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Node positivity in T1b gallbladder cancer: A high volume centre experience

Mahesh Goel, Saneya Pandrowala, Prerak Patel, Shraddha Patkar*

Gastrointestinal and Hepato-Pancreato-Biliary Service, Department of Surgical Oncology, Tata Memorial Hospital and Homi Bhabha National Institute, Mumbai, India

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ABSTRACT

Introduction: Identification of early stage gallbladder cancer (GBC) is difficult with simple cholecystectomy being considered curative for T1a GBC but T1b requires radical cholecystectomy due to chances of lymph node metastasis. However there is no consensus regarding the optimal treatment strategy for T1b disease.

Methodology: A retrospective review of a prospectively maintained database of GBC patients operated at our institute from March 2010 to March 2021 was conducted. Only patients with proven gallbladder adenocarcinoma on final histopathology report were included.

Results: A total of 1245 patients of suspected GBC who underwent surgery during this period with 76 patients of T1b stage were analysed. We divided the group into a node positive cohort (n = 16, 9 received neoadjuvant treatment due to uptake in periportal nodes and 7 patients were pN1) and a node negative cohort (n = 60). The median nodal harvest was 8 nodes (2–24 nodes). Considering the radiological and pathological parameters, the rate of lymph node positivity was 21% (16/76). The overall major morbidity was 5.2% and there was no mortality. After a median follow up of 47.5 months, 3-year OS and DFS of the node negative and positive cohort was 96.7%, 91.7% and 75% and 62.5% (p = 0.058). The node positive cohort had 43% recurrences whereas the node negative cohort had 8.3% with all recurrences limited to periportal lymph nodes, distant nodes or liver metastasis.

Conclusion: Nodal positivity for T1b gall bladder cancer ranges around 21% and radical surgery with complete peri −portal lymphadenectomy should be considered as standard of care.

1. Introduction

Gallbladder cancer (GBC) is the most common biliary tract malignancy with incidence as high as 10–22 per 100,000 population, particularly in the northern part of India [1]. GBC is an inherently aggressive disease with poor 5 year survival (<5%) especially for advanced stage disease [2]. In the era of laparoscopic cholecystectomy, incidental GBC (iGBC) has increased with about half of patients staged as pT2 and one third pT1 [3]. Incidental diagnosis is particularly common for GBC owing to the fact that early GBC is difficult to recognise by imaging and this leads to the need of completion surgery. As with other solid tumours, lymph nodal involvement is a poor prognostic factor for GBC and appropriate lymph nodal staging of T1b GBC could change from stage I to stage III or IV and impact survival [4]. Failure to evaluate regional lymph nodes leads to inaccurate disease staging thus potentially resulting in suboptimal use of indicated adjuvant therapies. Retrospective studies with small numbers not showing difference in survival outcomes for simple versus radical cholecystectomy for T1b tumours has resulted in a debate regarding the optimal surgical extent for these tumours [5,6]. However, these data need to be interpreted with caution, as definite criteria for selection of the type of surgery are not always available. Secondly, incidence of lymph nodal metastasis in pT1b has been reported to be as high as 15.2% with an average overall risk of 10.9%. This warrants a complete staging procedure in order to timely initiate adjuvant systemic therapy [7–9]. In keeping with this, NCCN guidelines also recommend complete peri-portal clearance for T1b tumours [10].

* Corresponding author. GI and HPB Surgery Department of Surgical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Ernest Borges Marg, Parel, Mumbai, 400 012, India.
E-mail address: drshraddhapatkar@gmail.com (S. Patkar).

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Current literature has also given rise to conflicting evidence regarding the need for radical surgery and its effect on survival with a recent multicentre study showing no effect on disease specific or overall survival with radical surgery [11]. The National Cancer Database analysis for T1b GBC showed a detriment in 5-year overall survival from 64.4% to 48.3% if simple cholecystectomy alone was performed [12]. With this background, we have analysed the clinico-pathological features, rate of lymph nodes metastasis and survival outcomes of T1b GBC patients operated at our institute, which is a high volume tertiary care referral centre to better define the optimal surgical strategy for this subgroup.

2. Materials and methods

A retrospective review of prospectively maintained database of GBC patients undergoing surgery between March 2010 to March 2021 was performed. All patients with pT1b on final histopathology following either upfront radical cholecystectomy or revision surgery done post-simple cholecystectomy (laparoscopic/open) were included. Exclusion criteria were histology other than adenocarcinoma and unavailability of pathology slides for review. Preoperative evaluation was done as per institutional protocol with contrast enhanced computed tomography (CECT) scan of the chest, abdomen and pelvis for patients presenting upfront and within 4 weeks of index laparoscopic or open cholecystectomy. Positron emission tomography (PET) CECT was done in patients presenting after 4 weeks of index surgery. Apart from imaging, tumor markers, assessment of general health, comorbidities and nutritional status was done for all patients and they were preoperatively referred for nutritional rehabilitation and chest physiotherapy clinic as a part of our ERAS (enhanced recovery after surgery) protocol [13]. All patients were discussed in a multidisciplinary tumour clinic for management decisions. Patients with iGBC diagnosis were required to procure slides and blocks for pathological evaluation at our institute. Patients with early GBC as per imaging were planned for upfront surgery (without biopsy or fine needle aspiration cytology) with frozen section diagnosis and completion radical cholecystectomy. Our institutional protocol mandates completion radical cholecystectomy for all tumours $\geq$ T1b. After discussion in the multidisciplinary tumour clinic, decision for neoadjuvant therapy (NAT) was taken based on presence of FDG-avid residual disease in the gallbladder fossa and/or uptake in periportal nodes as per previously published "TMH criteria" for "high risk GBC". Neoadjuvant chemotherapy protocol for the patients included a combination of gemcitabine with either cisplatin or oxaliplatin for 3–4 cycles followed by response assessment. We have recently started adding nab-paclitaxel to this regimen based on a recent phase 2 trial suggesting excellent response rates [14]. Revision surgery (Fig. 1) encompassed excision of liver bed with negative margins along with complete peri-portal and retro-duodenal lymphadenectomy (stations 8, 12, and 13) as per institutional standardisation [15]. If cystic duct margin was not evaluated at the time of index surgery it was revised and sent for frozen section examination to confirm margin negative status. Final staging after revision surgery was assigned as per American Joint Committee on Cancer 8th edition [16]. Patients were again discussed in tumor board meeting for decision on adjuvant therapy based on tumor characteristics/nodal status and patient performance status. Patient's baseline demographic data, preoperative clinico-radiological data, pathological data from initial cholecystectomy, intraoperative details, postoperative complications according to Clavien-Dindo grading [17], final histopathology report and follow up data were recorded. Follow up protocol included 3 monthly visits for the first 2 years followed by 6 monthly for the next 3 years with CA 19.9 and an imaging either an ultrasound or CECT of the chest, abdomen and pelvis was performed annually for all patients up to 5 years.

3. Statistical analysis

The data was added using Statistical Product and Service Solutions (SPSS), IBM Corp, for Windows version 28.0.0.0, (SPSS Inc.). Descriptive analyses was performed for demographic variables, preoperative clinicoradiological data, pathological data, intraoperative details, postoperative complications and final histopathology report with special emphasis on lymph nodal metastasis. Overall survival (OS) was calculated from the date of diagnosis to death due to any cause and disease-free survival (DFS) was calculated from the date of diagnosis to recurrence of disease. OS and DFS were calculated using Kaplan Meier method.

4. Results

A total of 1245 patients of upfront and revision surgery for gallbladder pathology from March 2010 to March 2021 were reviewed. Stage-wise distribution revealed 88 (7%) pT1 disease which included 76 patients of T1b and 12 of T1a, 296 (24%) Stage II

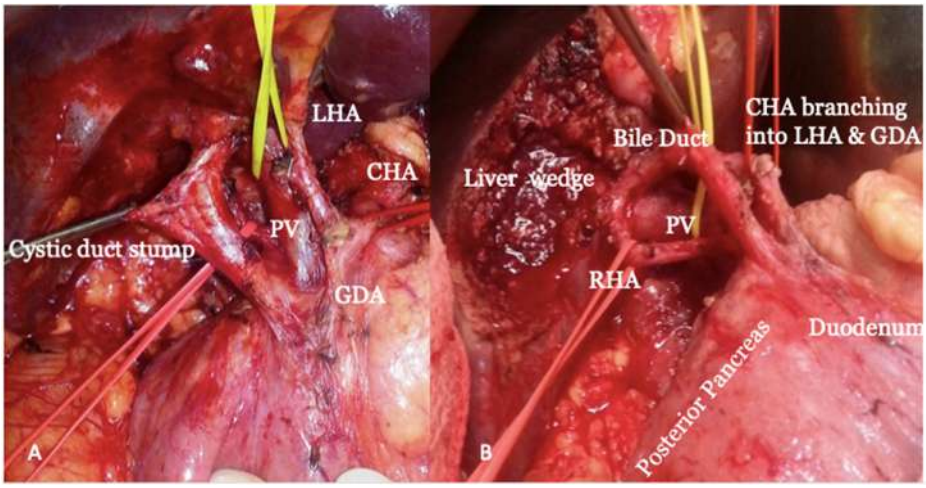

Fig. 1. A-Completed periportal clearance with structures labelled as – PV-portal vein, LHA-left hepatic artery, cystic duct stump, CHA-common hepatic artery, GDA-gastroduodenal artery. B-Completed periportal clearance with liver wedge.

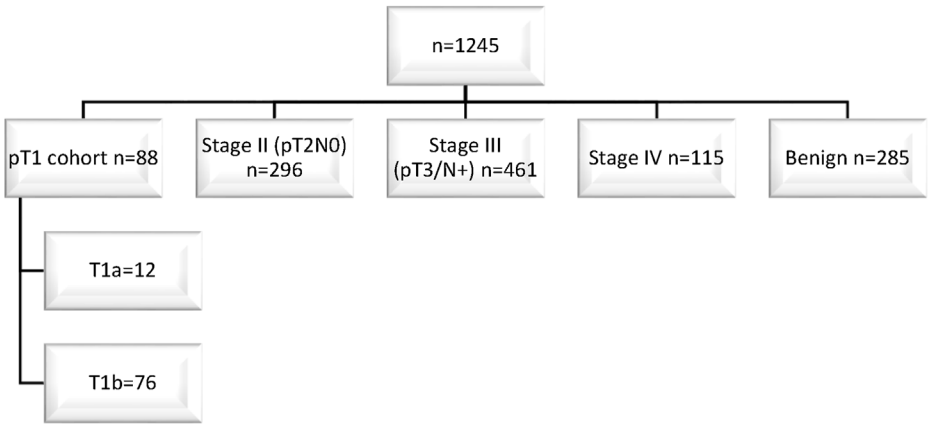

Fig. 2. Consort diagram with stage-wise distribution.

(T2N0), 461 (37%) Stage III, 115 (9%) Stage IV and 285 (23%) benign histopathology (Fig. 2). Amongst 76 patients, 11 patients underwent upfront surgery and 65 patients were subjected to completion surgery with liver wedge resection and periportal lymphadenectomy post either a laparoscopic or open cholecystectomy (Table 1). Neoadjuvant treatment was given to 9 patients due to metabolically active residual disease in gallbladder fossa and/or in periportal nodes and they were included in the final analysis combined with node positive disease.

In final analysis, there were 16 patients in the node positive cohort and 60 patients in the node negative cohort. Node positive cohort included 7 patient with node positive disease as per final histopathology report and 9 patients who were given neoadjuvant therapy based on PET-uptake in periportal nodes and/or GB fossa residual disease. Median age of presentation was 50 years (range 29–72 years) with female preponderance (73%). Median preoperative CA 19.9 levels were 44.6 IU/ml (2–1830 IU/ml). Histopathological grading included most commonly moderately differentiated adenocarcinoma (64.5%) followed by well differentiated (23.6%) and poorly differentiated adenocarcinoma (7.9%). Median postoperative hospital stay of patient was 6 days (3–23 days). Only four patients (5.2%) out of 76 had Clavien-Dindo grade 3 or higher post-operative complication. There was no post-operative mortality. Median numbers of nodes harvested were 8 (range: 2–24). Node positive cohort comprised 21% (16/76) of all patients with pT1b in final histopathology report. Average number of positive nodes in the N1 disease stage was 3 [1–7]. Elevated CA 19.9 levels were not able to predict lymph nodes metastasis for pT1b disease.

After a median follow up of 47.5 months (range 2–120 months), 4 (25%) out of 16 node positive cohort had succumbed due to disease, 3 were alive with disease and 1 were lost to follow up with OS of 75% and DFS of 62.5% at 3 years whereas amongst the node negative cohort 2 (3.3%) out of 60 had died due to disease and 3 were alive with disease with an OS of 96.7% and DFS of 91.7% at 3 years. Although the difference was not significant as per the log rank test, this was likely due to the small sample size (Fig. 3). Patterns of recurrence were also peculiar (Table 2) with node positive cohort having 43% recurrences whereas the node negative cohort had 8.3%. All the recurrences were limited to periportal lymph nodes, distant nodes or liver metastasis. There was no recurrence in the gallbladder fossa in either group.

Table 1
Demographic data with intraoperative, postoperative and survival outcomes.

Age (years)	50 (29–72)
Sex (M:F)	20:56 (27:73%)
Preop CA 19.9	44.60 (2–1830)
Surgery-	
Radical cholecystectomy	11
Revision radical cholecystectomy	65
ASA I/II/III	39/34/03
BMI	24.40 (17.72–36.00)
Surgical details-	
Operative time (min)	150 (120–360)
Blood loss (ml)	560 (50–1700)
Primary HPR Grade	
Well differentiated	18 (23.6%)
Moderately differentiated	49 (64.5%)
Poorly differentiated	06 (7.9%)
Adenocarcinoma (no comment)	03 (3.9%)
Nodal yield	8 (2–24)
Node positive cohort (N1 = 7, NAT = 9)	21% (16/76)
Postoperative outcomes	
Post operative Hospital stay	6 (3–23)
Clavein Dindo ≥ IIIa	5.2% (4/76)
30 day mortality	0

NAT- Neoadjuvant therapy, N1- Node positive on final histopathology.

5. Discussion

GBC presents a therapeutic challenge due to its aggressive clinical behaviour and poor long-term outcomes. The impact of multi-modality therapy including neoadjuvant chemotherapy or adjuvant chemotherapy and radiotherapy along with a complete radical clearance have improved survival of locally advanced disease [18–20]. As with advanced GBC, the presence of lymph node metastasis in pT1b GBC requires multimodality therapy to improve survival outcomes. The dilemma for pT1b arises from the studies that show equivalent outcomes of extended resections with periportal lymphadenectomy as compared to simple cholecystectomy. However, these are not randomised data and have small number of pT1b patients with inherent biases based on selection of surgery, reporting survival outcomes and recurrences [5,6]. Recurrence rates and lymph node metastasis in pT1b GBC can be as high as 85.7% and 15.2% respectively [5]. These reported outcomes exclude patients of pT1b diagnosed as iGBC who have residual disease and require neoadjuvant therapy, thus likely leading to a selection bias towards good biology. With such a high rate of lymph nodal metastasis there should be no doubt regarding standard regional lymphadenectomy to improve survival [21–23].

A decision analysis done for 5-year cancer specific survival depending on type of surgery revealed 61.3% versus 87.5% for simple cholecystectomy and radical cholecystectomy respectively [24]. This was corroborated by the recent National Cancer Database

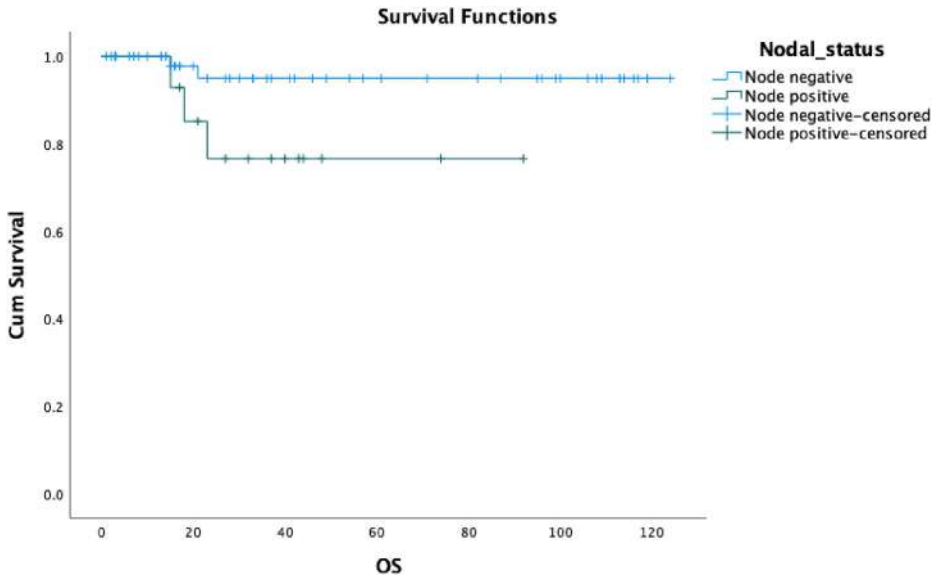

Fig. 3. Kaplan Meier curve comparing node positive and negative cohort survival with Log rank test (p = 0.058).

Table 2
Comparing Outcomes of node positive and node negative cohort.

	Node negative	Node positive
n	60	16
Final HPR-Liver wedge disease	Nil	Nil
Recurrence n	5/60 (8.3%)	7/16 (43.75%)
GB Fossa	0	0
Periportal nodes	2	3
Distant nodes/Liver metastasis	3	4

analysis for T1b GBC with a better OS for the radical cholecystectomy-regional lymphadenectomy arm and a 29% reduction in risk of death [12]. This database analysis also revealed similar rate of adjuvant therapy in simple cholecystectomy arm without node evaluation and radical cholecystectomy-regional lymphadenectomy arm of 10.9 versus 9.4%. The reasons for adjuvant therapy in simple cholecystectomy arm were not available. It only seems logical to correctly stage early GBC for the patients to benefit from adjuvant therapies especially with the recent molecular classification and its impact on therapeutic decision making [25]. The other technique to predict lymph nodal metastasis would be to apply nomograms based on risk factors and to use this information to decide on radical cholecystectomy [26]. However, the use of nomograms has not been validated across all ethnicities and it may be too premature to comment on its use in routine evaluation. Outcomes with respect to tumour size criteria of 1 cm has also shown to affect survival outcomes as well as lymph node metastasis [27]. Another important aspect is that most studies do not have the median lymph nodes evaluated to be as per current AJCC 8th edition [28,29]. A minimum of 6 lymph nodes need to be evaluated for a complete periportal lymphadenectomy. This would also suggest that apart from the inherent biases due to small numbers, there is a chance of inaccurate staging due to incomplete nodal clearance [29].

The morbidity and mortality in high volume centers such as ours balances the risk benefit ratio to allow for radical resection [30]. Apart from favourable perioperative outcomes, the adequacy of radical surgery is much better at a high volume center [31,32]. Our data demonstrates a morbidity of 5% and no perioperative mortality which justifies our rationale of radical surgery for staging. Recurrence patterns are also reflected by the radicality of surgery as shown by Lee et al. where the patterns of recurrence were significantly less in the extended cholecystectomy as compared to simple cholecystectomy arm (2.7 vs 12.5%) [5]. There were no locoregional recurrences in the extended cholecystectomy arm as opposed to 50% recurrences being locoregional in the simple cholecystectomy arm for T1b tumours [5]. Significantly lower locoregional recurrences combined with a lack of active follow-up in Indian population validates a more radical approach [33]. The predominant nodal rather than liver bed recurrence pattern in our cohort suggests the need to consider lymph nodal clearance for pT1b disease as a standard. A last point to be taken into consideration is that all patients that were iGBC did not have disease in liver wedge and no recurrences were noted in the GB fossa on follow-up, this suggests that for pT1b a complete periportal lymphadenectomy without a liver wedge is likely the ideal strategy. Thus in keeping with current guidelines we would also like to recommend a complete staging radical cholecystectomy with complete peri-portal nodal clearance for all T1b patients [34–36]. The limitations of the study is due to its inherent retrospective nature with a single center cohort. However, the adequacy of surgery was complete and patterns of recurrence were defined allowing us add to current literature on this topic.

6. Conclusion

Nodal positivity for T1b gall bladder cancer ranges around 21% and radical surgery with complete peri −portal lymphadenectomy should be considered as standard of care to correctly stage the disease from stage I to stage III. The predominant recurrence pattern of periportal lymph nodes without any gallbladder fossa recurrence also justifies complete lymphadenectomy with possibly avoiding liver bed excision in pT1b.

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CRediT authorship contribution statement

Mahesh Goel: Study concepts, Study design, Data analysis and

interpretation, Manuscript editing, Manuscript review. **Saneya Pandrowala:** Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review. **Prerak Patel:** Data acquisition, Statistical analysis, Manuscript preparation. **Shraddha Patkar:** Study concepts, Study design, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.

Declaration of competing interest

None.

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