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Incidental vs. non-incidental gallbladder cancer – a hospital-based clinicopathological study

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ABSTRACT

Introduction and aim. Most gallbladder cancers (GBCs) are discovered incidentally after routine cholecystectomy. The clinicopathological characteristics and prognostic implications of incidental gallbladder cancer (IGBC) versus non-incidental gallbladder cancer (NIGBC) is not known.

Material and methods. During this study, clinicopathological details compared between incidental and non-incidental GBC groups included age, sex, clinical presentation, preoperative radiological diagnosis, surgical management, and macroscopic and microscopic features. The primary outcome of the study was difference in overall survival (OS) between IGBC and NIGBC.

Results. Among 348 surgically treated patients, 56.6% weren't preoperatively suspected of GBC. Macroscopic examination showed characteristic thickened gallbladder wall without mass lesion (IGBC) vs. clear mass lesion (NIGBC) on imaging. Interestingly, NIGBC had higher LVI (27% vs. 14%) and T stage (68% T2b/T3 vs. 47% T1b/T2a) despite lower margin involvement ($p < 0.001$). The OS for all patients was 12.2 months (median). Among patients who underwent surgery with curative intent, the median survival time was 21.4 months. However, within this group, NIGBC cases had a worse median survival (17 months) compared to IGBC cases (21 months).

Conclusion. Rising incidental GBC necessitates routine microscopic examination of all gallbladder specimens. Surgeons in high-risk areas should remain vigilant for GBC in patients with atypical clinical

and ultrasound findings. Early detection and curative resection are paramount for long-term survival in gallbladder carcinoma, with IGBC potentially offering a survival benefit regardless of stage or tumor characteristics. Prospective studies including detailed pathology and molecular analysis are needed to confirm this observation.

Key words. Histopathology, incidental gallbladder carcinoma, non-incidental gallbladder carcinoma, prognosis, radiology

Introduction

Gallbladder cancers (GBC), the most common cancer of the biliary tract, carries a very poor prognosis when diagnosed at advanced stages due to its aggressive behavior and limited therapeutic options.[1] Surgery remains the only effective treatment for early GBC; therefore, an accurate preoperative diagnosis is crucial for guiding surgeons to select the most appropriate procedure, minimizing unnecessary surgeries, and optimizing patient outcomes.[2]

Unfortunately, despite its significant benefits, accurate preoperative diagnosis of GBC, allowing for a subsequent curative surgical approach, is achievable in only 30% of cases, as documented in the literature. The remaining 50–70% of GBC patients receives an incidental diagnosis postoperatively, typically following laparoscopic cholecystectomy for calculous cholecystitis or acalculous cholecystitis.[3,4]

Several factors contribute to the difficulty of preoperatively recognizing GBC. These include the non-specific nature of its clinical manifestations and the limitations of radiological diagnosis, particularly in differentiating GBC from other common conditions like calculous cholecystitis or acalculous cholecystitis, especially when presented with a thickened gallbladder wall or a flat tumor type.[5,6]

The impact of incidental or non-incidental diagnosis on oncological outcomes and the timing of curative-intent resection as a secondary operation in IGBC remain topics of debate. Studies have reported conflicting findings regarding survival outcomes between incidentally and non-incidentally diagnosed GBC.[7,8]

Aim

We aimed to investigate the clinicopathological characteristics and prognostic factors of IGBC compared to NIGBC cases.

Material and methods

This hospital-based study was conducted on patients who were diagnosed as carcinoma of the gallbladder and came to Acharya Harihar Post-Graduate Institute of Cancer (AHPGIC), Cuttack, Odisha, India, for further management over a period of 5 years from 01.04.2017 to 31.03.2022 were included as study subjects.

This study was approved by the Institutional Ethics Committee of Acharya Harihar Post-Graduate Institute of Cancer, Cuttack, (IEC-AHRCC-066/03.07.2018). All patients provided written informed consent.

The study populations were distributed in two groups: IGBC and NIGBC.IGBC was defined as cancer discovered unexpectedly during routine microscopic examination of a gallbladder specimen removed by laparoscopic cholecystectomy for presumed benign disease. Conversely, NIGBC cases had a preoperative radiological suspicion of gallbladder malignancy. During this study, clinicopathological details compared between IGBC and NIGBC groups included age, sex, clinical presentation, preoperative radiological diagnosis, surgical management, and macroscopic and microscopic features. The primary outcome of the study was the difference in OS between IGBC and NIGBC.OS was calculated from date of surgery to date of last follow up or death.

Categorical data are presented as frequencies and percentages, while continuous data are presented as means and standard deviations. Chi-square tests were used for comparing categorical variables, with a significance level of 0.05. All statistical analyses were performed using SPSS (version 22, IBM, Armonk, NY, USA).

Results

During this study period, a total of 1,232 GBC cases were referred to our centre, for further management. Of these, only 348 (28.24%) underwent surgical resection, while the remaining 884 cases (71.75%) were deemed inoperable due to advanced disease.

Out of 348 cases, 151 (43.39%) patients preoperatively diagnosed with suspected GBC, only 31 came to our centre for further management, while the others underwent surgery elsewhere. The remained 197 (56.6%) patients diagnosed with (calculous or acalculous associated inflammatory gallbladder disease by ultrasound underwent laparoscopic cholecystectomy elsewhere (Table 1).

Table 1. The ultrasonographical diagnosis of our included cases

Preoperative USG diagnosis		Total (n=348)	
		n	**%**
Non-suspicious of malignancy	Calculous cholecystitis	169	48.56
	Acalculous cholecystitis	28	8.04
Suspicious of malignancy	Gallbladder mass /? GBC	151	43.39

All patients presented with symptoms, lasting an average of 17 days. Abdominal pain with nausea was the most common complaint in both groups, but non-IGBC patients had a higher prevalence of clinical jaundice (Fig. 1).

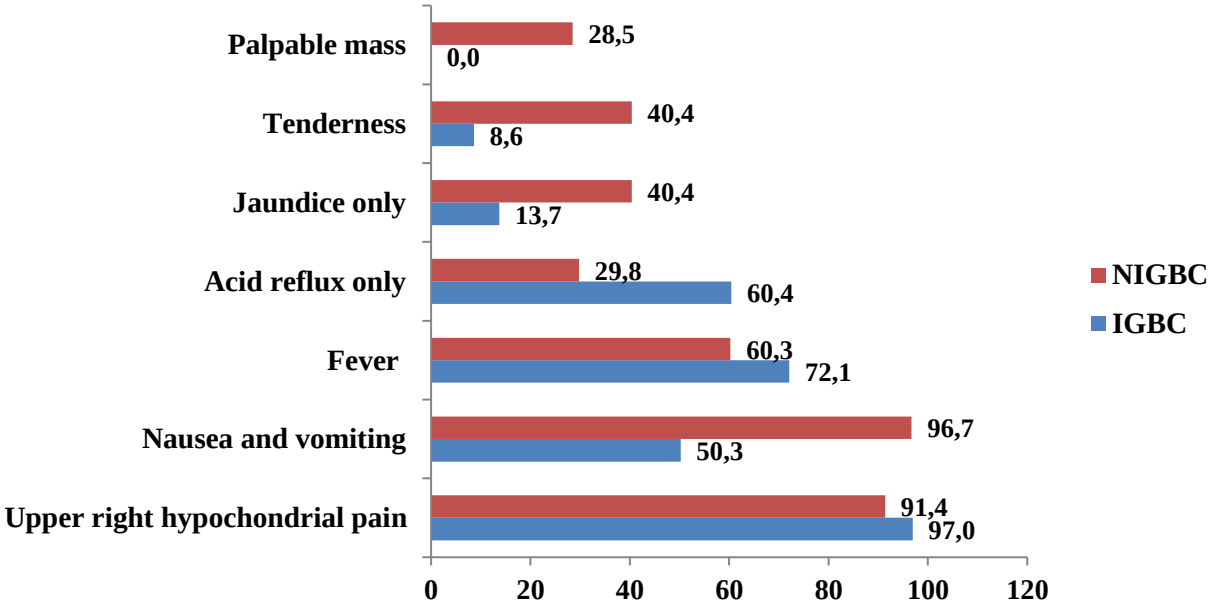

Fig. 1. Sign and symptoms of NIGBC vs. IGBC

For ultrasonographically suspected malignancies (gallbladder mass and/or wall thickening >8 mm), further CT scans were performed to know the disease extension. In USG abdomen and CECT, 13 % patients presented with multiple lymphadenopathies (pericholedochal, peri-pancreatic and para-aortic) and remaining 6% patients presented with either one of the lymphadenopathies. None of the cases showed radiologically regional or distant lymph node metastasis or hepatic or distant organ metastasis (M1 disease). Therefore, all these cases underwent for curative surgery.

Macroscopic examination revealed that 78% of non-suspicious GBC cases exhibited a thickened wall without a mass lesion in the cut section, but with a thickened wall and rugged, firm, and sludgy mucosa (Fig. 2).

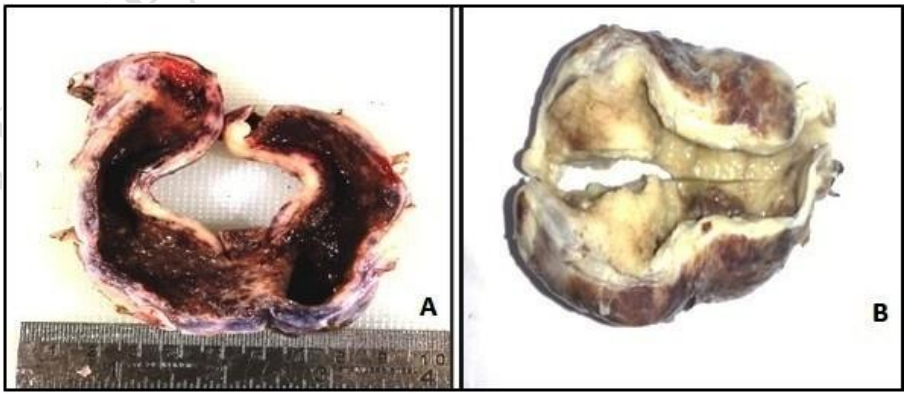

Fig. 2. A: Cut opened gallbladder showing wall thickening (measuring 0.8 cm) with sludge and rugged mucosa; B: Cut opened gallbladder with gallbladder mass (measuring 1.2×0.8 cm) with thickened wall 157×67 mm (96×96 DPI)

Mass lesions, such as flat or small nodular growths, were observed in only 20.81% of these cases. In contrast, all radiologically suspicious GBC cases presented with mass lesions during gross examination, including gray-white proliferative masses, cauliflower-like lesions, warty lesions, ulcerative lesions, nodular lesions, and warty polypoidal masses (Fig. 3) (Table 2).

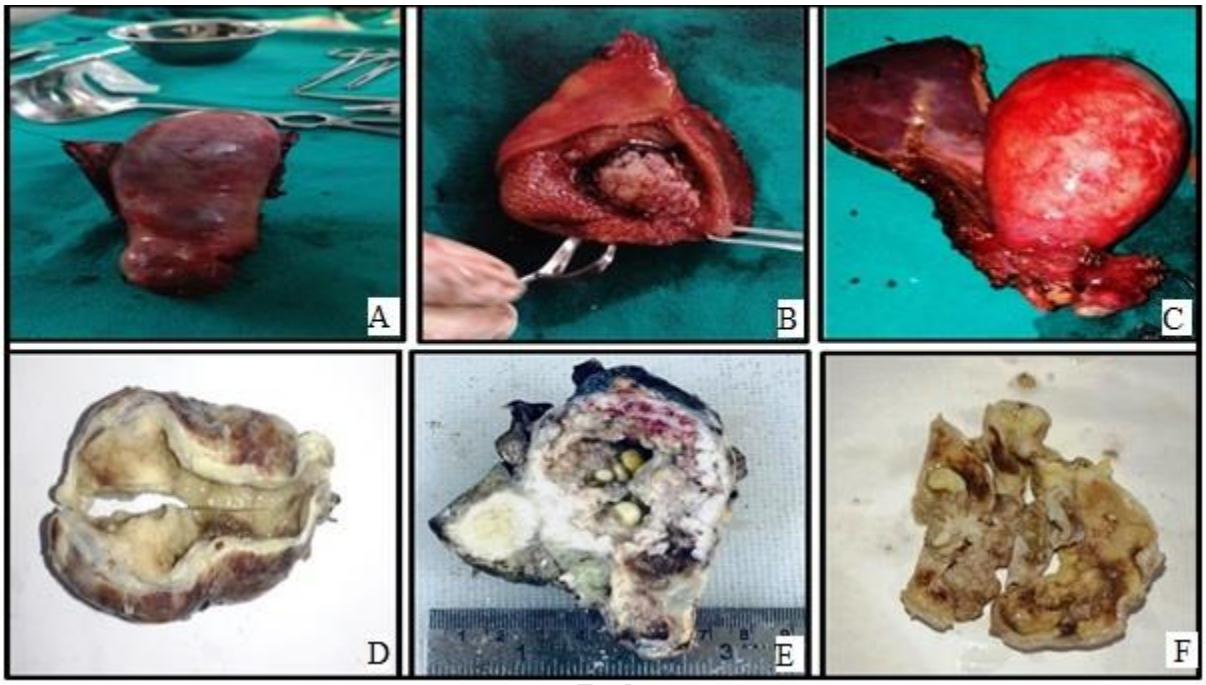

Fig. 3. A: Distended gallbladder measuring 7×4.5 cm, wedge resection; B: Specimen of gallbladder with polypoidal mass measuring 3.6×2.9 cm; C: Resected specimen of gallbladder with wedge of liver; D: Cut opened gallbladder with gallbladder mass (measuring 1.2×0.8cm) with thickened wall; E: Gallbladder (7.6×4.8 cm size) with adherent liver tissue, nodular mass at fundus (measuring 1.9×1.0cm); F: Cut opened gallbladder (6×4 cm size) with ulceroproliferative growth (3.4×2.2 cm at the body)

Table 2. Age, sex and macroscopic findings of incidental GBC vs. non incidental GBC cases*

Clinical variables		**Total (n=348)**		**IGBC (n=197)**		**NIGBC (n=151)**		**p**
		n	%	n	%	n	%	
Age	<50 years	120	34.4	76	38.6	44	29.1	0.06
	>50 years	228	65.5	121	61.4	107	70.9	
Sex	Male	99	28.4	59	29.9	40	26.5	0.8
	Female	249	71.5	156	79.2	111	73.5	
Gallstone	Present	273	78.4	169	85.78	104	68.8	0.0001
	Absent	75	21.6	28	14.2	47	31.1	

Gallstone numbers	One or two	68	24.9	27	15.9	41	39.4	0.0001
	Multiple	205	75	142	84.0	63	60.5	
Gallstone size	>3cm	86	31.5	49	28.9	37	35.5	0.2
	<3cm	187	68.5	120	71	67	64.4	
Nature of tumor	Only wall thick (0.3–0.7cm)	69	13.7	69	35	0	0	0.0001
	Wall thick only (> 0.7) cm	86	24.7	86	43.6	0	0	
	Mass/polypoidal growth	193	55.4	42	21.3	151	100	
Tumor site	Fundus	151	43.3	89	45.2	62	41.1	0.2
	Body	88	25.2	46	23.4	42	27.8	
	Neck	41	11.7	19	9.6	22	14.6	
	Diffuse	68	19.5	43	21.8	25	16.6	

* IGBC – incidental gallbladder cancer, NIGBC – non-incidental gallbladder cancer

Microscopic examination showed that most non-IGBC cases were classified as T2b/T3 stage tumors (68%), while most IGBC cases were classified as T1b/T2a stage tumors (47%). This difference was statistically significant ($p<0.0001$). Non-IGBC also had a higher prevalence of lymphovascular invasion (LVI) (27% vs. 14%; $p=0.002$). Additionally, IGBC cases had a higher rate of surgical margin involvement compared to NIGBC cases ($p=0.001$) (Table 3).

Table 3. Histopathological characteristics of IGBC and NIGBC cases*

Histopathological characteristics		**Total (n=348)**		**IGBC (n=197)**		**NIGBC (n=151)**		**p**
		n	%	n	%	n	%	
Tumor type	IAC	297	85.3	167	84.77	130	86.1	0.2
	PAC	16	4.6	13	6.60	3	2.0	
	MAC	15	4.3	7	3.55	8	5.3	
	ASCC	11	3.2	6	3.05	5	3.3	
	SCC	9	2.6	4	2.03	5	3.3	
Tumor grade	G1	121	34.8	72	36.55	49	32.5	0.2
	G2	164	47.1	95	48.22	69	45.7	
	G3	63	18.1	30	15.23	33	21.9	

T stage (pT)	T1b	16	4.6	15	7.61	1	0.7	0.0001
	T2a	127	36.5	79	40.10	48	31.8	
	T2b	139	39.9	83	42.13	56	37.1	
	T3	66	19.0	20	10.15	46	30.5	
PNI	Present	115	33.0	63	31.98	52	34.4	0.6
	Absent	233	67.0	134	68.02	99	65.6	
LVI	Present	69	19.8	28	14.2	41	27.2	0.002
	Absent	279	80.2	169	85.7	110	72.8	
Surgical margin	Positive	76	21.8	67	34.01	9	6.0	0.0001
	Negative	272	78.2	130	65.99	142	94.0	

***** IAC – Invasive adenocarcinoma (nos type), PAC – papillary adenocarcinoma, MAC – mucinous adenocarcinoma, ASCC – adenosquamous cell carcinoma, SCC – squamous cell carcinoma, G1 – grade 1, G2 – grade 2, G3 – grade 3, PNI – perineural invasion, LVI – lymphovascular invasion

Completion surgery was performed in only 38 (19.28%) of the total IGBC cases. The remaining cases could not undergo re-resection due to various reasons, including metastatic disease on staging imaging (n=77, 39%), loss of follow-up after diagnosis (n=39, 19.8%), patient refusal (n=22, 11.1%), and post-surgical complications (n=13, 6.6%). Completion surgery involved exploration of the abdominal cavity, limited liver resection, and dissection of regional lymph nodes. In total, curative surgery (radical/completion surgery following laparoscopiccholecystectomy) were performed in 189 (54.31%) cases. These cases underwent assessment of liver invasion, regional lymph node involvement, and AJCC TNM staging (Table 4). Interestingly, NIGBC patients more frequently had lymph-node-positive disease compared with IGBC patients (23.8% vs. 5.3%; p=0.02) (Table 4).

Table 4. Disease extension and staging status of IGBC and NIGBC cases

Histopathological characteristics		**Total (n=189)**		**IGBC (n=38)**		**NIGBC (n=151)**		**p**
		n	%	n	%	n	%	
Liver invasion	Present	56	29.63	9	23.7	47	31.1	0.3
	Absent	133	70.37	29	76.3	104	68.9	
Lymph node	N1	38	20.11	2	5.3	36	23.8	0.02
	N2	0	0.00	0	0.0	0	0.0	
	N0	151	79.89	36	94.7	115	76.2	
Metastasis	M0	189	100	38	100.0	151	100.0	0.2

	M1	0	0.0	0	0.0	0	0.0	
AJCC (TNM Stage)	IB (T1bN0M0)	3	1.6	2	5.3	1	0.7	0.2
	IIA (T2aN0M0)	55	29.1	8	23.7	47	31.1	
	IIB (T2bN0M0)	56	29.6	13	42.1	43	28.5	
	IIIA (T3N0M0)	31	16.4	7	18.4	24	15.9	
	IIIB (T1-3N1M0)	44	23.3	8	10.5	36	23.8	

Overall follow up time of our study population was 24 months**.** Median overall survival (OS) among all patients was 12.2 months. Median OS among only patients who underwent curative-intent resections was 21.4 months among which non-IGBC was associated with worse median OS (17 months) compared with IGBC (21 months) (Fig. 4).

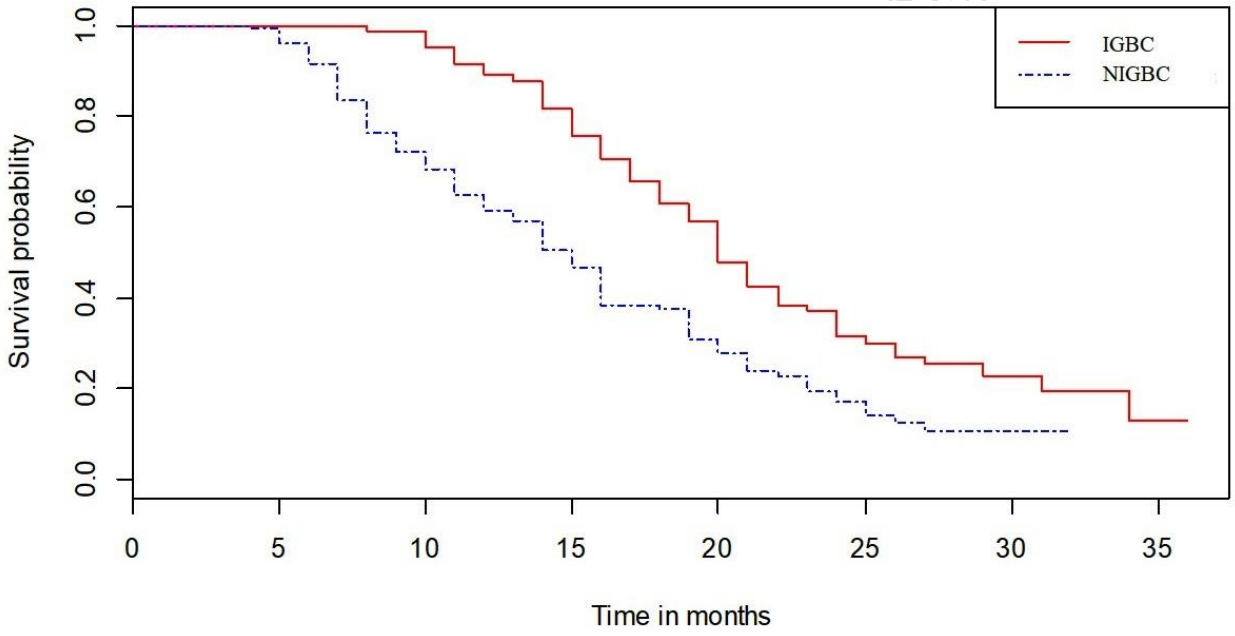

Fig. 4. Comparison the overall survival between IGBC AND NIGBC (Kaplan Meier survival plot)

Discussion

GBC carries a high mortality rate and relatively low 5-year survival rate.[9] Globally, in 2020, out of 19.3 million total cancer cases, 115,949 new GBC cases were reported, with 84,695 deaths.[10]India accounts for 10% of global GBC cases – approximately one million new cases annually – and experiences a concerning 33% mortality rate. The highest burden of GBC in India occurs in states like Uttar Pradesh, Bihar, West Bengal, Assam, Delhi, and Odisha.[9] This regional disparity highlights the need for locally tailored research to understand the high incidence of GBC cases reported in Odisha and determine potential preventive measures.

Another significant challenge is late-stage presentation. In our study, the majority (70%) of patients presented with advanced, unresectable disease. This aligns with studies from the Indian subcontinent, highlighting the importance of early GBC diagnosis to improve surgical outcomes.[11-13]

Accurate preoperative assessment is crucial for prognosis, selecting appropriate surgery, minimizing unnecessary procedures, and optimizing patient outcomes. However, non-specific symptoms and limitations in diagnostic methods often lead to misdiagnosis and inappropriate surgeries.[14]

In our study, only 151 (43.39%) of resectable GBC cases received a preoperative diagnosis suspicious of GBC, allowing for appropriate surgical intervention. The remaining 66% were preoperatively diagnosed as benign and underwent laparoscopic cholecystectomy. World literature suggests 50–70% of gallbladder cancers are diagnosed incidentally, highlighting the limitations of preoperative diagnosis.[3,4]

Ultrasonography of abdomen is the preferred imaging technique for suspected gallbladder lesions due to its safety, non-invasiveness, real-time capabilities, cost-effectiveness, superior resolution, and ease of use.[15,16] However, it can sometimes present diagnostic challenges.[3,15]

In our study, among ultrasonographically unsuspected GBC cases, 169 (85.7%) presented with only a thickened gallbladder wall, often alongside gallstones. This non-specific presentation, common in many gallbladder diseases, makes diagnosis challenging. However, factors like female sex, age over 50, and wall thickening exceeding 3 mm, with or without gallstones, may raise suspicion of malignancy.[17-19]

Even in macroscopic examination, suspicious cancer features were identified in only 20% of our cases. The remaining 80% showed no suspicious lesions. In these situations, histopathological examination (microscopic) of the cholecystectomy specimen is the gold standard for detecting occult malignancy. It also helps assess invasion depth in IGBC, guiding further management.[16,17] The Royal College of Pathologists recommends submitting all gallbladder specimens for histopathological examination because significant pathology can present with a normal macroscopic appearance.[16,17] Several studies support routine histopathological examination of all post-cholecystectomy specimens for increased detection of incidental GBC compared to a selective approach.[3,16] However, a few authors argue against histopathology for all surgically resected benign gallbladders due to the low IGBC incidence and potential for early-stage cases already receiving optimal treatment with simple cholecystectomy.[16]

Studies have shown that if GBC is diagnosed symptomatically after cholecystectomy without routine histopathological examination (HPE), the overall resectability rate is only 8%, compared to 70% with early detection based on HPE.[20]

Pathologists should report crucial factors like surgical margins, histological grade, lymphovascular invasion, perineural invasion, pT stage, and lymph node involvement, all of which are essential for treatment and prognosis of patients incidentally diagnosed with GBC.

Similar to previous reports, our study found that NIGBC cases were associated with indicators of advanced disease and poor prognosis, including clinical jaundice, major hepatectomy, high lymphovascular invasion

(LVI) positivity, positive lymph nodes, advanced T-stage, and disease stage.[8,21] Conversely, IGBC cases exhibited a higher rate of positive cystic duct cut margin. A study suggests that a positive cystic duct margin at initial cholecystectomy is a strong predictor of worse overall survival (OS) even if no further cancer is found at extended radical resection (ERR). Common bile duct resection in patients with a positive cystic duct margin and no recurrence at ERR can lead to improved outcomes.[22]

The role of re-resection after incidental GBC diagnosis is to remove residual microscopic local and regional disease from the surgical bed, aiming for an R0 resection, and to perform a complete staging lymphadenectomy. Re-resection is indicated for patients with pathologically confirmed T1b (muscularis layer invasion), T2 (perimuscular connective tissue invasion without serosal or liver involvement), or T3 (serosal perforation or liver invasion) disease without evidence of metastatic disease and adequate performance status to tolerate a potentially more extensive surgery.[23] The optimal timing of re-resection after incidental GBC remains debatable. Some studies suggest that TNM stage, rather than the interval between cholecystectomy and re-resection, is the primary prognostic factor. Others advocate for re-resection within 4 to 8 weeks of initial cholecystectomy, as procedures performed outside this timeframe may be associated with worse outcomes despite similar tumor stages.[24]

In our study, most patients who did not undergo curative-intent management had metastatic disease on staging imaging. Notably, a majority of patients who underwent re-resection received it after an average of four months following laparoscopic cholecystectomy. This finding emphasizes the importance of early surgical intervention, ideally within 4 weeks of initial cholecystectomy, whenever possible.

Unlike previous reports, we found no statistically significant difference in long-term survival between patients undergoing curative radical resection as a single procedure versus those undergoing two procedures (radical re-resection after simple cholecystectomy).[25,26]

Our study suggests that an IGBC diagnosis may offer a survival advantage, even for patients who receive surgical treatment, regardless of pathological stage and tumor characteristics. Further investigation through prospective studies is needed to explore the reasons behind this observation, including detailed pathological analysis and molecular gene expression analysis.

Conclusion

Rising incidental GBC necessitates routine microscopic examination of all gallbladder specimens. Surgeons in high-risk areas should remain vigilant for GBC in patients with atypical clinical and ultrasound findings. Early detection and curative resection are paramount for long-term survival in gallbladder carcinoma, with IGBC potentially offering a survival benefit regardless of stage or tumor characteristics. Prospective studies including detailed pathology and molecular analysis are needed to confirm this observation.

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Declarations

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Author contributions

Conceptualization, S.S., N.R., and M.R.; Methodology, S.D.; Software, S. D.; Validation, N.R., and S.S.; Formal Analysis, S.S., and P.A.; Investigation, S.S.; Data Curation, S.D.; Writing – Original Draft Preparation, S.S.; Writing – Review & Editing, M.R., S.S., and N.R.; Visualization, S.D.; Supervision, S.S., M.R., and N.R.; Project Administration, N.R.; Funding Acquisition, S.S.

Conflicts of interest

The authors declare that they have no conflict of interest.

Data availability

The data presented in this study are available on request to the corresponding authors.

Ethics approval

This study was approved by the Institutional Ethics Committee of Acharya Harihar Post-Graduate Institute of Cancer, Cuttack, (IEC-AHRCC-066/03.07.2018).

References

1. Roa JC, García P, Kapoor VK, Maithel SK, Javle M, Koshiol J. Gallbladder cancer. *Nat Rev Dis Primers*. 2022;8(1):69. doi: 10.1038/s41572-022-00398-y
2. Cassese G, Han HS, Yoon YS, et al. Preoperative Assessment and Perioperative Management of Resectable Gallbladder Cancer in the Era of Precision Medicine and Novel Technologies: State of the Art and Future Perspectives. *Diagnostics (Basel)*. 2022;12(7):1630. doi: 10.3390/diagnostics12071630
3. Nagarajan G, Kundalia K. Should every cholecystectomy specimen be sent for histopathology to identify incidental gall bladder cancer? *Indian J Cancer*. 2020;57(1):2-3. doi: 10.4103/ijc.IJC_1027_19

4. Wang Z, Xu Y, Hu D, et al. Laparoscopy Versus Open Reoperation for Incidental Gallbladder Carcinoma After Laparoscopic Cholecystectomy. *J Laparoendosc Adv Surg Tech A*. 2020;30(7):764-768. doi: 10.1089/lap.2019.0802
5. Levy AD, Murakata LA, Abbott RM, Rohrmann CA Jr. From the archives of the AFIP. Benign tumors and tumorlike lesions of the gallbladder and extrahepatic bile ducts: radiologic-pathologic correlation. Armed Forces Institute of Pathology. *Radiographics*. 2002;22(2):387-413. doi: 10.1148/radiographics.22.2.g02mr08387
6. Fujiwara K, Masatsugu T, Abe A, Hirano T, Sada M. Preoperative diagnoses and identification rates of unexpected gallbladder cancer. *PLoS One*. 2020;15(9):0239178. doi: 10.1371/journal.pone.0239178
7. Cavallaro A, Piccolo G, Di Vita M, et al. Managing the incidentally detected gallbladder cancer: algorithms and controversies. *Int J Surg*. 2014;12(2):108-119. doi: 10.1016/j.ijsu.2014.08.367
8. Ethun CG, Le N, Lopez-Aguiar AG, et al. Pathologic and Prognostic Implications of Incidental *versus* Nonincidental Gallbladder Cancer: A 10-Institution Study from the United States Extrahepatic Biliary Malignancy Consortium. *Am Surg*. 2017;83(7):679-686.
9. Kumar A, Ali M, Raj V, et al. Arsenic causing gallbladder cancer disease in Bihar. *Sci Rep*. 2023;13(1):4259. doi: 10.1038/s41598-023-30898-0
10. GLOBOCAN 2020. https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf. Accessed December 11, 2020.
11. Subedi R, Dhimal M, Budukh A, et al. Epidemiologic Pattern of Cancer in Kathmandu Valley, Nepal: Findings of Population-Based Cancer Registry, 2018. *JCO Glob Oncol*. 2021;7:443-452. doi: 10.1200/GO.20.00574
12. Pandit N, Neupane D, Nalbo D, et al. Resectability and prognosis of gallbladder cancer: a cross-sectional study of 100 cases from a tertiary care centre of Eastern Nepal. *Ann Med Surg (Lond)*. 2023;85(5):1755-1760. doi: 10.1097/MS9.0000000000000699
13. Rout N, Hota SK, Dash S, Samantaray S, Mallik RN, Agrawal O. Diagnostic Utility of Ultrasound-Guided Fine-Needle Aspiration Cytology in Gall Bladder Lesions: An Experience from a Tertiary Care Cancer Center in Eastern India. *J Cytol*. 2021;38(3):145-150. doi: 10.4103/JOC.JOC_166_20
14. Cassese G, Han HS, Yoon YS, et al. Preoperative Assessment and Perioperative Management of Resectable Gallbladder Cancer in the Era of Precision Medicine and Novel Technologies: State of the Art and Future Perspectives. *Diagnostics (Basel)*. 2022;12(7):1630. doi: 10.3390/diagnostics12071630
15. Fuks D, Regimbeau JM, Le Treut YP, et al. Incidental gallbladder cancer by the AFC-GBC-2009 Study Group. *World J Surg*. 2011;35(8):1887-1897. doi: 10.1007/s00268-011-1134-3

16. Jha V, Sharma P, Mandal KA. Incidental gallbladder carcinoma: Utility of histopathological evaluation of routine cholecystectomy specimens. *South Asian J Cancer*. 2018;7(1):21-23. doi: 10.4103/2278-330X.226802
17. Darmas B, Mahmud S, Abbas A, Baker AL. Is there any justification for the routine histological examination of straightforward cholecystectomy specimens? *Ann R Coll Surg Engl*. 2007;89(3):238-241. doi: 10.1308/003588407X168361
18. Pyo JS, Son BK, Lee HY, Oh IW, Chung KH. Incidental Carcinoma after Cholecystectomy for Benign Disease of the Gallbladder: A Meta-Analysis. *J Clin Med*. 2020;9(5):1484. doi: 10.3390/jcm9051484
19. Rammohan A, Cherukuri SD, Sathyanesan J, Palaniappan R, Govindan M. Incidental gall bladder cancers: Are they truly incidental? *World J Gastrointest Oncol*. 2014;6(12):441-443. doi: 10.4251/wjgo.v6.i12.441
20. Agarwal AK, Kalayarasan R, Singh S, Javed A, Sakhuja P. All cholecystectomy specimens must be sent for histopathology to detect inapparent gallbladder cancer. *HPB (Oxford)*. 2012;14(4):269-273. doi: 10.1111/j.1477-2574.2012.00443.x
21. Shih SP, Schulick RD, Cameron JL, et al. Gallbladder cancer: the role of laparoscopy and radical resection. *Ann Surg*. 2007; 245(6):893-901. doi: 10.1097/SLA.0b013e31806beec2
22. Vega EA, Vinuela E, Sanhueza M, et al. Positive cystic duct margin at index cholecystectomy in incidental gallbladder cancer is an important negative prognosticator. *Eur J Surg Oncol*. 2019;45(6):1061-1068. doi: 10.1016/j.ejso.2019.01.013
23. Alarabiyat M, Raza SS, Isaac J, et al. Incidental gallbladder cancer diagnosis confers survival advantage irrespective of tumour stage and characteristics. *World J Gastroenterol*. 2022;28(18):1996-2007. doi: 10.3748/wjg.v28.i18.1996
24. Zaidi MY, Abou-Alfa GK, Ethun CG, et al. Evaluation and management of incidental gallbladder cancer. *Chin Clin Oncol*. 2019;8(4):37. doi: 10.21037/cco.2019.07.01
25. Rathanaswamy S, Misra S, Kumar V, et al. Incidentally detected gallbladder cancer- the controversies and algorithmic approach to management. *Indian J Surg*. 2012;74(3):248-254. doi: 10.1007/s12262-012-0592-7
26. Fong Y, Jarnagin W, Blumgart LH. Gallbladder cancer: comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. *Ann Surg*. 2000;232(4):557-569. doi: 10.1097/00000658-200010000-00011