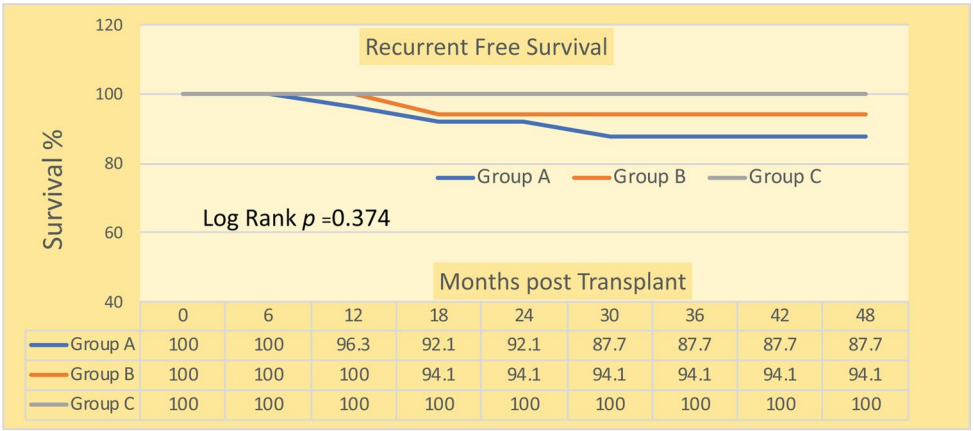

Fig. 2 Post-LTx HCC recurrence-free survival. Top: Group A, B, and C. Bottom: Group A1, A2, and B

and retransplantation may be necessary [3]. Interferon-based therapy in the post-LTx setting has remained suboptimal [16–18]. The introduction of an interferon-free regimen consisting of a nucleotide NS5B analog (sofosbuvir) in conjunction with NS5A inhibitor (ledipasvir) or NS3/4A protease inhibitor (simeprevir), with or without ribavirin, has been found to be potent and effective for various genotypes of HCV. SVR is observed in more than 90% of the cases, both in the non-LTx and post-LTx population, with the same DAA regimen [5–7].

There are reports suggesting that patients with HCV infection, when treated with interferon-based therapy with achievement of SVR, had a lower incidence of developing HCC [19, 20]. However, recently a controversy, has been raised from some of the European centers, which suggests the use of DAA therapy increases the risk of de novo HCC and recurrence of HCC. Reig et al. from Spain collected data from four hospitals; out of 103 patients with HCC who received DAA, 27.6% of patients showed an increased in size of HCC or de novo HCC with a median follow-up of 5.7 months [10]. Toyoda et al. from Japan studied 413 patients who achieved SVR with DAA therapy. He reported a significantly higher rate of HCC in patients greater than 65 years of age with cirrhosis, as well as a twofold increased rate of HCC after SVR from DAA therapy, on an annual basis [11]. Makiyama et al. in 2004 reported similar findings on interferon-based therapy in the older population with cirrhosis [21]. Conti et al. in 2016, from Italy, analyzed 344 patients who received DAA therapy [8]. Within a 24-week follow-up period, they found nine cases of de novo HCC out of 285 cases and 17 patients with rapid recurrence of HCC out of 59 stable, treated HCC patients. Kozbial et al., from the AURIC (Austrian Ribavirin/Interferon-Free Cohort) clinical trial, reported an unexpected high incidence of HCC in patients with HCV treated with DAA therapy [9].

Contrary to above reports, other European centers did not observe such an increased incidence of HCC with the use of DAA therapy. Cheung et al., from a UK group consisting of 406 patients treated with DAA therapy, did not find an increased risk of HCC nor decompensation [22]. Prospective data from the French multicenter ANRS (France Recherche Nord & Sud Sida-hiv Hepatites) cohort group compared 189 patients with HCC who received DAA therapy with 78 HCC patients who did not receive DAA [23]. The rate of recurrence was higher in patients treated with DAA therapy (0.73 versus 0.66/100 person-months). Among patients with cirrhosis, the HCC recurrence rate was still higher in those who received DAA (1.73 versus 1.11/100 person-months).

There are several editorial comments to this controversial topic. Nault et al., in their editorial, felt that different studies do not bring strong evidence of increased risk of HCC, but still he recommended HCC screening post-DAA therapy [24]. Zeng et al. from China have questioned similar alarm and recommended head-to-head comparison [25]. Kolly et al., in their editorial letter, commented that current knowledge is unclear and suggested well-designed studies with proper comparison [26]. More recently, at the 2017 American Association for the Study of Liver Disease (AASLD) annual conference, Ioannou et al. presented the results from a large veterans affairs data base. They found a 79% reduction in HCC rate with DAA-induced SVR [27]. Similarly, Mangia et al., at the same conference, presented data on 1170 cases treated with DAA with a rate of de novo HCC OF 1.2% and felt this was comparable to interferon-based therapy [28].

To our knowledge, there have been no studies available to address the issue of HCC recurrence in the post-LTx recipients who received DAA therapy.

In the present study, we compared 27 post-LTx HCC patients who received DAA therapy to treat HCV infection to 20 post-LTx patients who did not receive DAA therapy for HCV infection and to 16 post-LTx patients without HCV infection. The observed rate HCC recurrence was 11.1, 5, and 0% in groups A, B, and C, respectively, which was not significant ($p=0.8$). When we subdivide group A based on the response to the initial DAA therapy regimen into those who had ETR ($n=5$) or SVR ($n=20$) and compare them to HCV-positive patients who did not receive DAA therapy ($n=20$), the HCC recurrence rate was 60, 0, and 5%. This was highly statistically significant ($p=0.0038$). All three patients in group A who had HCC recurrence with DAA therapy exhibited ETR but did not achieve SVR. However, one of them subsequently achieved SVR after a third attempt using DAA with ribavirin, sofosbuvir, and simeprevir. Another remarkable factor is that the HCC recurrence occurred rapidly and with widespread metastases. Is this massive tumor burden secondary to the DAA therapy or just by chance? Admittedly, this is difficult to answer and is beyond the scope of this observational study. Another intriguing possibility is that viral relapse may induce some immune or oncogenic effect in the host that could promote HCC recurrence even after the LTx in an immunocompromised subject. To elucidate these uncertainties, we would need data from a larger population, involving multiple centers. If this is a true phenomenon, a major change in the practice of LTx for HCC within Milan criteria may be required. The recipient may need to be educated before LTx and certainly before starting DAA therapy. A modified approach in this situation could be considered. For example, on a trial basis, the concomitant use of sorafenib [29], possibly in a sub-therapeutic dose, could be considered to evaluate for prevention of HCC recurrence. Ono et al. have suggested transcriptome signature gene analysis to detect early recurrence of HCC after LTx [30]. Certainly in the future, the utility of transcriptome could be explored for this group of patients with cellular, biological, and immunology-based experiments.

Conclusion

In our present study of LTx recipients with HCC, HCC recurrence with metastatic lesions was observed in patients who achieved ETR to DAA therapy without SVR. The difference in the recurrence-free survival rate was significant when post-LTx patients with HCV were compared by DAA response rate: ETR without SVR, or with SVR, or without DAA therapy. Furthermore, recurrence-free survival rate was only 40% at 3 years for patients who received DAA therapy and achieved ETR, without SVR. Retrospective and prospective studies of a larger population are warranted to evaluate the true influence of DAA therapy with ETR without SVR in the post-LTx population.

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Authors' contributions Research design: AJ, ZK. Acquisition and analysis of data: AJ, ZK, DM, TR, RS. Interpretation of data: all authors. Drafting of the manuscript: all authors. Critical revision of the manuscript for important intellectual content: all authors. Study supervision: AJ, ZK.

Compliance with ethical standards

Conflicts of interest Ashokkumar Jain, Danielle Miller, Ian Schreibman, Thomas R. Riley III, Karen L. Krok, Takehiko Dohi, Rajeev Sharma, and Zakiyah Kadry have no conflicts of interest.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. As this was a retrospective study, the requirement for informed consent was waived by the institutional review board.

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