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ORIGINAL RESEARCH

Pattern of Computerized Tomographic Findings in Suspected Gallbladder Cancer in Nigeria

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Abstract

Background: Gallbladder (GB) cancer is a rare malignancy with a variable incidence worldwide. Imaging detection at an early stage is elusive. Preoperative imaging for tumour recognition and non-invasive staging is essential to triage patients to appropriate care.

Objectives: To describe the CT imaging findings of GB cancer among Nigerians.

Methods: A retrospective review of the CT images of 15 patients who had gall bladder carcinoma between January 2015 and June 2017 at a private diagnostic facility in Lagos was done.

Results: The age of the patients ranged from 39 to 73 years with a mean age of 60.9 years. The male to female ratio was 1:4.3. Clinical presentations included abdominal pain (61.5%) and jaundice (38.5%). Irregular GB wall thickening (61.5%) and focal mass lesions in the GB (38.5%) were the main features on imaging while 38.5% had associated gall stones. Infiltration of the adjacent liver was found in 76.9% and 60 % of those who had local infiltration of the liver also had intrahepatic metastasis.

Conclusion: A majority of gall bladder cancer cases are still diagnosed in their late stages. CT scan readily delineates regional spread into adjacent organs which may be obscured in other imaging modalities due to adjacent bowel gas.

Keywords: Cancer, Computerized Tomography, Gallbladder, Gallstones, Liver metastasis.

Introduction

Gallbladder cancer is a rare malignancy with a variable incidence worldwide. [1-3] The incidence follows a geographic pattern that correlates with the prevalence of gallstone disease and the highest incidences are found in India, Asia, Eastern Europe and South America. [4,5] It has a worldwide incidence of 1-2/100,000 and is responsible for nearly 7000 deaths annually in the

United States. [6,7] It is the eighth commonest gastrointestinal cancer in Nigeria.[8]

Although, rare cancer, it is the commonest biliary tract cancer and has a higher incidence than other extrahepatic biliary cancers. [9,10] Gallbladder carcinoma has a peak incidence in the sixth and seventh decades of life and is three to five times more predominant among females. [6] A study in the western part of Nigeria reported a male to female ratio of 1:2 while a more recent study in

the same region showed that gallbladder cancer affected women seven times more frequently than men. [11,12]

The gallbladder is a pear-shaped sac attached to the extrahepatic bile duct by the cystic duct. It is variable in size but normally measures up to 10cm in length and 3cm in diameter. The thickness of the wall varies with the degree of distension and is usually less than 3mm in diameter. [13] Early detection and diagnosis of gallbladder carcinoma are difficult because most patients present with non-specific findings of right upper quadrant pain, malaise, weight loss, jaundice, anorexia, and vomiting. [6] However, the risk is higher in those with chronic inflammation following cholelithiasis. Other precancerous lesions include porcelain gallbladder, sclerosing cholangitis, anomalous pancreaticobiliary junction and exposure to carcinogens.[7] It is diagnosed late usually following direct extension into adjacent organs and local lymph node metastasis resulting in high morbidity and mortality.

In cases of suspected gallbladder disease, ultrasonography is often the first imaging technique, because it is cheap, readily available and it excellently depicts the wall and the contents of the gallbladder. However, complete assessment of the gallbladder may be limited by bowel gas and posterior acoustic shadowing in the presence of stones. Assessment for distant metastasis may also be difficult. [3] Endoscopic ultrasound (EUS) consists of an endoscope equipped with an ultrasound probe and has recently played an increasing role in the diagnosis of gall bladder disease. It provides high-resolution images that can be useful for staging gallbladder carcinoma

Other cross-sectional imaging techniques including computed tomography (CT) and magnetic resonance imaging (MRI), can overcome these drawbacks. On computed

tomography, the density of the gallbladder lumen is generally that of water (0 to 20 Hounsfield Units). Computed tomography provides definite information regarding the invasion of the adjacent organs by the tumour, distant metastasis and delineation of the biliary tree. These are essential for non-invasive staging of gallbladder tumours, and triage patients for appropriate care.

MRI with magnetic resonance cholangiopancreatography (MRCP) is also useful and reliable in the staging of advanced gallbladder carcinoma and is sensitive in the detection of liver invasion. It is also sensitive in the detection of hepatic and lymph nodal metastasis but may be difficult to delineate invasion into the duodenum. However, MRI is very expensive and not readily available in a resource-constrained environment. The presentation of gallbladder carcinoma on cross-sectional imaging has three main patterns which include i) diffuse or focal mural thickening ii) intraluminal polypoid mass larger than 2cm and iii) subhepatic mass replacing or obscuring the gallbladder, often invading the adjacent liver parenchyma. [6,14]

This study described the CT imaging findings of gallbladder cancer, including the patterns of clinical presentation and the extent of invasion of adjacent organs in a Nigerian population.

Methods

This retrospective study included all the patients who presented for abdominopelvic computerized tomography (CT) examination at then Clinix Healthcare Limited, a private diagnostic facility in Lagos, Nigeria between January 2015 and June 2017. The facility serves as a radiologic referral base for many hospitals in south-west Nigeria.

The computed tomographic examinations were performed from the level of the dome of the diaphragm through the pubic symphysis using a 64 slice CT scanner (Siemens Somatom Perspective SN 59543, Siemens Healthineers India) and a dual slice CT scanner (Siemens Somatom Spirit, Siemens Healthineers India). The abdominal CT examinations of children were excluded. No study was excluded on account of poor image quality.

Triphasic CT examination was performed in all the patients and this included non -contrast scans, followed by contrast-enhanced scans (oral, arterial and venous phases). Iopamidol was injected at a dose of 80- 100ml (300mg of iodine per millilitre) and a rate of 2-3ml/s. Scanning was performed during the arterial and portal venous phases as determined with bolus tracking and automated triggering technology. All the reports of the abdominal examination were written by two experienced radiologists and were archived in the Radiology Information system.

The data of all the patients diagnosed by multidetector CT as carcinoma of the gallbladder was further extracted from the archived Radiology Information system. The age, gender and clinical features as documented on the radiology information sheet were retrieved. The archived CT images of the patients were also examined and re-interpreted by the researchers to ensure that no radiological feature was missed. The criteria for gallbladder carcinoma included diffuse or mural thickening of the gall bladder wall, intraluminal polypoidal mass larger than 2cm and subhepatic mass replacing or obscuring the gallbladder.

The patterns of gallbladder lesions were documented in a structured database. The common bile duct and intrahepatic biliary ducts were examined. The invasion of adjacent organs

and lymph node and distant metastasis were noted. The American Joint Committee on Cancer (AJCC) TNM system [6] was used to describe the stages of gallbladder cancer in the patients. The principle of Helsinki was adhered to in detail during the research. The privacy of the patients was protected by anonymizing all the data. Ethical approval for the research was obtained from the Health Research Ethics Committee of the Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria (OOUTH/HREC/250/2019AP).

The data were analysed using IBM-SPSS 20.0 (Chicago IL) software. Analysis of data was done using descriptive statistics. The results were presented as frequencies and percentages while continuous variables were presented as means and standard deviations.

Results

A total of 1,191 abdominopelvic CT examinations were carried out during the period of study. Of these, only 15 (1.25%) patients had CT features of gallbladder cancer. The patients were aged between 39 and 73 years with a mean of 60.3 ± 9.7 years. The mean age for the males was 52 ± 6 years and that of the females was 62.4 ± 9.5 years. The male to female ratio was 1:4 and the modal age group was 61 to 70 years with 6 female patients. All the patients (100%) presented with vague upper abdominal pain while 53.3% had associated jaundice.

On abdominal CT, 7 (46.7%) of the patients had an irregularly thickened gallbladder wall while 40% had a focal mass within the gallbladder and 2 (13.3%) had mildly thickened gallbladder wall with the gallbladder replaced by heterogeneously enhancing hypodense mass. (Table I, Figures 1 and 2).

Table I: Age distribution in relation to the pattern of gallbladder mass on Computerized Tomography examination

Age (Years)	Group	Mildly Thickened Gallbladder wall		Irregularly thickened Gallbladder wall		Focal mass with Gallbladder		Total
		Male	Female	Male	Female	Male	Female	
31-40		-	-	-	1	-	-	1
41-50		-	-	1	-	-	-	1
51-60		-	1	1	-	1	1	4
61-70		-	-	-	4	1	1	6
71-80		-	1	-	-	-	2	3
Total		-	2	2	5	2	4	15

Of the 15 patients, 14 (93.3%) had stages III and IV diseases with infiltration of the adjacent liver and other abdominal organs. Twelve (80%) patients had gallbladder wall masses that had infiltrated the liver. (Table II and Figure 3). Six (40%) patients had masses that had infiltrated the adjacent organs, namely the duodenum, antrum

of the stomach and the colon. Three (20%) patients did not have associated hepatic infiltration. Only one (6.6%) male patient, had an irregularly thickened wall without any feature of infiltration which was classified as a stage II disease. He had surgery and histology confirmed adenocarcinoma of the gallbladder.

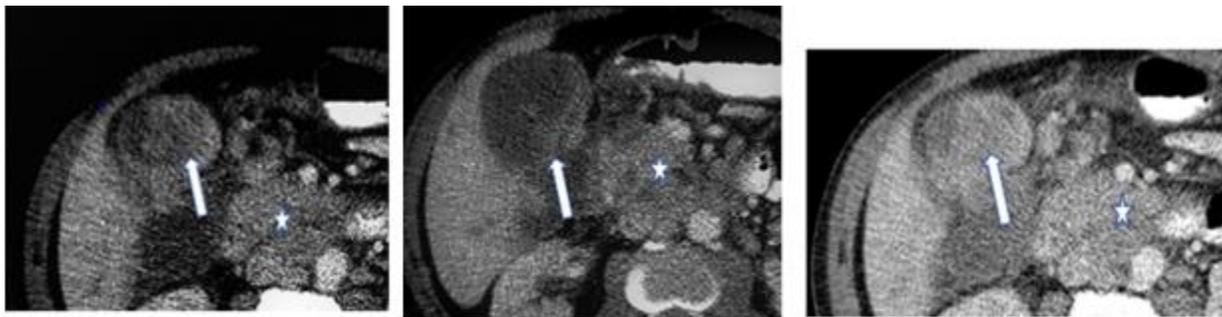


Figure 1: Post-contrast image of the abdomen showing the gall bladder of a 58-year old male with focal enhancing mass in the fundal region (white arrow). Multiple enhancing periportal nodes are noted (white star).

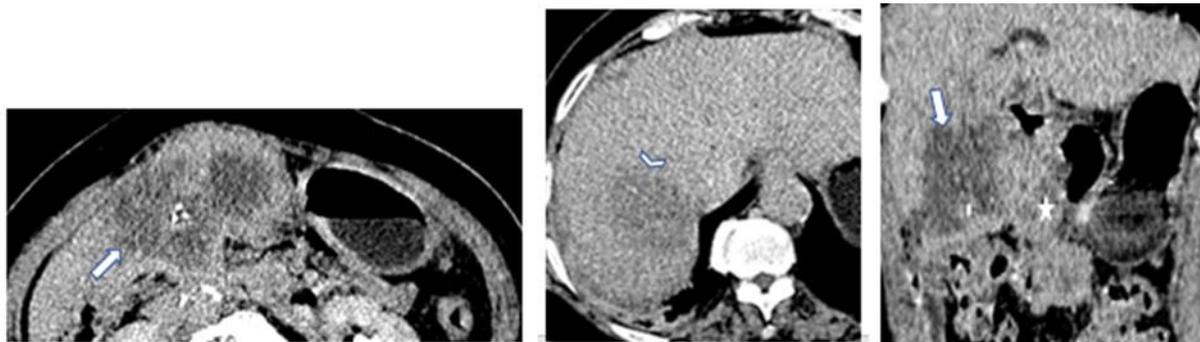


Figure 2: CT scan of the gall bladder of a 72-year old female with gall bladder replaced by minimally enhancing hypodense mass. Associated irregularly thickened wall noted (white arrow). Multiple stones are seen centrally. Infiltration of the adjacent liver, antrum of stomach and colon (star) and hepatic metastasis noted (arrowhead).

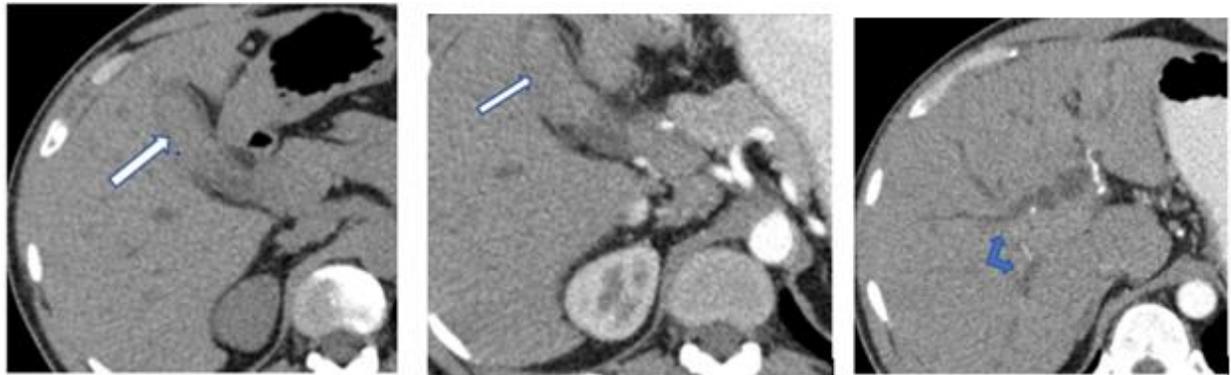


Figure 3: Pre and post-contrast CT image of the gall bladder of a 46-year-old male with irregularly enhancing mass eccentrically located (white arrow). Infiltration of the cystic duct with dilated common bile duct (star) and intrahepatic ducts (blue arrow).

Table II: Gender and age-group distribution of stages of gallbladder carcinoma

Age Group (Years)	Sex	Stage II	Stage III	Stage IV	Total
31-40	Male	-	-	-	-
	Female	-	1	-	1
41-50	Male	1	-	-	1
	Female	-	-	-	-
51-60	Male	-	2	-	2
	Female	-	1	1	2
61-70	Male	-	-	-	-
	Female	-	4	2	6
71-80	Male	-	-	-	-
	Female	-	1	2	3
Total		1	9	5	15

The gallbladder was distended in 8 (53.3%) patients and gallstones were detected in 6 (40%) of the patients but there was no CT feature of cholecystitis. Of these, 2 of the 3 (66.7%) males patients had gallstones compared to 33.3% of the females. (Figure 4). Metastatic hepatic deposits were detected in 8 (53.3%) patients and 6 (40%) of these patients had associated ascites while 3 (20%) had pleural effusion. Metastatic abdominal lymph nodes in the porta hepatis and para-aortic area were found in 11 (73.3%) patients while metastatic pulmonary nodule was detected in only 1 (6.7%) patient but there was no case with an osseous vertebral deposit (Table III).

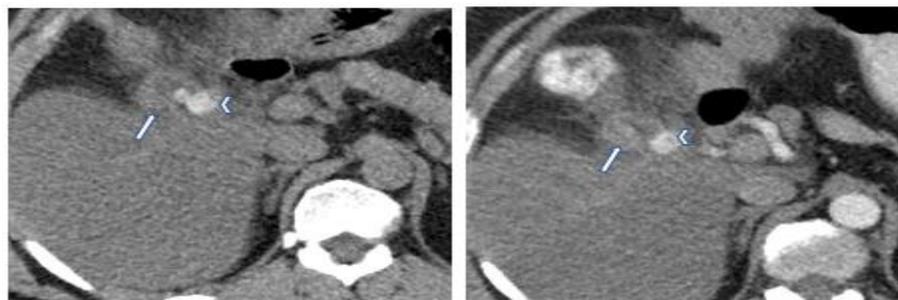


Figure 4: Pre- and Post-CT examination of the gall bladder of a 52-year old male with minimally enhancing, irregularly thickened gall bladder wall (white arrow). Multiple hyperdense stones are noted within it. (White arrowhead).

Table III: Age distribution in relation to other Computerized Tomographic (CT) features of Gallbladder cancer

Age Group (Years)	Infiltration of adjacent Liver		Infiltration of adjacent abdominal organs		Metastatic Hepatic deposits		Gall Stones		Metastatic lymph nodes	
	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent
31-40	1	-	1	-	-	1	-	1	1	-
41-50	-	1	-	1	-	1	1	-	-	1
51-60	2	2	2	2	2	2	2	2	2	2
61-70	6	-	2	4	4	2	1	5	5	1
71-80	3	-	1	2	2	1	2	1	3	-
Total	12	3	6	9	8	7	6	9	11	4
	(80%)	(20%)	(40%)	(60%)	(53.3%)	(46.7%)	(40%)	(60%)	(73.3%)	(26.7%)

Discussion

Gallbladder cancer is uncommon in Nigeria and from hospital-based studies, it accounts for 0.3% of cancer cases seen over 21 years [12] while Akute *et al.* [11] documented 20 cases over 14 years. In the present study, 15 cases of gallbladder cancer were documented over 18 months. The relatively high number of cases may be ascribed to the fact that the study was carried out in a diagnostic facility which is a referral centre for many hospitals in southwest Nigeria.

In this study, gallbladder cancer affected women four times more frequently than men. This corroborated female preponderance of gallbladder cancer noted in national and international reports. [3,11-13] Alatisse *et al.* [12] in Nigeria documented a male-to-female ratio of 1:7 and George *et al.* [3] in India reported a male-to-female ratio of 2:5. The reason for this pattern has been linked to female sex hormones. Further, gallbladder cancer is reportedly associated with high parity, although the role of oestrogen receptor and progesterone receptor expression may not be significantly different between men and women. [3,6,11-13]

Gallbladder carcinoma typically manifests as focal intraluminal mass, focal or diffuse wall thickening, and gallbladder replaced by the mass. The mass usually has a low attenuation with

variable enhancement, most commonly irregular peripheral enhancement. When gallbladder cancer manifests as diffuse wall thickening, it is challenging to make the diagnosis because it may mimic the appearance of many acute and chronic inflammatory conditions such as acute and chronic cholecystitis, primary sclerosing cholangitis and diffuse adenomyomatosis of the gall bladder. Soo *et al.* [15] studied 78 patients with diffuse gallbladder wall thickening and found that the pattern of the mucosa of the thickened wall helps differentiate gall bladder cancer from benign inflammatory diseases. The study reported that a heterogeneously enhancing thick layer of gallbladder mucosa was significantly associated with gallbladder cancer. Other mucosal patterns suggestive of cancer noted included a two-layer pattern with a strongly enhancing thick inner layer and weakly enhancing or non-enhancing outer layer. Focal masses with irregular borders or fungating appearance are also highly suggestive of gallbladder carcinoma. [15-17] Forty-seven per cent of the patients in the present study had irregular thickening of the wall of the gallbladder and 13.3% had mildly thickened gall bladder wall with the entire gallbladder replaced by hypodense mass. The present study did not document any intra-polypoidal masses, probably due to the late presentation of the cases. Afifi *et al*

[6] recorded polypoid lesions in 36% of 25 patients and polyps ranging from 2cm to 5cm in diameter.

Gallbladder cancer commonly manifests as diffusely infiltrating masses.[6] This may be because of the late presentation of patients. It may remain asymptomatic or present with vague abdominal symptoms until it has progressed to an advanced stage. Eighty per cent of the cases presented with infiltrating gallbladder masses involving the gallbladder fossa. All the post-contrast enhancement series showed the infiltration as hypodense or isodense areas. This is similar to the findings of George *et al.* [3] and Afifi *et al.* [6] who found similar percentages (76% and 60% respectively) of cases to have infiltrated the gallbladder bed but 60% of the cases appeared hypodense after contrast injection. The studies also stated that there may be mild to moderate heterogeneous enhancement of the gall bladder bed in the portal venous phase but absent in the arterial phase. This is important in differentiating the gallbladder tumour from hepatocellular carcinoma. Usually, hepatocellular carcinoma enhances vividly during the late arterial phase and becomes indistinct or hypodense in the portal venous phase. In the present study, there was no enhancement of the gall bladder bed in the arterial nor portal venous phase.

Gall stones represent an important risk factor for malignancy, being present in about 85% of patients with gall bladder cancer. [18] In this study, gall stones were seen in association with gall bladder carcinoma in 40% of the patients. This is similar to the finding in the study by Afifi *et al.* [6] who also detected gall stones in 40% of the 25 patients who were diagnosed with gallbladder carcinoma on multidetector CT. A review of the epidemiology of gallbladder cancer done by Hundal and Shaffer, [20] showed a different perspective, stating that the overall risk of gallbladder cancer occurring in those with gallstones may be low, but other gall stone

characteristics including increasing stone size, stones greater than 3cm in diameter and cholesterol gallstones, influence the risk of gallbladder carcinoma. [19-21]

Metastatic abdominal lymph nodes in the porta hepatis and paraaortic area were noted in 73% of the patients in the present study while infiltration of the adjacent organs was recorded as seen in 40%. This common mode of presentation is due to the lack of muscularis mucosa and submucosa in the gallbladder. [20] Reformatted images were beneficial in the assessment of the extension and origin of the gallbladder masses.

The retrospective design as well as the limited access to the clinical notes of some of the patients in a private diagnostic facility are limitations to the study.

Conclusion

Gallbladder cancer can present as irregular wall thickening, focal mass or mild thickening of the gallbladder wall with the lumen replaced by hypodense mass. It is frequently diagnosed in the late stages with extensive gallbladder bed infiltration, local infiltration of adjacent organs and metastatic lymph nodes. A high index of suspicion in elderly patients with vague right hypochondrial pain should warrant basic abdominal imaging. Gall bladder cancer has different radiological patterns and a high index of suspicion is required by the radiologist who must be familiar with the variable appearances on imaging. Multidetector CT is an excellent choice that can be used to diagnose and stage gallbladder cancer.

Authors' Contributions: O-BMA and OAA participated in the conception and design of the study. O-BMA did data acquisition, analysis and interpretation. AAO participated in data acquisition. O-BMA drafted the manuscript while OAA, AOI and

AAO revised the manuscript for sound intellectual contents. All the authors approved the final version of the manuscript.

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