How to Cite:
Asmita, A., & Kumar, S. (2022). To study the gallbladder carcinoma with finding under MR imaging. *International Journal of Health Sciences*, *6*(S8), 1175–1188.
https://doi.org/10.53730/ijhs.v6nS8.11322

To study the gallbladder carcinoma with finding under MR imaging

Asmita
Ex. SR, Department of Radiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India
Corresponding author email: drasmitasmita06@gmail.com

Sunil Kumar
Professor and head, Department of Radiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India
Email: anitasunilk@yahoo.co.in

***Abstract*---**Aim: To study the Gallbladder carcinoma with finding under MR imaging. Methods: This prospective study was undertaken at Department of Radiodiagnosis Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow association with departments of Gastromedicine and Surgical Gastroenterology. This study was approved by the institution ethics committee, SGPGI. Study included 30 patients in our study who diagnosed as gall bladder carcinoma. The consent process included an initial examination for MRI compatibility and discussion of major safety criteria. Patients in the age range of 20-75 years with a diagnosis of gall bladder carcinoma and presenting with obstructive jaundice or abdominal mass, who were referred for MRI, were selected for the study. Results: Total 30 patients were included in our study. Pathological confirmation was done in all patients, 28 patients under gone cytopathology from GB mass and in two patients from surgical specimens. Among our 30 patients, the peak incidence age group was between 41 to 60 years. The age of patients ranged from 30 to 70 with a mean age of 51 years for female and 49 years for males with a gender distribution of 11 males (36%) and 19 females (63%). The most common presenting symptom was jaundice (n = 24, 80%) in our study. Associated abdominal pain was also common and occurred in 13 patients (43%). These symptoms were often indistinguishable from gallstone disease and many patients(n=23) were subjected to MR imaging with the presumed diagnosis of cholelithiasis and choledocholithiasis. Most common site for GBC was neck (30%). Conclusion: GBC is a lethal cancer typically because of its early spread and late clinical presentation diagnosed, so early diagnosis is a real challenge. Use of standard T1, T2 sequences and DWI are important in early diagnosis

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
Manuscript submitted: 27 April 2022, Manuscript revised: 18 June 2022, Accepted for publication: 9 July 2022

of GBC. MRCP is quite useful to delineate anatomy and congenital anomalies and level of biliary duct invasion and obstruction which is important for surgical planning and palliative management. In dynamic contrast enhanced study, early irregular enhancement of outer margin is important to differentiate GBC from benign diseases like chronic cholechystitis.

***Keywords*---**GBC, MRI, gallbladder carcinoma.

Introduction

Gall bladder carcinoma (GBC) is the common malignant tumour of the gall bladder mucosa. It is the 5th most common tumour of gastrointestinal tract and accounts for 3% of all the gastro-intestinal tumours.[1-3] GBC demonstrates considerable geographic and gender variation in incidence varying greatly in different parts of the world. While it is more frequent in northern and eastern India, Japan, Chile, China, Eastern Europe and South America, its prevalence is relatively low in many western countries.

It affects women two to six times more frequently than men. The incidence of GBC increases steadily with age. GBC has a peak incidence in the 6th to 7th decades of life. It is one of the obesity associated cancers and positively correlates with prolonged cholelithiasis (gallstone) and cholecystitis. Other risk factors include gallbladder polyps, anomalous pancreaticobiliary duct junction, chemical carcinogens, and chronic infections.[4] Most GBCs are adenocarcinomas (80–95%), and can be papillary, tubular, mucinous, or signet cell type. Less common types of GBC are undifferentiated or anaplastic carcinoma (2–7%), squamous cell carcinoma (1–6%), and adenosquamous carcinoma (1–4%). The five year survival in most of the large series is less than 5%, with a median survival of less than six months.[5-10] Jaundice or an abdominal lump is common, present in 74% of the patients with GBC.[11] The disease is advanced at presentation because the tumour directly involves the liver early and also invades the adjacent organs. The disease clinically mimics the benign gall bladder diseases and it usually escapes detection until late in its course.[3] Primary carcinoma of the gall bladder is an unexpected histopathological finding in 1–3% of the resected specimens of elective cholecystectomy which are performed for benign gall bladder diseases.[5-9] Prior to the era of ultrasonography and Computed tomography (CT) scanning, the rate of the correct pre-operative diagnosis was only 8.6%[5], which has improved considerably to 75–88%, with the use of these newer imaging techniques.[12] Despite being first described more than two centuries ago, there has been little progress in its early diagnosis, prognosis and effective treatment.

Material and Methods

This prospective study was undertaken at Department of Radiodiagnosis Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow association with departments of Gastromedicine and Surgical Gastroenterology. This study was approved by the institution ethics committee, SGPGI.

Study included 30 patients in our study who diagnosed as gall bladder carcinoma. The consent process included an initial examination for MRI compatibilityand discussion of major safety criteria.
Inclusion Criteria: Patients in the age range of 20-75 years with a diagnosis of gall bladder carcinoma and presenting with obstructive jaundice or abdominal mass, who were referred for MRI were selected for the study.
Exclusion criteria: Patients having other malignancy than gall bladder carcinoma. Patients with contraindication for MR imaging.

Methodology

MR Imaging Protocol

All patients were scanned for MRI on 3T MR scanner (Signa HDxt, GE, USA) using TORSO PA abdominal coil with the following sequences. A 3 plane localizer of the upper abdomen was taken. An axial respiratory- triggered T2-weighted (SSFSE) (TR/TE5000/80, echo train length12, section thickness 5 mm) and axial T1 (TR msec /first TE msec/second TE msec150– 200/4.2/1.8, flip angle 80°, section thickness 5 mm) were taken covering from dome of diaphragm till iliac crest.

Respiratory triggered diffusion weighted imaging with a b value of 1000 s/mm2 was done in the axial plane (TR/TE14000/70, echo train length 1, section thickness 5 mm, flip angle 80°). For the evaluation of biliary system Oblique radial steady state fast SE T2-weighted imaging (14 sections) (TR/TE minimum/500, section thickness 40 mm); oblique right anterior steady state fast SE T2-weighted imaging (TR/TE minimum/160, section thickness5 mm); oblique left anterior steady state fast SE T2-weighted imaging (TR/TE minimum/160, section thickness 5 mm); 3D fat- saturated MR cholangiopancreatography (TR/TE 4000/500–600, section thickness 1.4 mm) 3D and 2D SSFSE sequences were used in oblique coronal plane and a 3D slab in radial planes to cover the primary and secondary confluences as well as the lower end of the pancreatobiliary ductal system.

Subsequently multiphase contrast study was done in axial plane covering the entire liver and pancreas. Pre contrast axial 3D fat-suppressed spoiled gradient-echo imaging to cover the entire liver was taken. A breath hold 3D axial lava sequence was used for this using fluoro trigger to begin the sequence in arterial plane after injection of the Gd-contrast at the dose of 0.1mmol/kg body weight at 2-3 mL/sec; axial 3D fat- suppressed spoiled gradient-echo imaging (TR/TE4.5/1.9, flip angle 12°, section thickness 4–5 mm) to cover the entire liver. Portal and hepatic venous phases were acquired after a gap of 15 and 20 seconds in between phases. Additionally a post contrast study was also acquired in coronal plane.

Image Analysis

Analysis of the following structures were done: Gall bladder, liver, pancreas, biliary system, lymph nodes, hepatic and mesenteric arteries, portal venous system and hepatic veins. Details of any abnormality in terms of morphology signal characteristics, enhancement and displacement documented. For liver

lesions, diffusion weighted images (DWI) analysed and ADC (apparent diffusion coefficient) values calculated using company provided software and workstation. ADC of gall bladder mass, adjacent involved liver, normal liver and liver lesions were calculated.

Statistical analysis

All statistical analysis was performed by using SPSS, version 21 (SPSS, Chicago, IL, USA). Sample sizes were estimated using PASS 6.0, and all other statistically analysis were done using SPSS, version 21.0 (SPSS, Chicago, IL, USA). Statistical significance was referred at a confidence level of 0.05. Comparison was done between ADC value of GB masses and adjacent involved liver parenchyma to see difference between ADC value of GB masses and adjacent involved liver parenchyma with an independent student's t test. We also compared MR findings withCT findings by applying the chi-square test.

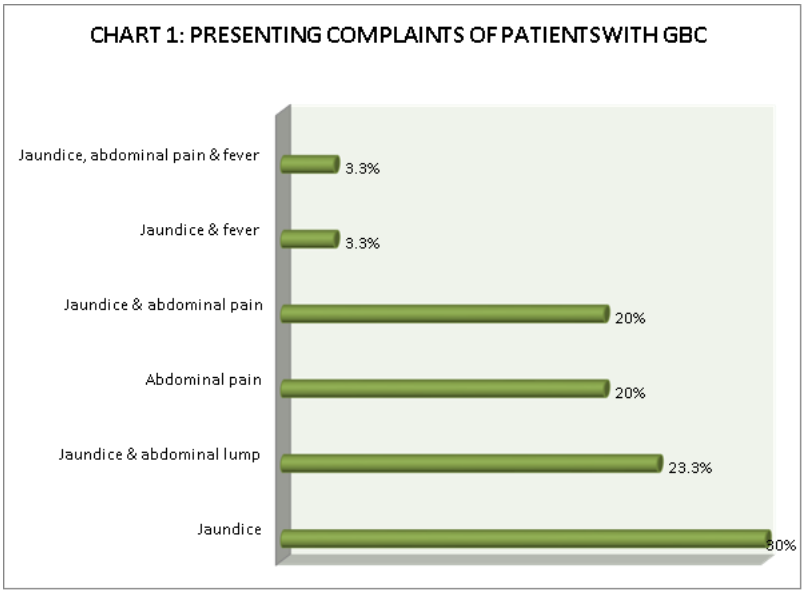
Results

Total 30 patients were included in our study. Pathological confirmation was done in all patients, 28 patients under gone cytopathology from GB mass and in two patients from surgical specimens. Among our 30 patients, the peak incidence age group was between 41 to 60 years. The age of patients ranged from 30 to 70 with a mean age of 51 years for female and 49 years for males with a gender distribution of 11 males (36%) and 19 females (63%). There was definite female preponderance with female: male ratio 1.7:1 in our study. Age and sex distribution is listed in Table 1.

Table 1. Shows age and sex distribution in our thirty patients

AGE GROUP	MALE	FEMALE	TOTAL	PERCENTAGE
20-30	1	0	1	3.3
31-40	2	4	6	20
41-50	2	6	8	26.7
51-60	4	4	8	26.7
61-70	2	5	7	23.3
TOTAL	11	19	30	100

The most common presenting symptom was jaundice (n = 24, 80%) in our study. Associated abdominal pain was also common and occurred in 13 patients (43%). These symptoms were often indistinguishable from gallstone disease and many patients(n=23) were subjected to MR imaging with the presumed diagnosis of cholelithiasis and choledocholithiasis. The presenting complaints of patients are depicted in Chart 1.



Most common site for GBC was neck (30%). The sites of GB masses in our all thirty patients are listed in Chart 2 and Table 2.

Table 2. Shows different sites of GBC in our patients (n=30)

Site of GBC	No of Cases	Percentage
Neck	9	30
Body	7	
		23.3
GB fossa	6	20
Fundus	5	16.7
Body and fundus	3	10

In our study the predominant patterns of GBC were of mass-forming (n=21, 70%) and asymmetrical wall thickening (n=9, 30%). Among mass forming pattern, GB was replaced by mass in 28.5 % (n=6/21) cases.

Characteristic of GBC on MRI

Signal intensity on T1WI and T2 WI

The GBC showed as predominantly T1 heterogeneously hypointense (n=26; 86.7%) and iso to hypointense (n=4; 13.3%) and T2 heterogeneously hyperintense (n=17; 56.7%) and iso to hyperintense (n=13; 43.3%) (Table .3)

Table 3. Shows signal intensity of GBC on T1WI and T2 WI in our patients (n=30)

Signal characteristic of GBC on MRI	No. of patients	Percentage
MR SI ON T1 WI		

1.Heterogenously hypointense 2.Iso to hypointense	26 4	86.7% 13.3%
MR SI ON T2 WI 1. Heterogenously hyperintense 2.Iso to hyperintense	 17 13	 56.7% 43.3%
Total	30	100%

Diffusion weighted imaging

All thirty patients GB masses revealed bright signal on diffusion weighted imaging as compared to control normal liver parenchyma and restriction on ADC map. The mean ADC value was 1.30 ± 0.18× 10^{-3} mm^2/s with range from 0.96 to 1.76× 10^{-3} mm^2/s for GBC. The box plots of the ADC values of GBC and normal liver parenchyma are shown in Fig.1.

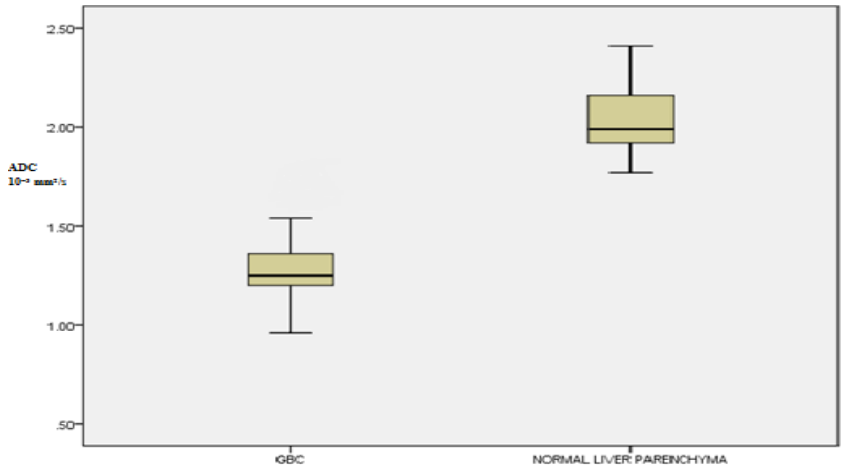


Fig. 1: Box and whisker plot of mean ADC values for GBC and normal liver parenchyma. Box represents data from the 25th to the 75th percentile (middle 50% of observations); the horizontal line through each box represents the mean value. The mean ADC values of the GBC and normal liver parenchyma showed significant differences ($p > 0.05$).

Dynamic contrast enhanced imaging

On contrast enhaced multiphase dynamic sequences, in 28 patints of GBC (n=28) showed predominatly irregular heterogenous enhancement. Two patients showed predominatly irregular homogenous enhancement. All twenty eight patients showed early arterial and persistent delayed enhancememt. Time intensity curve was plotted with mean MR units of precontrast, arterial, portal and hepatic venous phase, showed early arterial and also persistent in hepatic venous phase (Fig.2). The mean value of SI units in different phase of dynamic contrast study are listed in Table 4 and 5.

Table 4. Shows mean of SI units of GB masses in different phase of dynamic contrast study

SI (MR units) of GBC in different phase	No. of patients	Minimum	Maximum	Mean		Std. Deviation
				Mean	Std. Error	
Precontrast phase	3	1	6	3	2	111.5
	0	52.00	23.40	05.44	0.36852	6298
Arterial phase	3	2	1	5	4	239.5
	0	53.00	079.90	78.33	3.73728	5895
Portal phase	3	2	1	6	5	288.5
	0	69.00	333.00	61.52	2.68228	5273
Hepatic phase	3	2	1	6	5	289.7
	0	79.00	360.20	83.75	2.89724	3012

Table 5. Shows mean of SI units of normal liver parenchyma in different phase of dynamic contrast study in our patients (n=30)

SI (MR UNITS) of normal liver in different phase	No. of patients	Minimum	Maximum		Mean	Std. Deviation
				Mean	Std. Error	
Precontrast phase	3	2	6	3	1	95.2
	0	44.00	70.00	76.0833	7.38133	0146
Arterial phase	3	3	1	6	3	197.
	0	20.00	090.00	19.8300	6.02786	33272
Portal phase	3	4	1	8	4	245.
	0	70.10	601.00	44.0500	4.75724	14551
Hepatic phase	3	4	1	7	4	230.
	0	45.90	519.00	86.8300	2.14938	86168

Other organ involvement

Duodenum and hepatic flexure involvement seen in 23.3% (n=7/30) & 10% (n=3/30) respectively. Ascites, omental nodule, bony metastasis, lung metastasis were seen in 23.3% (n=7), 10% (n=3), 3.3% (n=1), 6.7% (n=2) cases respectively (Table 6).

Table 6. Shows different other important finding in GBC in our patients

OTHER FINDING	NO. OF CASES	%
Duodenum involvement	7	23.3%
Hepatic flexure involvement	3	10%
Ascites	7	23.3%
Omental nodule/ thickening	3	10%
Bony metastasis	1	3.3%
Lung metastasis	2	6.7%

Associated risk factor

In associated risk factor, 50% (n=15) showed cholelithiasis and 10% (n=3)cases were associated with choledochal cyst.

Comparison with MDCT

In present study 21 patient also underwent for CT multiphasic contrast angiography,we compared findings for hepatic invasion, biliary system invasion, lymph nodal metastasis and vascular invasion. MR showed 90.5 % for hepatic invasion, 90.5% for bile duct invasion, 66.7% for venous invasion, 66.7% for lymph node metastasis and 28.6% for arterial invasion, while MDCT was showing 90.5 % for hepatic invasion, 90.5% for bile duct invasion, 57.1% for arterial invasion, 66.7% for venous invasion, and 66.7% for lymph node metastasis (Table 7). In three patients (3/21) arterial system could not be assessed but CT revealed invasion of right hepatic artery in all three patients.

The MRI findings in hepatic invasion, biliary invasion, venous and lymph nodal metastasis revealed significantly correlation with MDCT findings ($p < 0.05$), However arterial syetem was not consistent with MDCT finding ($p > 0.05$). In our study, MRI including MRCP, DWI and dynamic contrast study showed similar results as compared to MDCT in detecting hepatic, biliary, lymph nodal and portal veins involvement with no stastically significant difference.

Table 7. Shows comparisons between CT and MRI findings in 21 patients

FINGINGS	MRI (% of cases)	CT(% of cases)
GB MASS	100% (n=21)	100% (n=21)
ADJACENT LIVER INVASION	90.5% (n=19/21)	90.5% (n=19/21)
LYMPH NODE	66.7% (n=14/21)	66.7% (n=14/21)
BILIARY INVASION	90.5% (n=19/21)	90.5% (n=19/21)
ARTERIAL INVASION	28.6% (n=6/21)	57.1% (n=12/21)
PV INVOLVEMENT	66.7% (n=14/21)	66.7% (n=14/21)

Gall bladder carcinoma: shows mass formingmorphological pattern

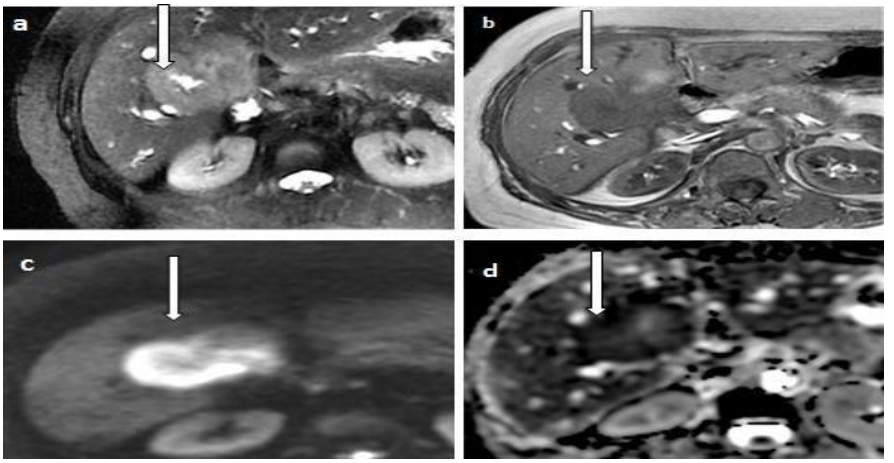


Fig. 2: MRI of a 60-year-old female of GBC. Axial T2 image (a) shows an ill defined hyperintense signal intensity mass (arrow) in GB fossa which is hypointense (arrow) on axial T1-weighted (b) image. The DWI image (c) (b=1000 s/mm2) (arrow) shows hyperintense signal and corresponding ADC map (d) shows diffusion restriction (arrow).

Dynamic contrast enhanced imaging shows enhancement pattern in gall bladder carcinoma

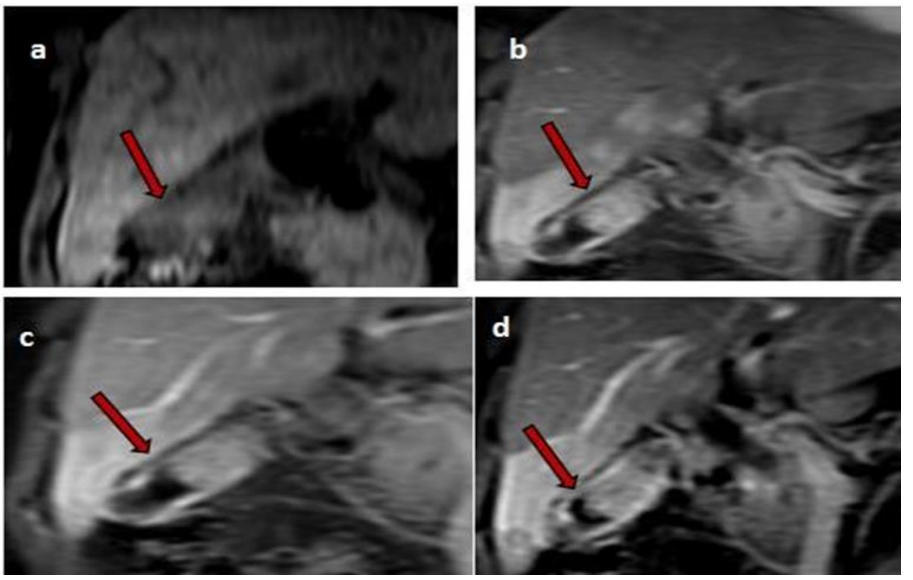


Fig. 3: MRI of a 52-year-old female of GBC. Precontrast coronal dynamic contrast image (a) shows hypointense mass in body of the GB (arrow). On post contrast coronal dynamic arterial phase (b) shows avid enhancement of the mass (arrow) shows with persistent enhancement in portal venous phase (c) and hepatic venous phase (arrow) (d).

Discussion

Gall bladder carcinoma is the common malignant tumour of the gall bladder mucosa.[1-3] Affected patients usually present with nonspecific symptoms of jaundice, abdominal pain, which can be identical to symptoms of benign gall bladder disease, such as cholelithiasis and choledocholithiasis.[13] Those with obstructive jaundice usually present in advanced stages of the disease.[3] In our study, the most common presenting symptom was jaundice (n = 24; 80%), possibly due to the fact that this was a population that presented at a tertiary referral centre in advanced stage. Associated abdominal pain was also common and occurred in 13 patients (43%). These symptoms are often indistinguishable fromgallstone disease and many patients were subjected to MRI imaging with the presumed diagnosis of cholelithiasis, choledocholithiasis.

Histopathologically, approximately 90% of GBCs are adenocarcinomas.[3] In our study all 30 cases were confirmed as adenocarcinoma of GB. The exact etiology of carcinoma GB is unknown; however, several associated risk factors have been identified. The closest association is with cholelithiasis, which is seen in 65 –95 % of patients as reported in different series.[4] Other factors related are calcification of GB wall (porcelain GB), genetic factors, anomalous pancreatic biliary duct junction, choledochal cyst, infections and environmental carcinogens.[1-3] In our study, 15 (50%) patients had associated gallstones and 3 (10%) patients had associated choledochal cyst (type 1).

GBC is three times more common in women than men and typically occurs in patients 65 years and older.[14] In the present study, the mean age for the entire group was 51 years, with a gender distribution of 11 males (36%) and 19 females (63%). Maximum patients were between 36 -50 age group with female predominance (n= 8/30; 26%). The male: female ratio was 1:1.7 (F > M) and the mean age of presentation was 51 years for females and 49 years for males, which is almost a decade less than the reported mean age in western literature. In our study the predominant patterns of GBC were of mass-forming (n=21; 70%) and asymmetric wall thickening (n=9; 30%), similar to previous studies.[15] Gallbladder cancer usually arises in the fundus or neck, but its rapid spread may obscure the site of origin.[16] In our study, the commonest site for GBC was neck (n=9; 30%). In six patients (20%), gall bladder fossa was replaced by mass so exact site of origin was obscured.

Signal characteristic on T1WI and T2 WI

GBC is typically T1 hypointense and T2 hyperintense compared to the surrounding liver parenchyma. Our study shows signal characteristics of GB mass as T1 hypointense (n=26; 86.7%) and iso to hypointense (n=4; 13.3%) and T2 heterogeneous hyperintense (n=17; 56.7%) and iso to hyperintense (n=13; 43.3%) consistent with published literature.[17]

Diffusion weighted imaging

Our all thirty cases GB masses revealed bright signal on diffusion weighted imaging and restriction on ADC map. We found lower ADC value with a mean

ADC value of 1.30 ± 0.18× 10^{-3} mm^2/s with range from 0.96 to 1.76 × 10^{-3} mm^2/s for GBC as opposed to 2.06 ± 0.22 × 10^{-3} mm^2/s with range 1.77 to 2.41 × 10^{-3} mm^2/s for control normal liver parenchyma. Sugita et al. [18] reported, a mean ADC values for GBC was 1.28 ± 0.41 × 10^{-3} mm^2/s, as compared to control benign gallbladder lesions (1. 92± 0.21) × 10^{-3} mm^2/s) with mean sensitivity and specificity of 83% and 100%, respectively.

Dynamic contrast enhanced imaging

The enhancement of GBC after the administration of gadolinium based contrast agent is suggestive of vascularity unlike sludge which can be a mimicker of GBC masses especially polydoidal form of GBC. All gallbladder cancers show enhancement in early arterial phase and persistent in hepatic venous phase. Xanthogranulomatous cholecystitis, an uncommon form of chronic cholecystitis, is notorious for mimicking GBC, both clinically and on imaging. Xanthogranulomatous cholecystitis show slight enhancement at early phase and strong enhancement at late phase on dynamic study, this enhancement differentiates from GBC.[19]

In 28 patients of our patients, gall bladder lesions showed heterogeneous irregular enhancement and in remaining two patients showed predominatly homogenous irregular enhancement. In all patients GB lesions showed early arterial phase enhancement and persistent in the delayed hepatic venous phase also. These findings correlate to previous studies.[20,21]

According to Yoshimitsu et al (2012), all gall bladder cancers show enhancement after the administration of gadolinium based contrast agent. In the early phase of dynamic contrast-enhanced imaging, the outer margin of enhancement is irregular, whereas it appeared smooth in chronic cholecystitis. The late phases of enhancement are less useful because of the spread of enhancement toward the outer wall in both chronic cholecystitis and gallbladder carcinoma. This early irregular enhancement of outer margin is important to differentiate GBC from benign diseases like chronic cholechystitis.[17, 19]

Other organ involvement

Duodenum and hepatic flexure involvement seen in 23.3% (n=7/30) & 10% (n=3/30) respectively. Ascites and omental nodules were seen in 23.3% (n=7), 10% (n=3) cases respectively.[21]

Comparison of mri findings with MDCT

In the present study 21 patients underwent for CT multiphasic contrast study also. MR showed hepatic invasion, bile duct invasion, lymph node metastasis, venous invasion and arterial invasion in 90.5%, 90.5%, 66.7%, 66.7 % and 28.6% cases respectively while MDCT showed hepatic invasion, bile duct invasion, lymph node metastasis, venous invasion and arterial invasion in 90.5 %, 90.5%, 66.7%, 66.7% and 57.1% cases respectively.

These results was similar to study by Kim et al.[22] The arterial system was not fully assessed in three patints but CT revealed invasion of right hepatic artery in all three patients. We compared the MRI findings for biliary invasion, venous invasion and lymph nodal metastasis which revealed significant correlation with MDCT findings ($p < 0.05$). However arterial system was not well evaluated compared to MDCT findings ($p > 0.05$). The reason for this descrepancy is likely due that as sequences used in our study were tailored for dynamic evaluation and so for were not angiographic sequences. In our study, MRI including MRCP, DWI and dynamic contrast study showed similar results as compared to MDCT in detecting hepatic, biliary, lymph nodal and portal veins involvement with no stastically significant difference.

Conclusion

GBC is a lethal cancer typically because of its early spread and late clinical presentation diagnosed, so early diagnosis is a real challenge. Use of standard T1, T2 sequences and DWI are important in early diagnosis of GBC. MRCP is quite useful to delineate anatomy and congenital anomalies and level of biliary duct invasion and obstruction which is important for surgical planning and palliative management. DWI is useful in differentiating liver metastatic lesions from other benign lesion on basis of signal intensity on DWI and ADC values. DW MR imaging has the potential to be a reasonable alternative technique to contrast-enhanced imaging in patients who cannot receive gadolinium-based contrast agents/iodinated contrast agents. In dynamic contrast enhanced study, early irregular enhancement of outer margin is important to differentiate GBC from benign diseases like chronic cholechystitis.

References

1. Veloso MGP, Rodrigues DN. Gallbladder carcinoma: a clinicopathological studyof 24 cases. J Bras Patol Med Lab 2011;47:439-44.
2. Shivani MH. Surgical management of gall bladder carcinoma. European Gastroenterology Review 2005;17:1-5.
3. Symiyoshi KN, Chijiiwa K. Pathology of carcinoma of the gall bladder. World J Surg 1991;15:315-21.
4. Gore RM, Yaghmai V, Newmark GM, Berlin JW, Miller FH. Imaging benign and malignant disease of the gallbladder. Radiol Clin North Am 2002;40: 1307–1323..
5. Shukla VK, Khandelwal C, Roy SK, Vaidya MP. Primary carcinoma of the gall bladder: A review of a 16-year period at the University Hospital. J Surg Oncol 1985;28:32-35.
6. Hamrick RE, Liner FJ, Hastings PR, Cohn I Jr. Primary carcinoma of the gall bladder. Ann Surg 1982;195:270-73.
7. Kwon SY, Chang HJ. A clinicopathological study of unsuspected carcinoma of thegall bladder. J Korean Med Science 1998; 12(6):519-22.
8. Thorbjarnarson B. Carcinoma of the gall bladder and acute cholecystitis. Ann Surg 1960;151:241-44.
9. Kokudo N, Makuuchi M, Natori T et al. Strategies for the surgical treatment of gall bladder carcinoma based on the information which was available before theresection. Arch Surg 2003;138:741-50.

10. Khan RA, Wahab S, Khan MA, Siddiqui S, Maheshwari V. Advanced presentation of gall bladder cancer: An epidemioclinicopathological study to evaluate the risk factors and to assess the outcome. J Pak Meds Assoc 2010;60:217-19.
11. Varma V ,Gupta S, Soin A, Nundy S. Does the Presence of Jaundice and/or a Lump in a Patient with Gall Bladder Cancer Mean that the Lesion Is Not Resectable. Dig Surg 2009;26:306-311.
12. Balaroutsos C, Bastonnis E, Karamanakos P, Golematis B. Primary carcinoma of the gall bladder; an analysis of 22 cases. Ann Surg 1971;40:605-08.
13. Zatonski WA, Lowenfels AB, Boyle P, et al. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. J Natl Cancer Inst 1997; 89:1132– 1138.
14. Levin B. Gallbladder carcinoma. Ann Oncol 1999; 10:129–130.
15. Stahlberg F, Brockstedt S, Thomsen C, Wirestam R. Single-shot diffusion-weighted echo-planar imaging of normal and cirrhotic livers using a phased-array multicoil. Acta Radiol 1999; 40:339.
16. Sherlock S, Dooley J. Tumours of the gallbladder and bile ducts. In: Sherlock S, Dooley J, eds. Diseases of the liver and biliary system. 11th ed. Malden, Mass:Blackwell, 2002; 647– 656.
17. Tseng JH, Wan YL, Hung CF, et al. Diagnosis and staging of gallbladder carcinoma. Evaluation with dynamic MR imaging. Clin Imaging 2002; 26:177–182.
18. Sugita R, Yamazaki T, Furuta A, et al. High b-value diffusion-weighted MRI fordetecting gallbladder carcinoma: preliminary study and results. Eur Radiol 2009;19(7):1794e8.
19. Demachi H, Matsui O, Hoshiba K, Kimura M, Miyata S, Kuroda Y. Dynamic MRI using a surface coil in chronic cholecystitis and gallbladder carcinoma: radiologic and histopathologic correlation. J Comput Assist Tomogr 1997; 21:643 – 651.
20. Kaza RK, Gulati M, Wig JD, Chawla YK. Evaluation of gall bladder carcinoma with dynamic magnetic resonance imaging and magnetic resonance cholangiopancreatography. Australas Radiol 2006 ; 50(3):212-7.
21. Yoshimitsu K, Nishihara Y , Okamoto D et al. Magnetic resonance differentiation between T2 and T1 gallbladder carcinoma: significance of subserosal enhancement on the delayed phase dynamic study. Magn Reson Imaging 2012;30(6)854-859.
22. Kim JH, Kim TK, Eun HW, et al. Preoperative evaluation of gallbladder carcinoma: efficacy of combined use of MR imaging, MR cholangiography, and contrast-enhanced dual-phase three-dimensional MR angiography. J Magn Reson Imaging 2002;16:676enhancement on the delayed phase dynamic study. Magn Reson Imaging 2012;30(6)854-859.
23. Kim JH, Kim TK, Eun HW, et al. Preoperative evaluation of gallbladder carcinoma: efficacy of combined use of MR imaging, MR cholangiography, and contrast-enhanced dual-phase three-dimensional MR angiography. J Magn Reson Imaging 2002;16:676 .
24. Thaib, P. K. P., & Rahaju, A. S. (2022). Clinicopathological profile of clear cell renal cell carcinoma. *International Journal of Health & Medical Sciences*, *5*(1), 91-100. https://doi.org/10.21744/ijhms.v5n1.1846

25. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Health and treatment of diabetes mellitus. *International Journal of Health Sciences*, *5*(1), i-v. https://doi.org/10.53730/ijhs.v5n1.2864