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ORIGINAL RESEARCH

Neuroendocrine Carcinoma of Gallbladder: A Step Beyond Palliative Therapy, Experience of 25 Cases

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Abstract

Purpose Published literature on gall bladder neuroendocrine tumors (GB NETs) is limited with none reporting the role of multimodal therapy.

Methods Patients with histologically confirmed GB NETs treated at Tata Memorial Hospital, Mumbai, from January 2010 to June 2017 were analyzed. Staging was done by contrast-enhanced computed tomography (CECT) of abdomen and chest or a positron emission topography (PET) scan. Tumor marker (CA19-9) was measured. WHO-2017 guideline was used to classify GB NETs. GB NETs were categorized as early disease (ED) (T1, T2, N0, i.e., stages I and II); locally advanced disease (LAD) (T3, T4, or N+, i.e., stage III); and metastatic disease (MD). Response to treatment was assessed with RECIST1.1 criteria.

Results Twenty-five patients of GB NETs were identified; 19 with neuroendocrine carcinomas (NECs) and 6 with mixed adenoneuroendocrine carcinomas (MANECs). Two patients (8%) presented with ED, 9 (36%) with LAD, and 14 (56%) had MD. Those with ED underwent open revision radical cholecystectomy. Both received adjuvant chemotherapy (ACT) with six cycles of carboplatin-etoposide and were disease-free at 3 months of follow-up. Of the nine patients with LAD, six received three cycles of neoadjuvant chemotherapy (NACT) (carboplatin-etoposide) and three operated upfront. All six patients showed partial response to NACT and five underwent open radical cholecystectomy with R0 resection. All patients operated after NACT received three cycles of ACT. Their median follow-up was 7 months (range 3–22 months). Three patients with LAD developed metastasis after median disease-free survival of 5 months. The median survival in patients with MD was 12 (range 6–23) months.

Conclusions In carefully selected patients of GB NECs, downsizing with NACT facilitates radical resection with negative margins.

Keywords Neuroendocrine carcinoma of gallbladder · Multimodal therapy · Radical cholecystectomy

Introduction

Gallbladder cancer (GBC) is the sixth most common malignancy of gastrointestinal tract and is the most common malignancy of the biliary tract [1]. Prevalence of GBC shows a distinct geographical variation. High incidence rates, up to 2–4 in men and up to 4–6 in women, have been reported from various countries in central and south America, central and eastern Europe, and Japan [1]. In India, it exhibits a definite geographical divide with highest incidence in north and north eastern regions. The highest GBC incidence rates worldwide were reported in women from North India (21.5/100,000) [2].

The commonest histological type of GBC is adenocarcinoma (75.8%) with squamous cell carcinomas, neuroendocrine tumors, and sarcomas being uncommon pathologies [3]. The first case of primary gallbladder neuroendocrine tumor (GB NET) was reported in 1929 by Joel [4]. Since then, small- and large-cell carcinomas of the gallbladder have been described to have neuroendocrine differentiation. Although north India is a high risk region for GBC, data on GB NETs from this part of world is limited. In the SEER registry, only 278 cases have

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been reported between 1973 and 2005, and represent 0.5% of all neuroendocrine tumors, and 2% of all GBCs [5].

As GB NETs are uncommon, there is uncertainty regarding further evaluation and treatment when identified during pathological examination of cholecystectomy specimens. We analyzed our patients with GB NETs and describe clinico-epidemiological profile and treatment strategies used for management of this rare disease.

Patients and Methods

Patients with histologically confirmed GB NETs treated at Tata Memorial Hospital, Mumbai, from January 2010 to June 2017 were analyzed from a cohort of patients treated for GBC. Staging work-up included contrast-enhanced computed tomography (CECT) of abdomen and chest or a positron emission topography (PET) scan and tumor markers (carbohydrate antigen 19–9). World Health Organization (WHO) 2017 guidelines were used to classify GB NETs into well-differentiated NETs (classified as grades 1, 2, and 3) and poorly differentiated (neuroendocrine carcinomas (NEC), small and large cell) and mixed adenoneuroendocrine carcinomas (MANECs) [6].

GB NETs were categorized as early disease (ED) (T1, T2, N0, i.e., stages I and II); locally advanced disease (LAD) (T3, T4, or N+, i.e., stage III); and metastatic disease (MD). Response to treatment was assessed with CECT of abdomen and pelvis or PET scan using RECIST1.1 criteria [7]. In situations where response could not be quantified by RECIST, the response was quantified based on collusion between treating physician and the gastrointestinal radiologist as follows: complete response (CR), disappearance of all baseline lesions; partial response (PR), significant regression of lesions at baseline; stable disease (SD), no significant regression of baseline lesions and no new lesions; and progressive disease (PD), appearance of new lesions or significant increase in baseline lesions.

Statistical Analysis

Descriptive statistics including median, frequency, and percentage for categorical variables was used to describe age, gender distribution, treatment, and response to treatment. Survival outcomes in terms of overall survival (OS) were analyzed. Median OS was calculated from the date of diagnosis until last follow-up or death. OS was calculated separately for the potentially resectable and unresectable cohorts.

Results

Twenty-five out of 835 (2.99%) patients of GBC treated were identified as having GB NETs, 19 with NECs and 6 with MANECs (Fig. 1). All the patients were from high-risk regions for GBC (North Eastern India). The median age was 50 years (range 31 to 77 years); male/female ratio was 1:4. Most common presenting symptom was abdominal pain. None had obstructive jaundice or secretory symptoms.

Two patients (8%) presented with ED, 9 (36%) patients presented with locally advanced disease, and 14 (56%) had

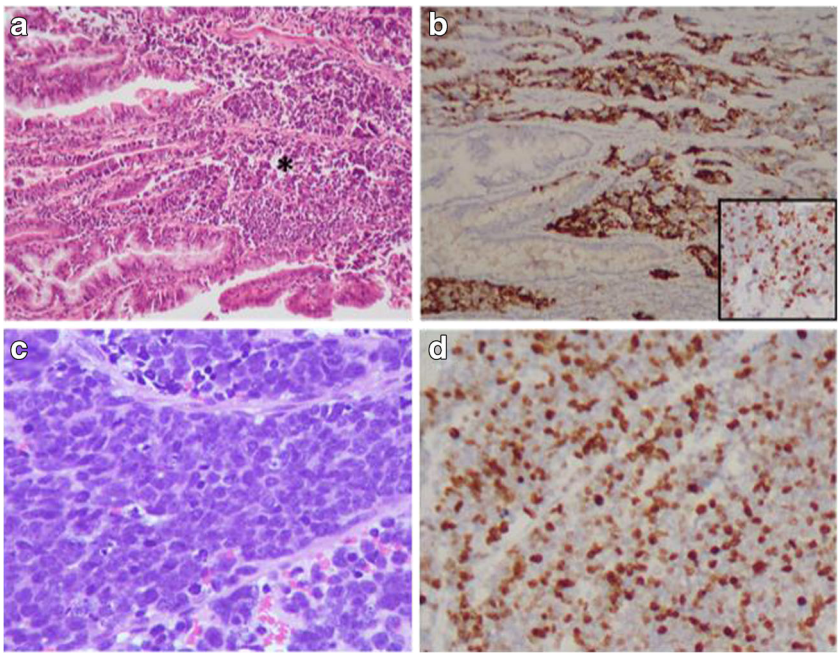

Fig. 1 **a**, **b** Mixed adenoneuroendocrine carcinoma. **a** Adenocarcinoma intermixed with solid sheets of poorly differentiated neuroendocrine carcinoma component (asterisk). **b** Neuroendocrine carcinoma component of the tumor is highlighted by strong immunoreactivity for chromogranin; Inset: MIB1 labeling index of 20% in the neuroendocrine component. **c, d** Small cell carcinoma. **c** Histology shows closely packed small neuroendocrine carcinoma cells with brisk mitosis and apoptosis. **d** MIB1 labeling index of 70%

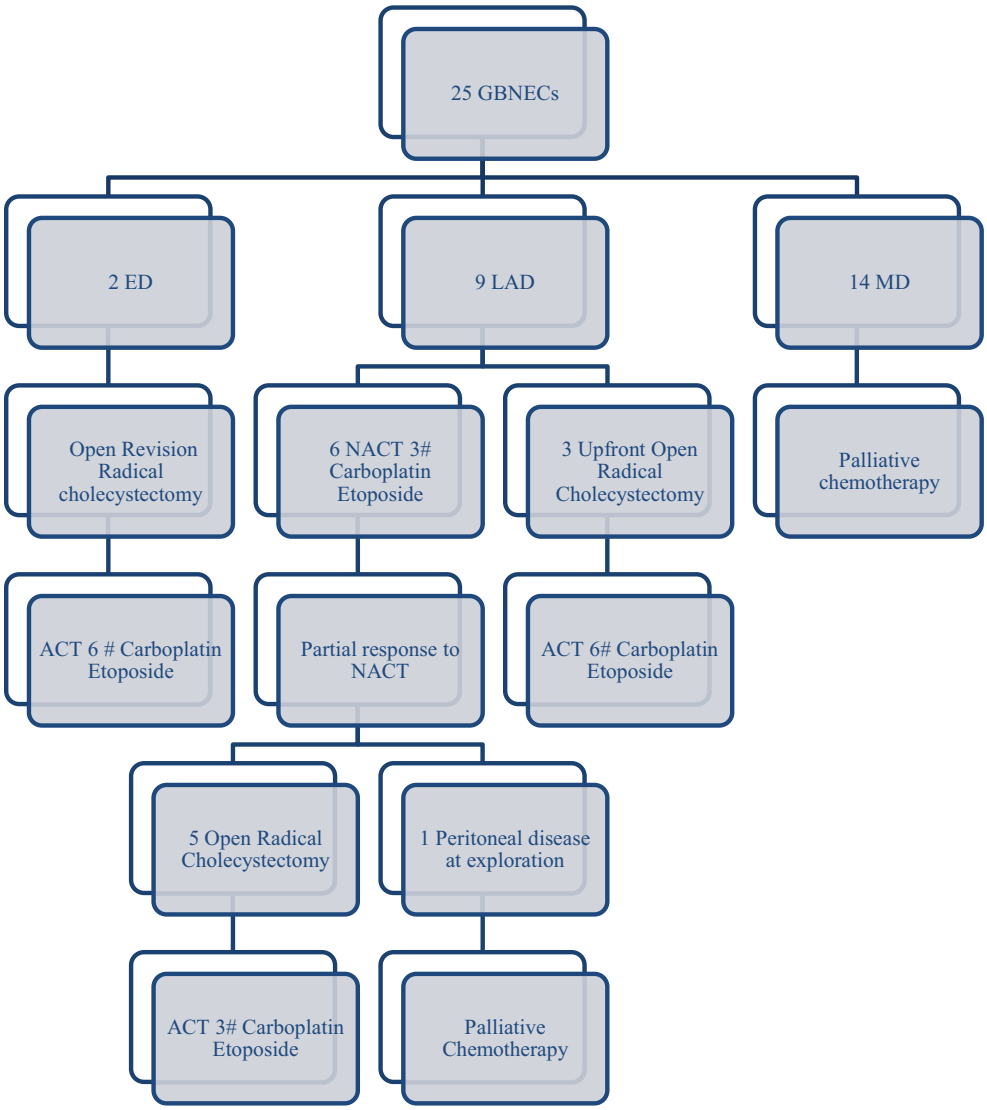

Fig. 2 Flow of patients included in the study

metastatic disease (Fig. 2). Patients with ED underwent upfront surgery with open revision radical cholecystectomy (Table 1) and received adjuvant chemotherapy (ACT) with six cycles of carboplatin-etoposide. Both were disease-free at 3 months of follow-up.

Of the nine patients with LAD, six patients received three cycles of neoadjuvant chemotherapy (NACT) (carboplatin-etoposide) and three were operated upfront (Table 1). All the six patients showed partial response to NACT (Fig. 3) and five underwent open radical cholecystectomy with R0 resection (Fig. 4). One patient post NACT had peritoneal disease at exploration and was deemed as having metastatic disease. Pathological complete response after NACT was seen in one patient. There was no significant peri-operative morbidity or mortality. Median hospital stay was 5 days (range 4 to 7 days). All patients operated after NACT also received three cycles of adjuvant chemotherapy with carboplatin-etoposide. Their median follow up was 7 months (range 3–22 months). Three patients with locally advanced disease developed metastatic disease after median disease-free interval of 5 months.

Five out of 14 patients with metastatic disease (MD) were lost to follow-up. The median OS was 12 (range 6–23) months.

Discussion

The incidence of GBC in north and north eastern India is high where population based cancer registries observed average age-adjusted rates of GBC over 5.0 per 100,000 persons [8]. GB NETs represent 0.5% of all neuroendocrine tumors, and 2% of all GBCs [5]. GB NETs probably originate from a multipotent stem cell or neuroendocrine cells in intestinal or gastric metaplasia of the gallbladder epithelium, which occurs

Table 1 Overview of patients who underwent surgical resection

	Age/sex	Stage	CA19-9	Presentation	NACT	Response to NACT	Surgery	Disease-free interval (months)	Follow-up (months)	Histology
1	77/F	IIIb	7.2	LAD	Y	PR	RC	6	6	MANEC
2	46/F	IIIb	157	LAD	Y	PR	RC	5	5	SCC
3	43/F	IIIb	9.46	LAD	Y	PR	RC	4	4	SCC
4	59/F	IIIa	2	LAD	Y	PR	RC	3	3	SCC
5	63/F	II	4	ED/Incidental	N	NA	Revision RC	3	3	MANEC
6	50/M	II	2	ED/Incidental	N	NA	Revision RC	3	3	MANEC
7	47/F	IIIa	2	LAD	N	NA	RC	22	22	MANEC
8	49/F	IIIb	–	LAD	N	NA	RC	12	21	SCC
9	54/F	IIIb	2	LAD	Y	PR	RC	8	12	SCC
10	64/F	IIIb	5	LAD	N	NA	RC	4	7	MANEC
11	43/F	IIIb	115	LAD	Y	PR	RC	NA	16	SCC

ED early disease, *LAD* locally advanced disease, *MANEC* mixed adenoneuroendocrine carcinoma, *N* no, *NA* not applicable, *PR* partial response, *RC* radical cholecystectomy, *SCC* small cell carcinoma, *Y* yes

following chronic inflammation in the background of gallstone disease [9]. All the cases of gallbladder NECs included in our series were from north and northeastern Indian states and accounted for 2.99% of all GBCs. Incidence of gall bladder NEC has been reported to be higher in females with median age of presentation being 65 years [10, 11]. In our group of patients, there was clear female dominance with a younger age at presentation at 50 years. As reported in other series [12], they had an advanced clinical stage at presentation with 23 out of 25 (92%) patients presenting in stage III/IV disease.

GB NETs do not have specific clinical presentation. Differentiation of gallbladder NECs from adenocarcinoma of gallbladder is almost impossible on pre-operative imaging. It is well supported by the fact that only two patients diagnosed incidentally following laparoscopic cholecystectomy were neuroendocrine cancers in our series. None of our patients presented with obstructive jaundice and secretory symptoms were absent even in the presence of distant metastases.

Nine cases of LAD were identified as gallbladder NEC on pre-operative biopsy. We could successfully downsize locally advanced disease with three cycles of carboplatin-etoposide [13] in six out of nine patients [Fig. 2]. Five patients who showed partial response to neoadjuvant therapy could undergo radical cholecystectomy with negative margins (R0). This strategy allowed us to select patients with good disease biology (test of time) for radical resection. All resected patients subsequently completed adjuvant chemotherapy (carboplatin-etoposide, three cycles). This novel approach of multimodality therapy (neoadjuvant chemotherapy-radical surgery-adjuvant chemotherapy) has not been reported earlier for gallbladder NECs (Table 2). Most series report use of chemotherapy as primary treatment modality as most of the tumors are unresectable or metastatic.

Pathological assessment of tissue biopsy and resection specimen showed 19 NECs (small cell carcinomas) and 6 mixed adenoneuroendocrine carcinomas (Fig. 1). Median

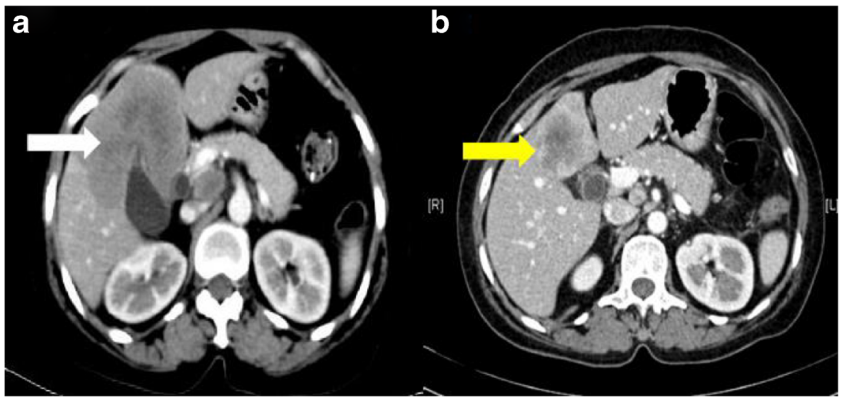

Fig. 3 Response of disease to neoadjuvant chemotherapy. **a** Pre-chemotherapy (white arrow: liver infiltration). **b** Post chemotherapy (yellow arrow: disease response)

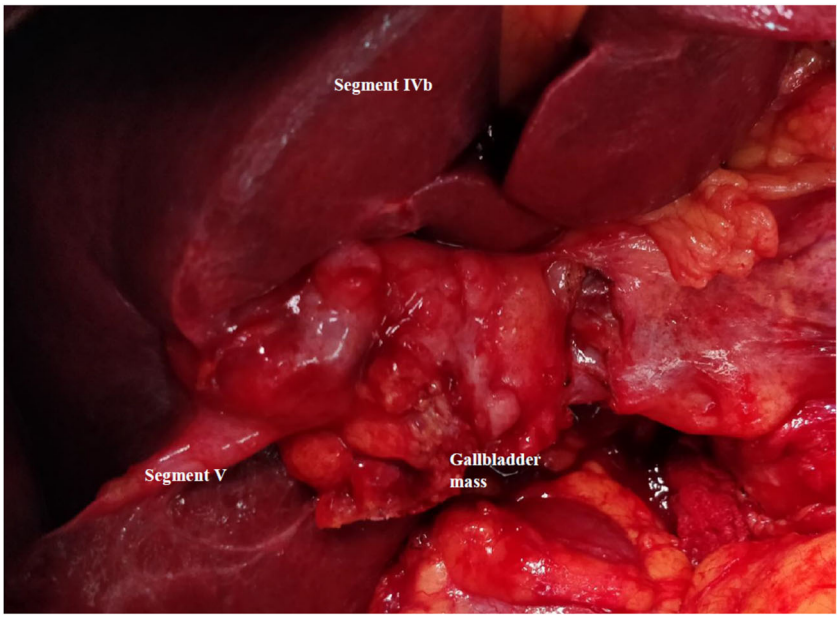

Fig. 4 Intra operative photograph of gallbladder neuroendocrine carcinoma

Mib 1 labeling index was 70% in NECs. MANECs were intermixed with solid sheets of poorly differentiated neuroendocrine carcinoma component. Neuroendocrine carcinoma component of the tumor showed strong immunoreactivity for chromogranin with a Mib 1 labeling index of 20% in the neuroendocrine component. One out of five patients did not show residual disease in the resected pathology specimen indicating the chemo sensitive nature of these tumors. All patients had uneventful post operative recovery and no significant peri-operative morbidity (Clavien-Dindo grade 3 or above) [14] or mortality.

Our study was a retrospective analysis and follow-up was limited. We did not have adequate events in any of the groups to perform a valid survival analysis. Though we had a limited sample size of 25 cases, it is still the largest among the published series from this part of the world. This experience has allowed us to report feasibility and peri-operative safety of multimodality therapy for gallbladder NECs.

Conclusion

GB NETs usually have advanced clinical stage at presentation and are poorly differentiated. In carefully selected patients, downsizing with NACT can facilitate radical resection with

Table 2 Comparison of present data with similar studies

Parameter		Lee et al.	Kumboj et al.	Present series
Clinical stage	I–II	–	0	2
	III	–	0	8
	IV	–	19	15
Histopathology	Well differentiated NETs	1	0	0
	SCCs	6	16	19
	LCCs	0	2	0
	MANECs	5	1	6
Primary treatment modality		Chemotherapy	Chemotherapy	Multimodal therapy with aggressive surgery in the absence of distant metastases
Survival for metastatic disease		8 months	3 (1–9.5 months)	12 months (6–23 months)

MANEC mixed adenonueroendocrine carcinoma, *SCC* small cell carcinoma

negative margins. However, long-term follow-up is required to ascertain effectiveness of this multimodality approach.

Compliance with Ethical Standards

Informed consent was obtained.

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