

Original article

Profile of hepatocellular carcinoma and the role of radiological surveillance: A three year single centre experience

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Abstract:

Introduction : Hepatocellular carcinoma(HCC) is fifth most common cancer worldwide with increasing incidence. There is relative lack of clinicoradiological analysis of this entity from tertiary level centers in india with no significant data available on its surveillance .

Aims and objectives : To analyse the clinicoradiological characteristics of HCC in a tertiary care hospital and the effect of surveillance for HCC in patients with cirrhosis on the stage at diagnosis and treatment .

Materials and methods : 96 patients with cirrhosis or underlying chronic liver disease with HCC over a period of three years from Dec 2012 till Dec 2015 were included .Stage at diagnosis and respective treatment instituted was assessed .The presence of regular surveillance was noted . Influence of regular surveillance on the stage of the disease and the resultant treatment instituted was analysed .

Results : Increasing number of patients under surveillance present in the early and intermediate stage disease . In these early and intermediate stage tumors either curative or effective palliative transarterial therapies can be instituted . Patients under no regular surveillance usually present at an advanced stage . Being on regular follow ups with surveillance imaging in an equipped tertiary care setting is an important factor in detecting HCC at an early stage and affecting curative treatments .

Conclusions : The study provides insights on how HCC is presenting in our country in a typical advanced urban institutional settings and highlights the usefulness of regular surveillance .

Key words : Hepatocellular carcinoma , stage , surveillance

Introduction :

Hepatocellular carcinoma(HCC) is the fifth most common cancer worldwide with cirrhosis being an important risk factor (1). HCC differs from other malignancies in that the prognosis of the patient depends not only on the extent of tumor but also on

underlying liver disease .Hence staging systems for HCC use radiological extent in combination with clinical parameters . Of these Hongkong liver cancer staging (HKLC) has been in vogue in staging and treatment guidance of Asian patients , some studies found this system to have better ability to distinguish

between the patients compared to conventional BCLC staging and also recommended more aggressive treatments for intermediate and advanced stage patients with more survival benefits (2) .The five year cumulative risk of developing HCC in cirrhosis ranges between 5 and 30 % (3) . Usually symptomatic tumors in patients with cirrhosis are far beyond curative stage , hence the emphasis on diagnosing lesions at early stage to effect curative treatments (4) . Towards this end there are various surveillance guidelines for early detection in patients with underlying cirrhosis and chronic viral hepatitis . By definition surveillance refers to repeated application of test or combination tests in the same person temporally over a period of time to affect early detection early (5). The surveillance commonly recommended is with liver ultrasound and alphafetoprotein (AFP)levels .Ultrasound(USG) has moderate sensitivity of 60 % and specificity of 85 to 90 % for HCC detection , AFP levels have much less sensitivity and specificity however since it is inexpensive , noninvasive and widely available , has been incorporated with USG as a surveillance tool (6) . Neither CT nor MRI have been generally advocated for surveillance purposes , except in the settings of obesity where USG is limited or in those with very high risk of HCC development (7)(8) . The recommended interval for HCC surveillance is 6 to 12 months(biannual or annual).A recent metaanalysis showed that six monthly surveillance USG detects significantly more HCC than annually (9). Six months interval strategy also appears appropriate based on tumor doubling time(10) . If surveillance test is abnormal , triphasic CT or dynamic MRI are next investigation for confirming diagnosis , histopathology is needed if imaging does not show features typical of HCC . Worldwide studies have

reported benefits of HCC surveillance with diagnosis at early stage , greater likelihood of receiving curative treatments and improved survival (6) .

Curative options for early stage HCC include ablations(radiofrequency), surgical resection or liver transplant (11) . Microwave ablation and cryoablation are the newer additives to the percutaneous ablation options (12)(13) .For intermediate stage transarterial therapies are optimal having survival benefits . Palliative sorafenib chemotherapy remains the last option with some possible survival benefit. (14)(15) .Majority of patients with HCC present at an advanced stage in our country with resultant poor outcomes.The management of HCC varies widely in our country depending upon the patient factors , socioeconomic conditions and disease status . While few tertiary centres in urban areas have requisite expertise , these facilities are largely lacking in major parts of the country (16-18). There is scarce literature highlighting the benefits of regular surveillance on early detection of HCC in India . In one multicenter retrospective study , surveillance was found to result in detection of HCC at early stage (19) . In this study we analyse how HCC presents in a tertiary care hospital settings like ours (a referral center for chronic liver disease with all possible treatments for HCC under one roof including gastroenterology , interventional radiology , medical oncology and hepatobiliary surgical unit with livertransplant expertise) and the effect of regular surveillance on stage at diagnosis and treatment .

Aims and Objectives:

This study aims to analyse the clinicoradiological profile of HCC in a tertiary care hospital and the effect of regular radiological surveillance for HCC in patients with cirrhosis on the stage at diagnosis and treatment

Materials and methods :

Patients with cirrhosis or chronic liver disease without overt cirrhosis diagnosed with HCC over a period of three years from Dec 2012 till Dec 2015 were included .Since all the patients with suspected HCC undergo imaging and diagnosis of HCC is invariably first made on CT or MR imaging in our institute , search on the HIS and PACS of the radiology reports and image data revealed 184 patients had a suspected diagnosis of HCC . After analysis and application of exclusion criteria 96 cases of HCC with cirrhosis or fibrosis were included , these were consecutive cases over period of three years in whom first diagnosis of HCC was established and had sufficient clinical data and follow up for analysis . 93 cases had cirrhosis identified on imaging while 3 cases were seropositive (2 HBV , one HCV) without overt cirrhosis on imaging but with evidence of fibrosis on elastography (2 cases) or histopathology (one case) .The diagnosis of HCC was based on EASL diagnostic criteria (noninvasive criteria for diagnosis of HCC in cirrhotic patients based on four phase multidetector CT scan or dynamic MRI , lesions beyond 1cm in diameter can be diagnosed if they demonstrate typical hall marks of HCC that is arterial hypervascularity and venous or delayed phase washout) , rest of the lesions were diagnosed on histopathology (20).The exclusion criteria were 1. HCC arising in noncirrhotic nonfibrotic liver 2.cases in which definitive diagnosis of HCC could not be established 3. known HCCs ,being on follow up in our hospital or on treatment in outside hospitals and referred here for additional treatment or assessment 4. cases in whom sufficient clinical data and follow up were not available.The clinical parameters analysed included , the demographic profile of the patient , the etiology of

liver disease and biochemical data relating to AFP levels . The radiological images were reviewed by three radiologists , which included the first and second author . Clinicoradiological staging was done using HKLC staging system . According to this tumors are early (<3nodules <5cm in size) , intermediate (<3nodules <5cm in size with intrahepatic venous invasion ,>3 nodules <5cm or <3nodules >5cm with no venous invasion) or locally advanced (>3 nodules <5cm or >5cm <3nodules with venous invasion , >5cm >3nodules or diffuse tumor) . Stage I consists of early tumor , stage 2 consists of intermediate tumor , for both these curative treatments are recommended (ablation , liver transplant or resection) . Stage3 consists of locally advanced tumors , for which resection or transarterial therapies are indicated while Stage 4 consisting of extrahepatic vascular invasion or metastases with recommendation for systemic therapy and stage 5 consisting of Child C or ECOG 2-4 with recommended liver transplant in early tumors and best supportive care with advanced tumors (2). For our study purpose we included HKLC stage 1, 2 as early stage with curative treatment intent , stage 3 as locally advanced disease but intermediate stage with recommendation of transarterial therapies and stage 4, 5 as late stages.The presence of regular surveillance for HCC was noted . The surveillance when present was in our hospital (an equipped tertiary care centre) or in smaller peripheral speciality hospitals in the region for which our hospital serves as referral centre . Influence of surveillance on the stage of the disease at the time of diagnosis and the resultant treatment instituted was analysed .

Results :Clinical features :

96 patients were diagnosed with HCC in patients with cirrhosis or fibrosis from Dec 2012 till Dec 2015

. 77 (80.20%) were males and 19 (19.79%) females .The mean age was 63.89 years and the age range 41 to 88 years . The etiologies of cirrhosis are depicted in Fig 1 .The AFP levels are depicted in Table 1 . 72.9 % patients had some elevation in AFP levels Table 1.

AFP Levels	No. of Patients (%)
>400	32(33.3)
100-400	11(11.4)
5-100	27(28.1)
<5	26(27)

Radiological features and staging :

The key radiological features are listed in Table 2 .Ultrasonography was the most common modality which first detected the tumors .Of the early HCCs 18 out of 23 cases(78.2%) were detected on USG, while 4 cases were detected on CT and one case on MRI, also 13 out of 19 tumors (68%)less than 3cm were first detected on USG, rest 5 cases were detected on CT. USG failed to pick up diffuse HCCs in 6 out of 14 cases , where further CT or MRI were done to image the portal vein thrombosis detected on USG or because of strong clinical suspicion primarily raised AFP levels .In patients under surveillance USG detected the tumors in 43 out of 54 cases (79%)

Table 2.Radiological characteristics of HCC

Radiological characteristics		No.of patients(%)
Modality*	USG	75(78.1%)
	CT	20(20.8%)
	MRI	1 (1.04%)
Portal vein involvement	Total	52(54.1%)
	Intrahepatic ¹	29 (30%)
	Extrahepatic ²	23 (24%)
Radiological Pattern	Single lesion	33(34.3%)
	Multinodular	40(41.6%)
	Diffuse infiltrative	14((14.5%)
	Combined**	09 (9%)
Hepatic vein & IVC involvement		1(0.1%)
Obvious metastatic disease		13(13.5%)

*Modality which first detected the tumor **Combined diffuse infiltrative and multinodular pattern ¹Involvement confined to intrahepatic portion ²Involvement of main extrahepatic portal vein in thehilum or beyond .

On staging 34(35%) were early stage (HKLC stage 1, 2) 20(21%) were intermediate stage (HKLC stage 3) , 42(44%) were late stage (HKLC stage 4, 5) .

while the values were normal in remaining 27% of cases . The diagnosis of HCC was established by histopathology in 35 cases (36.4%) in 61 cases(63.5%) noninvasive EASL imaging criteria was used

, 23out of 25 (92%cases) in our hospital and in 20 out of 29 (or 69%) in the peripheral hospital settings .Only in 10 cases under regular surveillance , was the lesion first detected on CT and one case in MRI , in 2 of these cases CT was done as additional periodic assessment tool due to patients willingness for additional surveillance , while in the 8 other cases it was done to evaluate mildly elevated AFP levels or to evaluate portal vein thrombosis which had been detected on USG . The additional preferred cross sectional imaging employed for further assessing the lesions detected on USG was CT in 90 cases , MRI was used in 5 patients .

Treatments :

A curative treatment intent was adopted in 36 cases(37.5%) , in 52 cases(54.1%) life prolonging palliative care , in 8 cases(8%) in terminal stage only best supportive care was instituted . The cases with curative treatment intent , 12 cases underwent RFA alone , 12 cases TACE followed by RFA or RFA with combination therapies , 5 cases surgical resection mainly hepatectomies , one case was taken up for liver transplant while an additional 6 cases have been listed in the transplant category awaiting transplantation ,bridging has been done with RFA or TACE . Among those with life prolonging palliative intent 6 cases underwent serial TACE , 8 cases underwent TACE and sorafenib therapy while 38 cases found suitable only for palliative chemotherapy with sorafenib .

Influence of follow up and surveillance :

54 cases(56.25%) had been under surveillance for HCC . The surveillance in our hospital consisted of

periodic imaging(3 or 6monthly) , with USG or in some instances with CT /MRI combined with AFP levels . In the peripheral hospital settings surveillance was considered to be present if the patients were evaluated with periodic USG screening at interval of atleast six months combined with serum AFP evaluation ,over a period of atleast one year . 25 cases(26%) were in surveillance in our hospital (the surveillance period range of 1 to 8 years ,average 3 years) , 29 patients(30%) under surveillance in peripheral hospitals (range 1 to 6 years , average 3.2 years). 42 patients(43.7%) did not receive surveillance or their follow up had been erratic with long periods of lost followup . In fact in 14 patients both chronic liver disease or cirrhosis and HCC were detected for the first time in the concurrent admission.The influence of surveillance on various aspects of the disease is listed in Table 3 .

Table 3 .Influence of surveillance on various aspects of HCC detection .

Parameters	Surveillance in tertiary care (n=25)	Surveillance in peripheral hospitals (n=29)	No regular surveillance (n=42)
Early stage(HKLC 1,2)	15(60%)	13(45%)	6(14%)
Intermediate stage(HKLC 3)	5(20%)	4(13.7%)	11(26%)
Late stage(HKLC4,5)	5(20%)	12(41%)	25(59.5%)
Curative treatments	16(64%)	13(45%)	18(19%)
Palliative life prolonging treatments	8(32%)	15(51.7%)	29(69%)
Transarterial therapies	5(25%)	5(17.2%)	4(9.5%)
Best supportive care only	1(4%)	1(3%)	5(12%)
Portal vein involvement	8(32%)	14(48.2%)	30(71%)
Extra hepatic portal vein involvement	2(8%)	7(24%)	14(33%)
Metastatic disease	0(0%)	2(6.8%)	11(26.1%)

Statistics :

There was statistically significant difference between the surveillance and non surveillance group (P<0.01) with respect to early stage at diagnosis and curative treatments (Tables 4 , 5) . The corresponding variables between surveillance at our hospital (tertiary centre) and peripheral hospital settings did not show statistical significance despite difference in the absolute percentages .

Table 4. Showing association between surveillance and stage of disease

		HKLC			Total
		early	intermediate	late	
surveillance	yes	31	9	14	54
	no	6	11	25	42
Total		37	20	39	96

Chi-square value: 18.99, p-value- <0.001(Statistically significant)

Table5. Showing association between surveillance and type of treatment

		Type of treatment		total
		curative	palliative	
surveillance	yes	29	25	54
	no	8	34	42
Total		37	59	96

Chi-square value- 11.9, p-value<0.001(statistically significant)

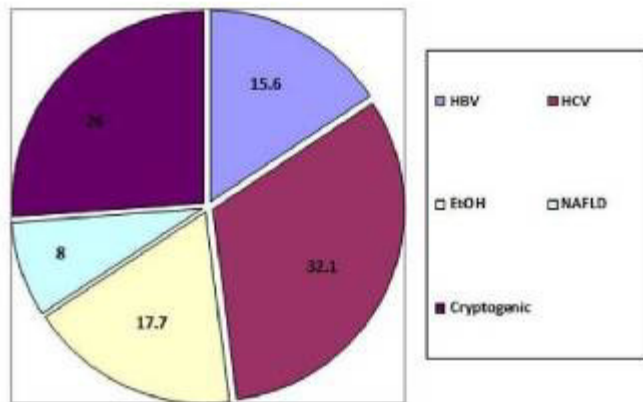


Fig 1 : Etiologies for underlying chronic liver disease or cirrhosis

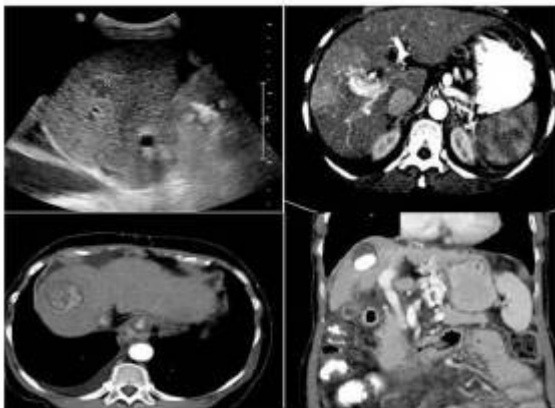


Fig 2 : Top left :small early HCC detected on surveillance USG , top right :an intermediate stage HCC with tumor thrombus in right portal vein , the left and main portal vein were normal , the pt underwent serial transarterial chemoembolization(TACE) , bottom left :early HCC on CT , underwent lipiodol TACE followed by RFA, bottom right : on follow up CT complete necrosis of the lesion with no residual

component , (note bright lipiodol deposited in the inferior aspect of the lesion).

Discussion :

This study provides insights on how HCC is presenting in our country in a tertiary care setting like our hospital . The role of AFP level as a diagnostic or screening tool is controversial ,in 27% the levels were normal and in 28% cases minimally elevated , however there were few cases mostly of diffuse or small early HCCs which could not be detected on USG and elevated AFP level prompted further investigation with higher modalities . Thus AFP levels do collaborate the imaging findings and when elevated prompt evaluation with higher imaging modalities and thus serve as additional surveillance tool in combination with USG . USG works well in HCC detection , it is the most common surveillance tool , is cheap , widely available and free from radiation and is sensitive in detecting small lesions. There were certain diffuse HCCs not identified on USG and were difficult to distinguish from changes of cirrhosis . USG however picked up portal vein involvement which is invariably present in these cases and prompted further imaging . There were few cases who had been under regular surveillance in our hospital who presented in advanced stage , whether these were cases in whom USG failed to detect early tumors is difficult to conclude but can be a possibility . As increased percentage of patients who were on periodic USG surveillance in peripheral hospital settings , presented with intermediate or advanced disease , though difficult to conclude solely based on our study , operator experience may play a role in diagnosing early tumors, an advantage in tertiary care settings having advanced hepatobiliary services , where radiologists are exposed to high volumes of these patients with resultant more expertise in

diagnosing these subtle lesions .The role of MRI in these settings either solely as a screening tool or alternating with USG and its cost effectiveness needs to be established .

The present study on presentation of HCC indicates a favourable trend of increasing number patients being identified at a sufficiently early stage to permit curative treatments , in addition an increasing number of patients presented at intermediate or certain early advanced stage disease such that transarterial therapies could be instituted , which are proven to have significant life prolonging effect and constitute an effective form of palliation in these patients(Fig 2) . The percentage of patients who underwent curative therapies and number of additional patients who underwent effective transarterial therapies , does indicate a favourable trend of increasing utilization and effective surveillance in urban tertiary centers and peripheral hospitals as compared to other studies from our country .Our patient population is however mostly drawn from urban and semiurban areas in an advanced region of our country , with studies in the past (especially multicenter studies)having shown much higher presentation in the advanced stage (17-18).Surveillance in an equipped tertiary care center like ours is most optimal with a well defined surveillance program ,detection of the lesions at early stage and institution of curative or effective palliative treatments including ablations , resections , liver transplants, transarterial therapies and various combination therapies .Surveillance in such an environment effects important variables in HCC including detection of very early lesions , smaller lesions amenable to combination of TACE and RFA , confined multinodular disease amenable to liver transplants and also resectable larger lesions .Portal venous involvement , a crucial prognostic variable

also tends to be uncommon in this subgroup with extrahepatic portal vein involvement being even rarer . The effect of surveillance in peripheral hospital settings is more variable with overall number of patients receiving curative treatments being lesser (45%) compared to those with surveillance in tertiary center (though the difference was not statistically significant) as is those receiving transarterial therapies while those receiving only palliative chemotherapy was higher .Yet the majority of patients even in these settings did receive curative treatments . The cases presenting at an advanced stage form the largest subgroup ,44% . Majority of these patients were under no regular surveillance or were under surveillance previously and had been lost to follow up .Majority of the patients in this subgroup (60%) could undergo only palliative chemotherapy . 26% of these patients presented with metastatic disease . The number of patients undergoing only best supportive care with no tumor directed therapy was also higher in this subgroup (12%) . Only 28% of patients without any surveillance or follow up presented with early or intermediate stage where a curative approach or significant life prolonging therapeutic measures like trans-arterial chemo-embolisation could be undertaken . Hence regular surveillance and follow up for patients with chronic liver disease is essential for early diagnosis of HCC .The usual protocol for surveillance in our hospital consists of biannual or three monthly ultrasounds and AFP levels . Few affording patients also have intermittent periodic MRI or CT instead of USG depending on their preference . This may have some

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advantage as noted in some cases who were under surveillance and had their tumors detected on surveillance CT instead of USG . Early diagnosis and rate of curative treatments are lesser with surveillance in smaller peripheral hospitals as noted above . Having some follow up rather than none is preferable however with cases under no previous follow up and neglected liver disease frequently presenting with advanced disease. With the high end expertise being severely limited in our country , being confined to certain large urban conglomerates only , the peripheral hospitals and smaller centers will continue to have an increasing role in managing different aspects of liver disease including HCC and more prudent would be to developed better coordination between these centers and tertiary hospitals with sensitization programs , training facilities and timely referral .Limitation of this study included , retrospective nature , the intermediate group with surveillance in peripheral smaller hospitals being inhomogenous with respect to the treating facility and the physicians and radiological expertise in diverse clinical settings and lack of long term follow up and ultimate survival benefit of those who underwent different curative treatments

Conclusions :

The study provides insights on how HCC is presenting in our country in an advanced institutional settings. There are clear benefits of regular surveillance and follow up in tertiary care settings .In the absence of regular surveillance and follow up patients usually presents at an advanced stage with limited therapeutic options .

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