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Locoregional Therapy for HCC Patients Prior to Living Donor Liver Transplantation

AHMED R.I. DRAZ, M.Sc.; MAHMOUD A. ABD EL-AZIZ, M.D.; MAGDY A. MUBARAK ALI, M.D. and MAGDY M. MOSTAFA, M.D.

The Department of Surgery, Faculty of Medicine, Al-Azhar University

Abstract

Background: Hepatocellular carcinoma occurs in chronic liver disease and cirrhosis. Loco-regional therapies have the potential to bridge patients within Milan criteria and downstage patients to transplantation.

Aim of Study: This study aimed to assess the overall survival and HCC recurrence in patients with HCC undergoing living donor liver transplantation with or without locoregional therapies as bridging or downstaging before transplant.

Patients and Methods: This study included 60 HCC patients. Patients were classified into 2 independent groups: The locoregional therapy group (26 patients), and the Non-therapy group (34 patients).

Pre-operative assessment in the outpatient clinic. Follow-up after transplantation for two years; every three months using alpha-fetoprotein and ultra-sonography. Dynamic contrast CT scan as routine every 6 months for the first year, then every year.

Results: In the studied population, the mean age of all patients was (52.5±4.4) years, The recurrence rate was (25%), with (6.7%) of recurrence patients had open RFA, (33.3%) had a resection, (6.7%) had re-transplantation, and (53.3%) had supportive treatment. The mortality rate was (28.3%). We found significant decrease in recurrence rate in locoregional therapy group (11.5%); compared to non-therapy group (35.3%) (p=0.036). The survival probability regarding recurrence was markedly increased in Locoregional therapy (in 2011); compared to the non-therapy group in survival curves of the 2 groups.

Conclusion: Locoregional therapies have been the mainstay for treating intermediate-stage disease, but they are finding special applications for early and advanced disease.

Key Words: *Locoregional therapy – HCC – Living donor liver transplantation.*

Introduction

HEPATOCELLULAR carcinoma (HCC) is an aggressive tumour that frequently develops in patients with chronic liver disease and cirrhosis **[1,2].**

Correspondence to: Dr. Ahmed R.I. Draz,
E-Mail: ahmed.draz@doctors.org.uk

HCC is becoming more common around the world. It is the sixth most common malignant tumour in the world 2 and the third leading cause of cancer-related death **[3]**, with a global annual incidence of over one million cases and at least 500,000 deaths per year **[1].**

The majority of HCC cases occur in the context of liver cirrhosis, specifically hepatitis B and C virus and iron overload states, with a minority of cases being non-cirrhotic **[4].**

HCC has a very poor prognosis due to the tumor's rapid progression, with a median survival time of only 3-6 months 5, and a 5-year survival rate of less than 5% **[6].**

To treat HCC patients, a multidisciplinary team of surgeons, hepatologists, oncologists, pathologists, and interventional radiologists is required. The only way to achieve long-term disease-free survival is to detect and treat hepatocellular carcinoma early **[7].**

Screening in high-risk patients aids in the early detection of HCC. There is no perfect screening modality. Screening may include measuring tumour markers like alpha-fetoprotein and using imaging modalities like ultrasound, CT, and MRI. Recent research has revealed that alpha-fetoprotein (AFP) has low sensitivity and specificity for proper surveillance and diagnosis. Nonetheless, an alpha-fetoprotein level greater than 200 is highly suggestive of HCC **[7].**

Arterial enhancement and delayed washout seen on dynamic MRI or triphasic CT are sufficient to diagnose HCC; no further investigation is required. Typically, liver biopsy is reserved for patients with indeterminate lesions on cross-sectional imaging **[8].**

The Milan criteria (MC) (1 nodule smaller than 5cm or no more than 3 nodules smaller than 3cm) are universally recognised as the standard indication for LT **[9]**.

Over the last decade, there has been significant progress in the management of HCC. There are now numerous treatment options available. For patients who meet the Milan criteria, liver transplantation remains the standard of care. The scarcity of donor organs lengthens the waiting period and thus increases the likelihood of dropout due to tumour progression. Transarterial chemoembolization (TACE) and radiofrequency ablation (RF) have the potential to bridge patients within Milan criteria and downstage patients to transplantation. The modes of action, response rates, and toxicity profiles of all of these treatments differ **[10]**.

The Barcelona Clinic Liver Cancer Strategy (BCLC) Classification has been validated in different settings for the selection of patients suitable for different treatment options and establishes treatment recommendations for all stages of hepatocellular carcinoma **[3,11]**.

Bridging treatments aim to reduce waiting list dropout before transplantation, reduce HCC recurrence after transplantation, and improve post-transplant overall survival **[9]**.

Advanced HCC may be downstaged in order to meet and maintain the current standard criteria for inclusion on the LT waiting list. Recent studies have shown that successfully down-staged patients have a 5-year survival rate comparable to patients meeting conventional criteria without the need for down-staging **[9]**.

The study sought to assess overall survival and HCC recurrence in HCC patients undergoing living donor liver transplantation with or without locoregional therapies (RFA/Microwave, Ethanol Injection, TACE, and TARE) as bridging or downstaging before transplant.

Patients and Methods

Patients:

A total of 60 patients with hepatocellular carcinoma who underwent adult-to-adult living donor liver transplantation were enrolled in the study.

Study design:

Retrospective, comparative study.

Setting:

Liver transplantation center in Maadi Military Medical Compound.

All cases had been conducted in Maadi Armed Forces Medical Compound from 2010 – 2013.

Target population:

HCC patients.

Inclusion criterion:

HCC patient fulfilling Milan criteria 12.

The threshold Milan criteria are as follows:

- One lesion smaller than 5cm; alternatively, up to three lesions, each smaller than 3cm.
- No extrahepatic manifestations
- No evidence of gross vascular invasion

Exclusion criteria:

Patients who are not fit for transplant as:

- Patients with severe systemic diseases; e.g., cardiopulmonary problems, severe renal impairment.
- Metastatic tumors, liver tumors other than HCC.
- Patients with other primaries.
- Patients with AFP more than 1000ng/dl.

Patients randomization:

The 60 liver transplantation patients were classified according to locoregional therapy into 2 independent groups:

- Locoregional therapy group (26 patients).
- Non-therapy group (34 patients).

Methods:

Patients were subjected to the following:

Pre-operative assessment has been done in the outpatient clinic.

They have been followed-up after transplantation in outpatient clinics for two years; every three months using alpha- fetoprotein and ultrasonography.

Cases have been investigated with dynamic contrast CT scan as routine every 6 months for the first year, then every year.

Ethical considerations:

All patients will be included in this study only after taking informed consent.

Statistical analysis:

Data entry, processing, and statistical analysis were carried out using MedCalc ver. 18.11.3 (MedCalc, Ostend, Belgium). Tests of significance (Mann-Whitney's, Chi-square tests, logistic regression analysis, ROC Curve analysis, and Kaplan-

Meier survival analysis) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable.

Results

In the studied population, the mean age of all patients was (52.5±4.4) years. Regarding the gender of the patients, the majority (90%) of patients were males; while (10%) were females.

Regarding pre-operative hepatic data; the average MELD score was (11.4±2.3), and the average AFP was (261.3±470) ng/dl, with (93.3%) of patients had HCV, and (8.3%) had HBV.

Regarding Child-Pugh class; (65%) of patients had class A, (28.3%) had class B, and (6.7%) had class C.

Regarding pre-operative HCC; the average HCC Lesions was (1.7±0.8), and the average size of the lesion was (3.8±1.1) cm, with (26.7%) of patients had LVI.

Regarding Milan criteria; (63.3%) of patients were fulfilling criteria, while (36.7%) were not.

Regarding locoregional therapy; (43.3%) of patients had locoregional therapy.

Regarding pre-operative management; (3.3%) of patients had RFA, (35%) had TACE, and (5%) had both TACE and RFA.

Regarding operative data; the average operative time was (10.9±2.1) h, the average graft size was (783.5 ± 55.2) g, the average GRWR was (1.008 ±1.0012) u, the average blood transfusion was (9.2 ±5.1) u, the average plasma transfusion was (19.8 ±10.88) u, the average CIT was (41.28±6.6) min, the average WIT was (64.1±12.9) min.

The average postoperative data, the average post-operative lesions was (1.8±0.76), and the average post-operative size was (3.8±1) g.

Regarding recurrence data; the recurrence rate was (25%), with (7.5%) of them had a bone recurrence, (66.7%) had a liver recurrence, (13.3%) had liver and lung recurrence, and also (13.3%) had multiple sites recurrences.

Regarding management of recurrence; (6.7%) of recurrence patients had open RFA, (33.3%) had to resection, (6.7%) had re-transplantation, and (53.3%) had supportive treatment.

Regarding mortality data; the mortality rate was (28.3%), with (17.6%) of them died with biliary obstruction, (52.9%) of them died with recurrence, and (5.9%) of them died with Fungal infection, MI, primary non-functioning, rejection, and stroke (respectively).

Comparative studies:

The 60 liver transplantation patients were classified according to locoregional therapy into 2 independent groups:

- Locoregional therapy group (26 patients).
- Non-therapy group (34 patients).

Regarding pre-operative data; a comparative study between the 2 groups revealed that:

- The a non-significant difference as regards age and sex of the patients ($p>0.05$).
- The non-significant difference as regards pre-operative all pre-operative hepatic data ($p>0.05$).
- Highly significant increase in the pre-operative size of the lesion in the locoregional therapy group ($p<0.01$).
- The non-significant difference as regards pre-operative HCC lesions, LVI, and fulfilling of Milan criteria ($p>0.05$).

Regarding operative data; a comparative study between the 2 groups revealed that:

Non-significant difference as regards all operative data ($p>0.05$).

Regarding postoperative data; a comparative study between the 2 groups revealed that; (Table 1):

Highly a significant decrease in the post-operative number of lesions in the locoregional therapy group ($p<0.01$).

Significant increase in the post-operative size of lesions in the locoregional therapy group ($p< 0.05$).

Table (1): Comparison between the 2 groups as regards postoperative data using Mann-Whitney's test.

Variable	Locoregional therapy group (26)	Non-therapy group (34)	Mann-Whitney's U test
	Median (IQR)	Median (IQR)	*p*-value
Post-operative lesions	1 (1-2)	2 (1-3)	= 0.0038**
Post-operative size (grams)	4.5 (3.5-4.8)	3.3 (2.5-4.5)	= 0.024*

Regarding outcome data; a comparative study between the 2 groups revealed that; (Table 2):

A significant decrease in recurrence rate in locoregional therapy group (11.5%); compared to non-therapy group (35.3%) ($p=0.036$).

Table (2): Comparison between the 2 groups as regards outcome data using Chi-square test.

Variable		Locoregional therapy group (26)	Non-therapy group (34)	Chi-square test *p*-value
Recurrence rate	+ve	3 (11.5%)	12 (35.3%)	= 0.036*
Mortality rate	+ve	5 (19.2%)	12 (35.3%)	= 0.1748

A non-significant difference as regards mortality rate ($p>0.05$).

Correlation analysis to predict recurrence:

As regard correlation studies between different postoperative outcomes; and their relative independent predictors (basic clinical, hepatic, HCC, laboratory, treatment, operative variables) revealed that:

Logistic regression analysis shows that; the increase in pre-operative AFP and LVI; had an independent effect on increasing the probability of recurrence occurrence; with a significant statistical difference ($p<0.05$ respectively) (Table 3).

Table (3): Logistic regression model for the Factors affecting recurrence occurrence using the Forward method.

Predictor Factor	Coefficient	OR	*p*-value
(Constant)	–5.27515		
Pre-operative AFP	0.012639	1.012	0.0094**
LVI	2.61685	13.69	0.03*

Other factors excluded from the model as (*p*-value >0.1).
β : Regression coefficient.
SE: Standard error.

By using ROC-curve analysis, locoregional therapy decreased recurrence, with poor (65%) accuracy, sensitivity=80% and specificity=51% ($p<0.05$).

The survival probability regarding recurrence was markedly increased in Locoregional therapy (in 2011); compared to the non-therapy group in survival curves of the 2 groups (Fig. 1).

Logistic regression analysis shows that; after applying (Forward method) and entering some predictor variables; the increase in LVI; had an independent effect on increasing the probability of mortality occurrence; with a significant statistical difference ($p=0.0059$) (Table 4).

By using ROC-curve analysis, locoregional therapy showed non-significant predictive values in discrimination of patients with mortality from patients without ($p>0.05$).

The survival probability regarding mortality was not significant in Locoregional therapy; compared to the non-therapy group in survival curves of the 2 groups (Fig. 2).

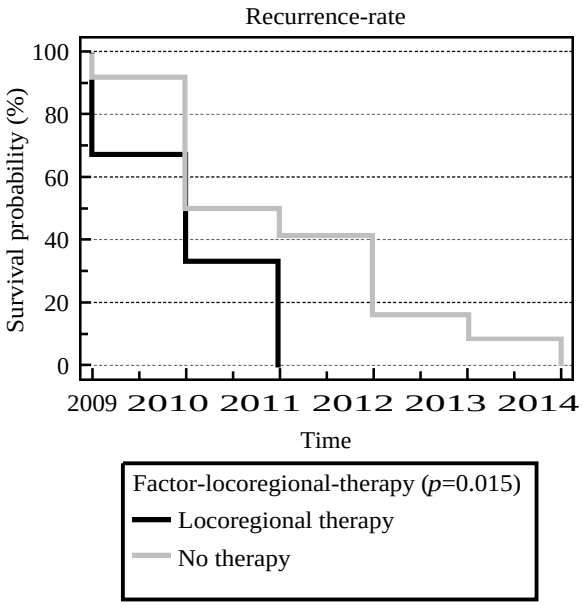

Fig. (1): Kaplan-Meier survival curve of the 2 survivor groups (recurrence).

Correlation analysis to predict mortality:

Table (4): Logistic regression model for the Factors affecting mortality occurrence using the Forward method.

Predictor Factor	Coefficient	OR	*p*-value
(Constant)	–1.50408		
LVI	1.7539	5.78	0.0059**

Other factors excluded from the model as (*p*-value >0.1).
β: Regression coefficient. SE: Standard error.

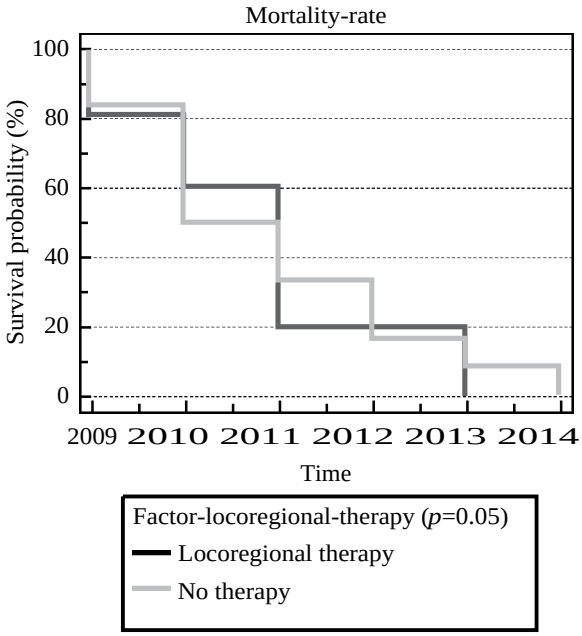

Fig. (2): Kaplan-Meier survival curve of the 2 survivor groups (mortality).

Discussion

This was a retrospective comparative study conducted on 60 liver transplantation patients; to assess the overall survival and HCC recurrence in patients with HCC undergoing living donor liver transplantation with or without locoregional therapies (RFA/Microwave, Ethanol Injection, TACE, and TARE) as bridging or downstaging before transplant.

Regarding pre-operative data: We found that; the mean age of all patients was (52.5±4.4) years. Regarding the gender of the patients, the majority (90%) of patients were males; while (10%) were females. Which came in agreement with Wang et al. **[13],** Kardashian et al., 2020 **[14]** and Adeniji et al., 2020 **[15].**

Wang et al. **[13]** reported that the mean age was 52.1 and 57.2 years in the SLT and CLRT groups; 84.9% and 78.7% were male's respectively **[13].**

Kardashian et al. **[14]** reported that, DS patients were older (59 vs 58 years, *p*=0.047) than No-DS patients, had a longer median wait time (134 vs 81 days, *p*0.001), lower median laboratory MELD (11 vs 12, *p*=0.045), and higher transplant match MELD **[14].**

Adeniji et al. **[15]** reported that, between 2008 and 2018, 302 patients received HCC transplants. The median age at HCC diagnosis was 60.0 years (range 17-73) and 62.0 years at transplantation (range 19-75). The majority of study participants [79.8 percent (n=241)] were male, and the majority were of Caucasian or Asian descent [68.9 percent (n=208)] **[15].**

Regarding pre-operative hepatic data; the average MELD score was (11.4±2.3), and the average AFP was (261.3±470) ng/dl, with (93.3%) of patients had HCV, and (8.3%) had HBV. Which came in agreement with Adeniji et al. **[15].**

Adeniji et al. **[15]** reported that, Hepatitis C (38.4 percent (n=116) and hepatitis B (18.5 percent (n=56) were the most common causes of HCC. The majority of patients [93.7 percent (n=283)] developed HCC in the context of cirrhosis. Just over half of the patients [52.6 percent (n=159)] had a history of decompensated liver disease, with ascites [42.7 percent (n=129)] or hepatic encephalopathy [35.4 percent (n=107)] being the most common causes **[15].**

Regarding Child-Pugh class; (65%) of patients had class A, (28.3%) had class B, and (6.7%) had class C. This came in agreement with Wang et al. **[13].**

Wang et al. **[13]** reported that the patients in the SLT and CLRT groups had a mean MELD score of 7.6 and 6.7, respectively, and were Child-Pugh class A in 67.8 and 85.1 percent of the cases **[13].**

Regarding pre-operative HCC; the average HCC Lesions was (1.7±0.8), and the average size of the lesion was (3.8±1.1) cm, with (26.7%) of patients had LVI. Which came in agreement with Bhatti et al. **[16].**

Bhatti et al. **[16]** reported that the median period of follow-up was 33 (1.9-88) months. The median age ranged from 30 to 68 years. On preoperative imaging, the median tumour size was 3.7 (1.2-12) cm. There were 1-6 tumour nodules on average. At the time of transplant, the median MELD score was 15 (6-29) **[16].**

Regarding Milan criteria; (63.3%) of patients were fulfilling criteria, while (36.7%) were not. Which came in agreement with Maccali et al. **[17]** and Adeniji et al. **[15].**

Maccali et al. **[17]** reported that, at the time of listing, 86.4 percent of patients (n=938) met Milan criteria, with 7.5 percent having AFP scores greater than 2 points. At the listing, 47.3 percent of the beyond Milan criteria group had AFP scores of 2 points **[17].**

Adeniji et al. **[15]** reported that, The average number of treatments per patient was 2 (IQR 2.0), with 10.6 percent (n=32) receiving 5 LRT. Patients with tumours that did not meet the Milan criteria had a higher median number of LRTs [3 (IQR 3.0) VS 2.0 (IQR 2.0), *p* 0.001] and were more likely to receive 5 LRTs (29.4% vs 8.0%) **[15].**

Regarding locoregional therapy; (43.3%) of patients had locoregional therapy. Which came in agreement with Kardashian et al. **[14],** Maccali et al. **[17]**, Zori et al. **[18]**, Bhatti et al. **[16]**, and Adeniji et al. **[15].**

Kardashian et al. **[14]** reported that, During the study period, 4,359 patients with a known pre-LT diagnosis of HCC underwent LT at the UMHTC, with 3,570 presenting within MC and 789 presenting beyond MC tumours **[14].**

Maccali et al. **[17]** reported that Locoregional bridging therapies were performed in 55.4% of the study cohort (n=601) **[17].**

Zori et al. **[18]** reported that To see if LRT caused decompensation in the 21 patients who

dropped off the waiting list, their charts were reviewed for hospitalizations, worsening liver tests, infections, and death within 30 days of receiving LRT. They had 50 LRT treatments in total, with 7 (14%) of them being TARE. A total of eight hospitalizations occurred after LRT, with three occurring after TACE, two occurring after TAE, two occurring after MWA, and one occurring after TARE **[18]**.

Bhatti et al. **[16]** reported that the majority of transplants (28/46) were performed within 24 weeks of the previous LRT (60.9 percent). LRT produced a radiological response in 30/46 (65.2 percent) of patients **[16]**.

Adeniji et al. **[15]** reported that 95% (n=287) of patients received bridging LRTs before transplantation. Fifteen patients (5%) did not receive any LRTs before transplantation due to decompensated liver disease **[15]**.

Regarding pre-operative management; (3.3%) of patients had RFA, (35%) had TACE, and (5%) had both TACE and RFA. Which came in agreement with Wang et al. **[13]** and Adeniji et al. **[15]**.

Wang et al. **[13]** reported that RH was used in six studies, RFA in four, transcatheter arterial chemoembolization (TACE) in two, and PEI in two. SLT was compared to CLRT in all studies, with deceased donor liver transplant in 5 studies and live donor liver transplant in 2 studies **[13]**.

Adeniji et al. **[15]** reported that, TACE was the most commonly used initial treatment [90.5 percent (n=257)], followed by ablative therapies [8.1 percent (n=23)] **[15]**.

Regarding recurrence data; the recurrence rate was (25%), with (7.5%) of them had a bone recurrence, (66.7%) had a liver recurrence, (13.3%) had liver and lung recurrence, and also (13.3%) had multiple sites recurrences. Which came in agreement with Bhatti et al. **[16]**, Maccali et al. **[17]**, and Adeniji et al. **[15]**.

Bhatti et al. **[16]** reported that, patients with no risk factors (score=0), one risk factor (score 1-3), and two or more risk factors (score 4-7) had recurrence rates of 9%, 18.1%, and 84.6%, respectively ($p<0.0001$) **[16]**.

Maccali et al. **[17]** reported that, at the time of listing, 68.6 percent of patients with HCC recurrence met Milan criteria, and median AFP levels were 41.6ng/mL. After excluding 10 patients with AFP values above 1000ng/mL (according to the UCSF-DS protocol), 70.5 percent of patients with recurrence met Milan criteria **[17]**.

Adeniji et al. **[15]** reported that, The overall 5-year post-transplant survival rate was 81 percent, the recurrence rate was 9.3 percent (n=28), and the 5-year recurrence free survival rate was 77 percent. The average time between follow-ups was 5.0 years. The transplanted liver graft [53.6 percent (n=15)], lungs [46.4 percent (n=13)], and bones (35.7 percent (n=10) were the most common sites of post-transplant HCC recurrence. Patients who received 5 LRTs were more likely to develop recurrent extrahepatic HCC **[15]**.

The 60 liver transplantation patients were classified according to locoregional therapy into 2 independent groups: The locoregional therapy group (26 patients) and the non-therapy group (34 patients).

A comparative study between the 2 groups revealed non-significant differences as regards the age and sex of the patients ($p>0.05$). Which came in agreement with Morris et al. **[19]** and Kardashian et al. **[14]**.

Morris et al. **[19]** reported that the age and sex distribution of the populations were similar for all studies (mean/median age 56.94-65, percentage male 72.8-85.3% were reported **[19]**.

Kardashian et al. **[14]** reported that the long-term outcomes of the two groups were comparable Post-OLT survival rates were comparable in low risk and downstaged high-risk patients **[14]**.

A comparative study between the 2 groups revealed non-significant differences as regards pre-operative all pre-operative hepatic data ($p>0.05$). which came in agreement with Schoenberg et al. **[20]**.

Schoenberg et al. **[20]** reported that there were no significant differences in patient characteristics between the study groups in terms of demographic factors, underlying diseases, or disease severity **[20]**.

Comparative study between the 2 groups revealed non-significant differences as regards pre-operative HCC lesions, LVI, and fulfilling of Milan criteria ($p>0.05$). Which came in agreement with Zori et al. **[18]**.

Zori et al. **[18]** reported that there were no significant differences between the two groups in tumor-related factors such as degree of differentiation, presence of a tumour on explant, or tumour

stage. Despite no difference in time on the transplant list, the TARE group required significantly fewer LRT treatments (1.46 vs. 2.43; p=0.001) to remain within Milan Criteria **[18]**.

A comparative study between the 2 groups revealed non-significant differences as regards all operative data (p>0.05). Which came in agreement with Zori et al. **[18]**.

Zori et al. **[18]** reported that during the study period, 103 patients with HCC who met the Milan criteria were listed for LT and were candidates for LRT. 65 (63.1 percent) of the 103 patients received an LT and met the inclusion criteria. Twenty-eight people underwent LT under the TARE protocol and 37 underwent LT under the TACE protocol. Aside from the TARE protocol's significantly lower number of LRT sessions per protocol, baseline patient characteristics and demographics were largely similar **[18]**.

Comparative study between the 2 groups revealed; significant decrease in recurrence rate in locoregional therapy group (11.5%); compared to non-therapy group (35.3%) (p=0.036). Which came in agreement with Kardashian et al. **[14]**, Bodzin et al. **[21]**.

Kardashian et al. **[14]** reported that, patients within MC had the highest overall (89.9 percent, 79.5 percent, 71.3 percent) and recurrence-free survival (87.6 percent, 76.2 percent, 68.2 percent) and lowest incidence of HCC recurrence (3.9 percent, 8.8 percent, and 11.1 percent) survival at 3, and 5 years post-LT **[14]**.

Bodzin et al. **[21]** reported that, over the course of the 30-year study, 106 of the 857 patients who received LT for HCC developed a post-transplant recurrence, with 87 of them dying. The median time to recurrence after LT was 15.8 months (IQR 6.8-33.1), with estimated 1-, 2-, and 3-year survival rates of 47 percent, 24 percent, and 18 percent, respectively. The median follow-up time after recurrence for the 19 recurrent HCC patients alive at last follow-up (18%) was 27.5 months, with 11 actual 2-year survivors, 8 3-year survivors, and five 5-year survivors **[21]**.

Correlation studies between different postoperative outcomes; and their relative independent predictors (basic clinical, hepatic, HCC, laboratory, treatment, operative variables).

Logistic regression analysis shows that; after applying (Forward method) and entering some predictor variables; the increase in pre-operative AFP and LVI; had an independent effect on increasing the probability of recurrence occurrence; with a significant statistical difference (p<0.05 respectively). Which came in agreement with Kardashian et al. **[14]**, Vine et al. **[22]**, and Bhatti et al. **[16]**.

Kardashian et al. **[14]** reported that, HCV cirrhosis (HR=0.55, CI 0.31-0.95; p=0.033), pre-LT NLR (HR=2.06 per log unit increase, CI 1.29-3.30, p=0.003), immediate pretransplant log AFP (HR=1.07 per 50% increase, CI 1.02-1.12; p= 0.008), microvascular invasion (HR=2.31, CI 1.45-3.67; p0.001), macrovascular invasion (HR=2.54) **[14]**.

Vine et al. **[22]** reported that, the exclusion of patients with AFP levels greater than 1000ng/mL from undergoing LT was discovered in 4.7 percent of cases with tumours within the MC, and it was strongly associated with mIV (OR, 6.8) and 5-year TR (47.3 percent). A recent study based on the UNOS database included 407 patients with HCC who underwent LT with AFP levels greater than 1000ng/mL, accounting for 3.8 percent of all cases. Of these, 23.9 percent reduced their AFP to less than 500ng/mL with LRT, which was associated with a significant decrease in TR (13.3 percent vs 35 percent) and a 5-year mortality rate (33 percent vs 51, 2 percent) **[22]**.

Bhatti et al. **[16]** reported that, On ROC, highest recorded AFP during treatment (AUC=0.7, p=0.02) and pretransplant AFP (AUC=0.69, p=0.03) were significant factors for recurrence **[16]**.

By using ROC-curve analysis, locoregional therapy decreased recurrence, with poor (65%) accuracy, sensitivity=80% and specificity=51% (p<0.05). Which came in agreement with Bhatti et al. **[16]**.

Bhatti et al. **[16]** reported that, based on low risk (score=0), intermediate risk (score=1-3), and high risk (score=4-7) scores, the estimated 5-year RFS was 86 percent, 76 percent, and 9 percent, respectively (p<0.0001). There was no recurrence in 4/4 (100%) of patients with macrovascular invasion in the low-intermediate risk group, whereas 5/6 (83.3%) of patients in the high-risk group developed recurrence **[16]**.

The survival probability regarding recurrence was markedly increased in Locoregional therapy (in 2011); compared to the non-therapy group in survival curves of the 2 groups. Which came in agreement with Kardashian et al. **[14]** and Schoenberg et al. **[20]**.

Kardashian et al. **[14]** reported that LRT was administered to all transplant candidates. This demonstrates a greater statistical impact on 5-year OS for CR of 85.7 percent compared to 19.3 percent for SD or PD ($p<0.01$) **[14]**.

Schoenberg et al. **[20]** reported that the overall outcome for HCC patients who received LT was excellent. 73.7 percent (63.4 percent; 81.5 percent) of patients were alive after 5 years of follow-up. 88.4 percent (78.3 percent; 94.0 percent) of patients were free of disease recurrence **[20]**.

Logistic regression analysis shows that; after applying (Forward method) and entering some predictor variables; the increase in LVI; had an independent effect on increasing the probability of mortality occurrence; with a significant statistical difference ($p=0.0059$). Which came in agreement with Berman & Berman et al. **[23]** and Bodzin et al. **[21]**.

Berman et al. **[23]** reported that, In most countries, ultrasound is used for surveillance, with or without serum-fetoprotein (AFP) levels (which is not always elevated in HCC). One Chinese randomised controlled trial (RCT) found that screening with ultrasound and AFP can reduce mortality by 37% **[23]**.

Bodzin et al. **[21]** reported that, factors associated with an increased rate of mortality included pretransplant MELD >23 (HR 1.90, $p=0.024$), donor serum sodium >138 meq/dL (HR 2.6, $p=0.012$), shorter time to recurrence (HR 2.08, $p<0.001$), greater AFP at recurrence (HR 1.82, $p<0.001$), >10 recurrent nodules (HR 2.77, $p<0.001$), and maximum recurrence tumor diameter (HR 1.46, $p=0.003$), with a trend toward increased mortality for patients with diabetes (HR 1.54, $p=0.095$), hypertension (HR 1.65, $p=0.051$), increasing number of radiologic tumors (2-3 lesions: HR 1.53, $p=0.087$; 4 lesions: HR 1.89, $p=0.066$), higher pathologic tumor grade (G3: HR 2.21, $p=0.094$; G4: HR 2.38, $p=0.130$), poorly differentiated tumors (HR 2.19, $p=0.072$), and bone recurrence (HR 1.52, $p= 0.079$) **[21]**.

The survival probability regarding mortality was not significant in Locoregional therapy; compared to the non-therapy group in survival curves of the 2 groups. Which came in disagreement with Schoenberg et al. **[20]** and Young et al. **[24]**.

Schoenberg et al. **[20]** reported that the response to therapy to an LRT procedure appears to have good predictive power for patient survival **[20]**.

Young et al. **[24]** reported that each LRT employs a unique method of inducing tumour death. These distinct methods of inducing tumour death may result in differences in post-treatment imaging characteristics. The sections that follow will discuss each technique briefly, followed by its key post-treatment imaging characteristics **[24]**.

Conclusion:

To conclude, Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality and only cancer for which the incidence and mortality are on the rise. Sensitive and specific screening and diagnostic approaches, robust staging regimens, multidisciplinary tumor boards, and patient/family education and engagement in the shared decision-making process help to identify a patient's optimal treatment options. Locoregional therapies have been the mainstay for treating intermediate-stage disease, but they are finding special applications for early and advanced disease.

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العلاج الموضعى لسرطان الكبد
ما قبل عملية زرع الكبد من متبرع حى

خلفية الدراسة : ينشأ سرطان الخلايا الكبدية فى الكبد المصاب بالتليف ومرضى الفشل الكبدى. يعد العلاج الموضعى لسرطان الكبد من الرسائل التى تستخدم قبل زرع الكبد لتقليل حجم الورم حتى يصبح المريض ملائما لاجراء زرع كبد من متبرع حى.

الهدف من الدراسة : لتقييم البقاء على قيد الحياة بشكل عام وتكرار الإصابة بسرطان الخلايا الكبدية فى المرضى الذين يعانون من سرطان الخلايا الكبدية الذين يخضعون لعملية زرع كبد من متبرع حى مع أو بدون علاجات محلية مثل التجسير أو التقليل من المرحلة قبل الزرع.

المرضى وطرق الدراسة : اشتملت الدراسة على ٦٠ مريضاً ، قسمت إلى مجموعتين، الأولى شملت ٢٦ مريضاً خضعوا لعلاج موضعى قبل عملية زرع الكبد، والمجموعة الثانية اشتملت على ٣٤ مريضاً، خضعوا لعملية زرع الكبد من متبرع حى مباشرة بدون أى علاج موضعى قبل زرع الكبد.

النتائج : كشفت دراسة مقارنة بين المجموعتين :

- عدم وجود فروق ذات دلالة إحصائية فيما يتعلق بعمر وجنس المرضى.
- زيادة كبيرة فى حجم الآفة قبل الجراحة فى مجموعة العلاج الموضعى. مقارنة بالمجموعة غير العلاجية.
- فرق غير مهم فيما يتعلق بآفات سرطان الخلايا الكبدية قبل الجراحة، واستيفاء معايير ميلان.
- فرق غير مهم فيما يتعلق بجميع بيانات المنطوق.
- انخفاض كبير فى عدد الآفات بعد الجراحة فى مجموعة العلاج الموضعى. مقارنة بالمجموعة غير العلاجية.
- زيادة كبيرة فى حجم الآفات بعد الجراحة فى مجموعة العلاج الموضعى. مقارنة بالمجموعة غير العلاجية.
- انخفاض ملحوظ فى معدل تكرار فى مجموعة العلاج الموضعى (١١.٥٪). مقارنة بالمجموعة غير العلاجية (٣٥.٣٪).
- فرق غير مهم فيما يتعلق بمعدل الوفيات. باستخدام تحليل منحنى ROC، قلل العلاج الموضعى من التكرار، مع دقة ضعيفة (٦٥٪)، حساسية = ٨٠٪ ونوعية = ٥١٪. زاد احتمال البقاء على قيد الحياة فيما يتعلق بالتكرار بشكل ملحوظ فى العلاج (فى عام ٢٠١١)، مقارنة بالمجموعة غير العلاجية فى منحنيات البقاء على قيد الحياة للمجموعتين.

لم يكن احتمال البقاء على قيد الحياة فيما يتعلق بالوفيات مهماً فى العلاج المحلى. مقارنة بالمجموعة غير العلاجية فى منحنيات البقاء على قيد الحياة للمجموعتين.

الخلاصة : سرطان الخلايا الكبدية هو السبب الرئيسى الثانى للوفيات المرتبطة بالسرطان، والسرطان الوحيد الذى يتزايد فيه معدل الإصابة والوفيات تساعد أساليب الفحص والتشخيص الحساسة والمحددة، ونظم التدريج القوية، ومجالس الأورام متعددة التخصصات، وتثقيف المريض / الأسرة والمشاركة فى عملية صنع القرار المشتركة على تحديد خيارات العلاج المثلى للمريض. كانت العلاجات المحلية هى الد عامة الأساسية لعلاج مرض المرحلة المتوسطة، لكنها تجد تطبيقات خاصة للأمراض المبكرة والمتقدمة.