ORIGINAL ARTICLE

"LIVER CT: IMAGING FEATURES ASSOCIATED WITH RECURRENCE FOLLOWING LIVER TRANSPLANT"

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ABSTRACT

The aim of this study is to determine the association of imaging spectrum of hepatocellular carcinoma with post-transplant pattern of metastatic disease.**METHOD AND MATERIAL:** A seven-year retrospective study (2014-2020) of live donor liver transplant (LDLT) patients at Shifa International Hospital (SIH) involved comparing pre-transplant CT scans to post-transplant dynamic CT images using a picture archiving and communication system (PACS). Disease recurrence in potential sites, including the hepatic graft, abdomino-pelvic viscera, lungs, bones, and more, was documented. Data was analyzed using frequency statistics, histograms, and tables. **RESULTS:** Out of 221 transplants, 36 individuals (4F, 32M) experienced recurrences; 27.8% had prior Transarterial chemo-embolization (TACE). Segment VII had the most HCCs (14 patients, 38.9%); Segments V and VI had 6 patients each (16.7%) with average sizes of 4.372 – 1.912 cm. Most patients (69.4%) showed capsular involvement on pre-transplant CT, followed by diaphragmatic involvement in 8, segmental portal venous (PV) tumor in 6, and APS in 3 individuals (22%, 16.7%, 8.3% respectively). Post-transplant CT showed recurrence in the lungs (44.4%), bones (41.6%), hepatic graft (30.5%), lymph nodes (22.2%), adrenals (8.3%), and other sites. Pre-transplant factors had varying associations with recurrence, but none were statistically significant (P-values > 0.05). **CONCLUSION:** Our study does not show significant association between presence of diaphragmatic involvement, hepatic capsular invasion, thrombosed segmental branches, and arterioportal shunting (APS) and the site of tumor recurrence. However, presence of significant capsular and diaphragmatic bulge particularly in segment VII and VIII HCCs, robust scrutiny should be carried out for evaluation of these areas both intra-operatively by surgeon and in post-transplant follow-up CT reporting by radiologist. Furthermore, in post-transplant CTs, comparison and correlation with pre-transplant CT findings should be carried out. The study also highlights the key role of radiologist in highlighting these features of HCCs for assistance in ensuring safe surgical practices.

Key Words: HCC; Liver Transplant; CT; Recurrence

Introduction

Live donor liver transplantation (LDLT) in patients with hepatocellular carcinoma (HCC) is currently widely accepted as the most effective curative therapy because of its oncological clearance while simultaneously effectively resolving the spectrum of chronic liver disease (CLD). Even though the major worldwide accepted criteria for the patients underwent LDLT is broadly based on the Milan[1] and UCSF[2] criteria, it is also true when patients are selected based on further broader criteria[3-8] that have been shown to have long-

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term outcomes that are comparable to the aforementioned criteria.

As imaging tools have become more advanced, the emphasis on tumor selection has evolved and now it s beyond the number and size of tumors visible on pre-LT imaging and perhaps more emphasis is on the biology of the tumor. A growing appreciation for the fact that the biology of tumor is critical and determines longterm outcomes[9-12] is reflected in the inclusion of tumor indicators such as alpha-fetoprotein (AFP) and PIVKA-II (Protein induced by vitamin K absence-II) levels, as well as tumor grade and avidity showed by FDG-18 PET scan in the selection criteria of patients. These predictors determine the longterm outcomes in HCC patients undergoing LT treatment. The likelihood of a recurrence depends on the number of criteria/ determinants included in the scope of the research. As a result of the difficulty in managing post-LT HCC recurrence to prolong survival in the majority of cases, it is still believed that recurrence is a significant cause of early mortality in the majority of cases. According to the available data, the majority of LT-related recurrences take place during the first two years following the treatment; nevertheless, reports of recurrences taking place more than ten years after the procedure have also been documented.[13-15]

The extra hepatic disease recurrence (up to 71 percent) is the most common pattern of recurrence followed by local recurrence of HCC in the hepatic graft alone whereas the recurrence of HCC in both the liver and extra hepatic sites remains third on the list.[16] One of the most important predictors of outcome is the number of tumors present at the time of the recurrence i.e. solitary vs. multiple nodules. As disease recurrence occurs at multiple sites more commonly than it does at a single site;it is more difficult to treat recurrence andhence is typically restricted to systemic therapy alone. Tyrosine kinase inhibitors and checkpoint inhibitors are the limited systemic therapy options accessible to patients in such case, both of which were recently approved by the United States Food and Drug Administration, demonstrating wide range of success.

Since the recurrence in post-transplant patient add immense anxiety among patients and clinicians as well as draw extra resources in managing these patients so currently, we undertook this study to assess if there are any additional determinants and variables in pre transplant CT studies such as diaphragmatic involvement, hepatic capsular invasion, and thrombosis of segmental branches of portal vein for HCC workup that might be helpful to predict possibility of recurrence and its pattern recurrence and/or any significant association between imaging pattern and possible post-transplant recurrence.

Methodology

The Hospital Management Information System (HMIS) was searched for patients who underwent LDLT during a period of 7 years from 2014 to 2020. Their pre-transplant and post-transplant CT scans were retrieved from PACS (picture archiving communication system). The scans were reviewed by a consultant radiologist having more than 10 years of experience in diagnostic radiology with special focus on diaphragmatic involvement, hepatic capsular invasion, thrombosed segmental branches, and arterioportal shunting (APS) in pre-transplant scans whereas the post-transplant CT scans were analyzed for presence of disease tumor recurrence, the site of recurrence (hepatic vs extra-hepatic and number of lesions (solitary vs multiple). All LDLT patients undergo a baseline follow up post-transplant CT after 6 months. The CT surveillance is continued 6 monthly for duration of 2 years according to our institutional policy and afterwards if required according to patients disease behavior. Few exceptions exist when more frequent scans are performed. These include scans performed in immediate post-transplant patient to look for hepatic artery patency (in case of deranged Doppler indices or non-visualization/ thrombosis of hepatic artery), for evaluation of peri-graft/ intra-hepatic collections (those which are suboptimally visualized on ultrasound), deranged LFTs and abnormal ultrasound findings (detection of space occupying lesion in liver or elsewhere, differential echogenicity areas in liver, regional lymphadenopathy and thrombosed portal vein). Ethical review board granted exemption due to retrospective design of study.

LDLT selection criteria in patients with HCC and cirrhosis:

Live donor liver transplant (LDLT) is one of the most

effective therapeutic options for HCC and underlying cirrhotic liver cure.[2] There are many criteria in practice for the liver transplant candidates having HCC. The established UCSF criteria (patients with a solitary tumor smaller than 6.5 cm, or patients having 3 orless number of nodules, size of largest lesion being less than 4.5 cm or largest tumor diameter less than 8.5 cm without vascular invasion and extra-hepatic metastasis) serves as the baseline for patient selection in our institution. Almost all patients selected for LDLT using UCSF criteria were offered upfront transplantation. Patients down staged (DS) by utilizing methods including trans arterial chemo embolization (TACE), radiofrequency ablation (RFA), microwave ablation (MWA) or percutaneous ethanol ablation (PEA) and fulfilling UCSF criteria were also offered liver transplantation.

Analytical Statistics

For continuous variables, the median standard deviation (SD) or median deviation (interquartile range, IQR) is reported. Statistics are categorically expressed as a percentage and frequency. For results following the LDLT, calculation of overall complete survival (OS) was done from the date of the transplant on or after death. Calculation of recurrence-free survival (RFS) was made from the date of the first or last retrieval, whichever was earlier. Thence we determined the overall survival rate (OS). Chi-square test was employed for categorical data, however for continuous variables, the independent t-test or ANNOVA was utilized. The Kaplan-Meier method was used for performing survival analyses, and survival curves were then compared using the log-rank test. The Cox proportional hazard model was used to conduct univariate and multivariate analysis of post-recurrence risk factors. P value less than 0.05 was defined as statistically significant. SPSS version 20.0 for Windows was used for all statistical analyses (SPSS Inc., Chicago, IL, USA).

Results

Out of a total of 221 individuals, 36 patients (04 females and 32 males) had recurrences, according to our findings (Tab.1). Ten of these patients (27.8 percent) had received TACE treatment prior to their

Description	N %
Gender	
Male	32(88.90)
Female	4(11.10)
Patients undergone TACE procedure to downstage HCC	
Yes	10(27.80)
No	26(72.20)
No. of HCC in Pretransplant	
One	13(36.10)
Two	10(27.80)
Three	6(16.70)
Four	3(8.30)
Five	1(2.80)
Five to eight	1(2.80)
Nine to ten	1(2.80)
More than ten	1(2.80)
Distribution of HCC in segments of Liver	
Segment I	1(2.80)
Segment III	3(8.30)
Segment IV	1(2.80)
Segment V	6(16.70)
Segment VI	6(16.70)
Segment VII	14(38.90)
Segment VIII	5(13.90)
Capsule involvement	
Yes	25(69.40)
No	11(30.60)
Diaphragmatic Involvement	
Yes	8(22.20)
No	28(77.80)
Segmental PV Tumor Thrombus	
Yes	6(16.70)
No	30(83.30)
Arterioportal shunting	
Yes	3(8.30)
No	33(91.70)
No. of HCC in Post-transplant Graft	
None	19(52.80)
One	7(19.4)
Two	3(8.30)
Nine to ten	1(2.80)
More than ten	2(5.60)

Table 1: Demographic and clinical data of patients (N = 36)

transplantation. In Segment VII, the greatest number of HCCs (14 patients) was seen (Fig.1), accounting for 38.9 percent of all HCCs, followed by 16.7 percent involvement in Segments V and VI (06 patients), with the mean average size of HCCs measuring 4.372 – 1.912 cm (Tabl.2). According to pre-transplant CT scans, the capsular involvement was found in the majority of patients (69.4 percent), followed by diaphragmatic involvement in 08 patients, segmental PV tumour thrombosis in 06 patients, and APS in 03 patientsaccounting for 22 percent, 16.7 percent, and 8.3 percent of the total patients, respectively. Following transplantation, post-transplant CT revealed recurrence in 16 patients (44.4 percent), with the majority of cases occurring in the lungs (44.4 percent), followed by bones in 15 patients (41.7 percent), hepatic graft in 11 patients (30.6 percent), lymph nodes in 8 patients (22 percent), adrenals in 3 patients(8.3 percent), abdominal wall in 2 patients (5.56 percent), omentoperitoneal in 2 patients (5.56 percent), and diaphragm in 2 patients ((5.56 percent) (Fig.2) & (Tab.3,4,5 & 6). One patient (2.7%) had pleural metastases, and one (2.7%) had a significantly elevated AFP > 20,000 but no post-transplant imaging was available. Those patients who exhibited capsular invasion, diaphragmatic involvement, and APS on pretransplant CT had shown maximum recurrence within the lungs, accounting for 33.3 percent, 13.9 percent, and 8.3 percent correspondingly, with P-values of 0.71, 0.4, and 0.07 for each of these factors (P-value <0.05 was taken as significant). However, in those who had segmental PV tumour thrombosis, recurrence within the bones (11.1 percent) was found to be the predominant pattern, with a P-value of 0.2. No significant relation was found between the site of recurrence and the pretransplant factors.

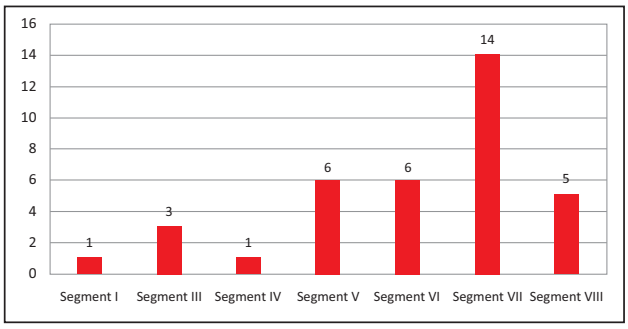

Figure 1: Distribution of HCC in hepatic segments

Description	Mean ± SD	Median(IQR)
HCC Size (in cm)	4.372 ± 1.912	4.250(4.250)
Months Post-transplant recurrence	13.333 ± 10.167	10.500(10.500)

Table 2: Descriptive statistics of clinical data of patients (N = 36)

Description	N	Capsule Involvement		
		No (11) N (%)	Yes (25) N (%)	P-value
Lungs				
No	20	7(19.4)	13(36.1)	0.718
Yes	16	4(11.10)	12(33.3)	
Lymph Nodes				
No	28	7(19.4)	21(58.3)	0.214
Yes	8	4(11.1)	4(11.1)	
Graft				
No	25	10(27.8)	15(41.7)	0.116
Yes	11	1(2.8)	10(27.8)	
Bones				
No	21	5(13.9)	16(44.4)	0.465
Yes	15	6(16.7)	9(25.0)	
Adrenals				
No	33	9(25.0)	24(66.7)	0.216
Yes	3	2(5.6)	1(2.8)	
Abdominal Wall				
No	34	10(27.8)	24(66.7)	0.524
Yes	2	1(2.8)	1(2.8)	
Omentoperitoneal				
No	34	11(30.6)	23(63.9)	1.000
Yes	2	0(0.0)	2(5.6)	
Diaphragm				
No	34	11(30.6)	23(63.9)	1.000
Yes	2	0(0.0)	2(5.6)	
Pleura				
No	35	11(30.6)	24(66.7)	1.000
Yes	1	0(0.0)	1(2.8)	
Raised AFP				
No	35	11(30.6)	24(66.7)	1.000
Yes	1	0(0.0)	1(2.8)	

* P values less than 0.05 were considered statistically significant.
**Fisher's Exact Test was used.

Table 3: Association between capsule involvement and post-transplant site of recurrence on CT

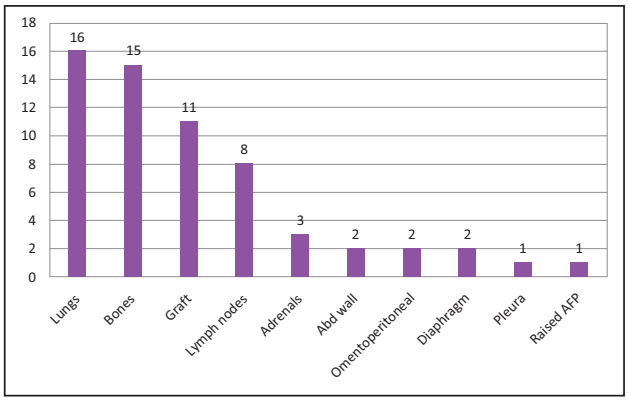

Figure 2: Post-transplant site of disease recurrence on CT

Description	N	Diaphragm Involvement		
		No (28) N (%)	Yes (8) N (%)	P-value
Lungs				
No	20	17(47.2)	3(8.3)	0.422
Yes	16	11(30.6)	5(13.9)	
Lymph Nodes				
No	28	21(58.3)	7(19.4)	0.651
Yes	8	7(19.4)	1(2.8)	
Graft				
No	25	20(55.6)	5(13.9)	0.678
Yes	11	8(22.2)	3(8.3)	
Bones				
No	21	14(38.9)	7(19.4)	0.465
Yes	15	14(38.9)	1(2.8)	
Adrenals				
No	33	25(69.4)	8(22.2)	1.000
Yes	3	3(8.3)	0(0.0)	
Abdominal Wall				
No	34	26(72.2)	8(22.2)	1.000
Yes	2	2(5.6)	0(0.0)	
Omentoperitoneal				
No	34	27(75.0)	7(19.4)	1.000
Yes	2	1(2.8)	1(2.8)	
Diaphragm				
No	34	26(72.2)	8(22.2)	1.000
Yes	2	2(5.6)	0(0.0)	
Pleura				
No	35	27(75.0)	8(22.2)	1.000
Yes	1	1(2.8)	0(0.0)	
Raised AFP				
No	35	27(75.0)	8(22.2)	1.000
Yes	1	1(2.8)	0(0.0)	

* P values less than 0.05 were considered statistically significant.
**Fisher's Exact Test was used.

Table 4: Association between diaphragm and posttransplant site of recurrence on CT

Description	N	Segmental PV Tumor Thrombus		
		No (30) N (%)	Yes (6) N (%)	P-value
Lungs				
No	20	17(47.2)	3(8.3)	1.000
Yes	16	13(36.1)	3(8.3)	
Lymph Nodes				
No	28	23(63.9)	5(13.9)	1.000
Yes	8	7(19.4)	1(2.8)	
Graft				
No	25	20(55.6)	5(13.9)	0.643
Yes	11	10(27.8)	1(2.8)	
Bones				
No	21	19(52.8)	2(5.6)	0.210
Yes	15	11(30.6)	4(11.1)	
Adrenals				
No	33	27(75.0)	6(16.7)	1.000
Yes	3	3(8.3)	0(0.0)	
Abdominal Wall				
No	34	29(80.6)	5(13.9)	0.310
Yes	2	1(2.8)	1(2.8)	
Omentoperitoneal				
No	34	28(77.8)	6(16.7)	1.000
Yes	2	2(5.6)	0(0.0)	
Diaphragm				
No	34	28(77.8)	6(16.7)	1.000
Yes	2	2(5.6)	0(0.0)	
Pleura				
No	35	29(80.6)	6(16.7)	1.000
Yes	1	1(2.8)	0(0.0)	
Raised AFP				
No	35	29(80.6)	6(16.7)	1.000
Yes	1	1(2.8)	0(0.0)	

* P values less than 0.05 were considered statistically significant.
**Fisher's Exact Test was used.

Table 5: Association between segmental PV tumor thrombus and posttransplant site of recurrence on CT

Description	N	Arterioportal shunting		
		No (33) N (%)	Yes (3) N (%)	P-value
Lungs				
No	20	20(55.6)	0(0.0)	0.078
Yes	16	13(36.1)	3(8.3)	
Lymph Nodes				
No	28	25(69.4)	3(8.3)	1.000
Yes	8	8(22.2)	0(0.0)	
Graft				
No	25	24(66.7)	1(2.8)	0.216
Yes	11	9(25.0)	2(5.6)	
Bones				
No	21	19(52.8)	2(5.6)	1.000
Yes	15	14(38.9)	1(2.8)	
Adrenals				
No	33	30(83.3)	3(8.3)	1.000
Yes	3	3(8.3)	0(0.0)	
Abdominal Wall				
No	34	32(88.9)	2(5.6)	0.162
Yes	2	1(2.8)	1(2.8)	
Omentoperitoneal				
No	34	32(88.9)	2(5.6)	0.162
Yes	2	1(2.8)	1(2.8)	
Diaphragm				
No	34	32(88.9)	2(5.6)	0.162
Yes	2	1(2.8)	1(2.8)	
Pleura				
No	35	33(91.7)	2(5.6)	0.083
Yes	1	0(0.0)	1(2.8)	
Raised AFP				
No	35	32(88.9)	3(8.3)	1.000
Yes	1	1(2.8)	0(0.0)	

* P values less than 0.05 were considered statistically significant.
**Fisher's Exact Test was used.

Table 6: Association between arterioportal shunting and posttransplant site of recurrence on CT

Discussion

According to the American Society of Hepatology (ASH), 10% to 20% of patients have recurring HCC following transplantation. Despite extensive medical efforts to improve the criteria for selecting patients for transplantation to achieve the best results,[5] the incidence remains constant over time. In line with a review of 61 studies published in 2015, we found a recurrence rate of 16% and an HCC median duration of 13 months (with a range of 2-132 months).[17] Also, the median period between repetitions was 16 months on the basis of our data (IQR 8-29 months). Increasingly, HCC patients not satisfying the Milan criteria are being transplanted around the world in more and more centers, raising the likelihood that HCC recurrence will be higher than previously estimated.[18]

The survival is thus the most significant consideration in post-LT HCC patients and as none of the therapeutic approaches currently available is guaranteed to be effective on a long-term basis. The main problems in this condition are primary extrahepatic recurrence at multiple sites, which makes it difficult to achieve treatment.

The HCC recurrence is often linked to poor prognosis in the early years of treatment.[19,20] We got the same result with recurrence in the first year of treatment. According to the American Cancer Society, the recurrence of early HCC may be caused by extrahepatic metastasis which was not apparent prior to liver transplant or may be caused by hematological spread of HCC tumor cells showing tumor growth in target organ after transplantation. For the first 1-2 years following the use of a strict post-LT surveillance regime (which covers the majority of recurrences), curable metastases can be detected early, particularly when they are solitary and resectable, which allows earlier treatment options. The monitoring and evaluation with modes which are very sensitive and disease-specific are indicated for regular pulmonary, osseous and hepatic graft metastatic spread (the most common recurrence sites). These include whole body FDG-18 PET scan with triple phase CT angiography of abdomen, or contrast enhanced computed tomography of abdomen and chest with bone scan. As a result of this study, 68% of the recurrence took place in initial two years following liver transplant. This is comparable with the other studies which found the median period of re-appearances of tumour to vary between 7 and 36 months.[21-25]

Because of its proximity to the liver and the lymph drainage system present during hepatectomy, the lung is the most often recurring location.[26] Our results also showed lung as the most common site of recurrence.

The presence of diaphragmatic involvement, capsular invasion and APS on pre-transplant CT as predictors for HCC recurrence are not evaluated in the past. This study is the first one to evaluate these parameters and analyze their relation with HCC recurrence.
Post-transplantation surveillance by CT scan ensures early detection of disease recurrence hence, providing better chances of survival. Resection remains the mainstay of curative treatment of local recurrence after LDLT.[27] The other treatment options for treatment of HCC remain valid in post LDLT disease recurrence as are in primary HCC.[28] In cases of extensive disease recurrence with involvement of liver, lung, or bone, excision is not possible and other modes including ablative therapy and SBRT should be utilized.[29,30]

Conclusion

Our study shows no significant association in pre-transplant additional imaging variables for HCC with the particular site oftumor metastasis. However, as observed in our study when significant capsular and diaphragmatic bulge being depicted especially in segment VII and VIII HCCs,robust intraoperative scrutiny should be carried out for these areas andsimilarly in post-transplant follow-up CT by radiologist to the recurrence at an early stage. Furthermore, in post-transplant CTs, comparison and correlation with pretransplant CT should be carried out in all three (axial, coronal and sagittal)planes. Radiologist can play a vital role in highlighting these features of HCCs for assisting in safe surgical practices and early detection of HCC recurrence.

Conflict of Interest: Authors declared no financial or institutional COI

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