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ORIGINAL ARTICLE

Reappraisal of T1b gallbladder cancer (GBC): clinicopathologic analysis of 473 in situ and invasive GBCs and critical review of the literature highlights its rarity, and that it has a very good prognosis

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Abstract

There are highly conflicting data on relative frequency (2–32%), prognosis, and management of pT1b-gallbladder carcinoma (GBC), with 5-year survival ranging from > 90% in East/Chile where cholecystectomy is regarded as curative, versus < 50% in the West, with radical operations post-cholecystectomy being recommended by guidelines. A total of 473 in situ and invasive extensively sampled GBCs from the USA ($n = 225$) and Chile ($n = 248$) were re-evaluated histopathologically per Western invasiveness criteria. 349 had invasive carcinoma, and only 24 were pT1. Seven cases previously staged as pT1b were re-classified as pT2. There were 19 cases (5% of all invasive GBCs) qualified as pT1b and most pT1b carcinomas were minute (< 1mm). One patient with extensive pTis at margins (but pT1b focus away from the margins) died of GBC at 27 months, two died of other causes, and the remainder were alive without disease (median follow-up 69.9 months; 5-year disease-specific survival, 92%). In conclusion, careful pathologic analysis of well-sampled cases reveals that only 5% of invasive GBCs are pT1b, with a 5-year disease-specific survival of > 90%, similar to findings in the East. This supports the inclusion of pT1b in the "early GBC" category, as is typically done in high-incidence regions. Pathologic mis-staging of pT2 as pT1 is not uncommon. Cases should not be classified as pT1b unless extensive, preferably total, sampling of the gallbladder to rule out a subtle pT2 is performed. Critical appraisal of the literature reveals that the Western guidelines are based on either SEER or mis-interpretation of stage IB cases as "pT1b." Although the prognosis of pT1b-GBC is very good, additional surgery (radical cholecystectomy) may be indicated, and long-term surveillance of the biliary tract is warranted.

Keywords Gallbladder carcinoma · pT1b · Pathologic sampling · Survival

Introduction

TNM staging protocol of the AJCC/UICC classifies gallbladder carcinomas (GBC) that are confined to and above the tunica muscularis as pT1, with pT1a if there is only lamina propria invasion, and, pT1b, if there is also invasion into the tunica muscularis.

The significance of the pT1b category, its frequency, prognosis, and management has been highly controversial. There are wide discrepancies in the literature regarding the relative frequency of pT1b cases among invasive GBCs, with the reported numbers ranging from 2 to 32% [1–33]. More importantly, the expected prognosis and the recommended treatment vary greatly by geographic region. Most studies from the Far East, especially Korea and Japan report an excellent behavior, indicating a 5-year survival of above 90% [4, 12, 22, 26, 29, 30, 32, 34–36] and a 10-year survival of > 85% [3, 4]. The studies from Chile, where GBC incidence is very high and where pathologic examination of gallbladder specimens is performed in detail with total sampling, also show a very good prognosis [37, 38]. As a result, in most of these countries, cholecystectomy is deemed adequate for pT1b GBCs, and no additional surgery is performed unless there is another adverse factor. In

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contrast, in the West, the prevailing opinion, mostly based on the data from the SEER (Surveillance Epidemiology End Results) database, is that pT1b GBCs constitute substantial proportion of GBCs and are fairly aggressive [14] with a 5-year survival below 50% [6, 11, 17, 19, 20, 31, 39, 40]. In fact, some authors report a 5-year survival as low as 0% [41] and even 1-year survival is reported to be only 50% [42, 43]. For this reason, established guidelines and consensus reports strongly recommend a more radical operation targeting the gallbladder bed and adjacent liver, "which involves portions of segments IVb and V of the liver, as well as portal lymphadenectomy" [44, 45]. Also, in several studies, pT1b cancers are grouped together with pT2 for the purposes of clinical outcome analysis [25, 27, 30, 45–48].

These major geographic discrepancies in the literature regarding pT1b-GBC were the subject during multiple annual meetings of the International Hepatobiliary Association (IHPBA), but without any resolution regarding the reasons and potential solutions. Among the speculations were the pathologic criteria and sampling issues. In 2017, IHPBA established the International Study Group for Gallbladder Cancer (ISG-GBC), which identified geographic differences in the literature for pT1b- and pT2-GBC as one of the main issues that need resolution before any clinical trials can be established [49]. For pT2-GBCs, international pathologic collaborative studies have shown that the geographic differences in survival were not as wide as the literature previously implied, but at the same time, minor prognostic differences between regions still persisted even when the histopathologic criteria were standardized by international collaborations, leading to the conclusion that these differences may partly be due to biologic, etiopathogenetic, management-related, populational, or healthcare practice-related factors [50]. However, for pT1b-GBCs, the reasons for these discrepancies have remained unclear due to the lack of a study addressing the issue with proper pathologic evaluation and international collaborations, and this study was undertaken to fundamentally address this issue.

The goal of the present study was to determine the frequency, clinicopathologic characteristics, and behavior of pT1b-GBC through an analysis of 473 in situ and invasive carcinomas from the USA and Chile, along with a reappraisal of the literature to clarify sources of an existing controversy.

Material and methods

This study was conducted in accordance with Institutional Review Board requirements.

Case selection

A total of 473 consecutive gallbladders with in situ or invasive gallbladder carcinoma were carefully re-evaluated for the presence and depth of invasion (pathological stage), by using the Western invasiveness criteria per AJCC/UICC 8th edition [51]. 248 of these were from Universidad de La Frontera, Temuco, Chile, and 225 were from the files of Wayne State University, Detroit, MI, USA, and Emory University, Atlanta, GA, USA, encountered between 1999 and 2014. All gallbladders from Chile had been submitted entirely for microscopic examination by total mapping per the protocol established by Roa et al. [37, 52–54]. All consecutive GBCs were included. Most of the US cases were not completely sampled, as is the general practice in this country, but rather targeted sampling focusing on the grossly abnormal-appearing areas had been performed and the reports indicated "random" sampling without any mapping or any documentation of the specific localization of the sections. Of note, close to two-thirds of the cases in the entire database were in the "clinically unapparent" category (i.e., carcinoma was not suspected clinically but discovered after the cholecystectomy was examined histologically) [55], and thus, even basic oncologic sampling protocols (including the margin evaluation) had not been applied in a significant proportion of the cases, an issue that has been identified as a problem and a recommendation is now being drafted by ISG-GBC to address it [49]. However, at the same time, the number of the reviewed slides of the USA cases was also substantial with an average of 9 ± 8.41 (median 7; range, 1–77 slides).

Case characterization

Original pT-stage diagnosis was obtained from the surgical pathology reports and patients' records. In the cases from the USA, the tumors had been staged per the AJCC/UICC TNM classification as pTis (in situ carcinoma), pT1a (tumor invading lamina propria), pT1b (tumor invading muscular layer), pT2 (invasive through the muscularis propria into the peri-muscular tissue), and pT3 (involving the serosal surfaces or invading into the liver). In the original reports, the cases from Chile had been staged per the protocol commonly used in the high-cancer incidence regions, with GBCs confined to the muscularis and above (corresponding to the pTis/T1 cases of TNM classification) being classified as "early GBC," and those with peri-muscular invasion (corresponding to the pT2/T3) being classified as "advanced GBC" [37]. In this Chilean classification, the "early" GBCs with recorded muscle involvement correspond to pT1b. In this analysis, all of the cases were re-evaluated by the authors and re-staged per the per AJCC/UICC 8th edition [51].

All the cases that had been classified as pTis/T1 ("EGBC" in Chile) as well as those with superficial invasion into peri-muscular tissue (subject of a different ongoing study [56]) were evaluated by four of the authors (NVA, JCR, GA, and BM) independently, by using liberal ("all inclusive") criteria

[57]. The cases determined to be potential pT1 or minimal pT2 (subject of a separate study [56]) were then evaluated in a consensus format by three of the authors (JCR, NVA, OB) in order to establish the precise stage and to exclude mimickers including but not limited to pseudoinvasion, Rokitansky-Aschoff sinus (RAS) involvement versus invasion, and potential impact of stromal changes in the staging. Controversial cases were also shared with other observers during the Santiago international consensus meetings in 2015 and 2017, respectively in which inter-observer agreement of some of these parameters was tested as a part of a separate project [57].

For the 24 cases that qualified as pT1 per this re-analysis, every attempt was made to further clarify the clinical information, especially the follow-up. For the Chilean pT1 cases, Universidad de la Frontera where these cases originated from, the hospital had been designated the regional referral center for Temuco where GBC incidence is very high, and the Chilean government has made a special effort to establish a registry of GBC. Accordingly, the information was obtained from The Civil Registry and from databases of death certificates available at the South Araucanía Health Service in Chile. Therefore, reliable information could be obtained for this group. For the USA cases (7 cases), the primary physicians of the patients as well as, as needed, the patients themselves were contacted to obtain the information.

Statistical analyses were performed using the standard statistical software package SPSS (version 23 for Windows; IBM Corp). Only institutional cases were included in the frequency analysis to determine the incidence of pT1b-GBC. Survival analysis was performed for pT1b-GBC cases, using Kaplan–Meier method. Survival information was obtained from the patient charts or by contacting the primary physicians. For the Chilean cases, survival information was obtained from The Civil Registry and from databases of death certificates available at the South Araucanía Health Service in Chile. Two patients who died within the first 30 days of the post-operative period were excluded from the survival analysis.

Results

Of the 473 GBCs (248 from Chile and 225 from the USA) re-evaluated by the authors, 349 (including 23 consults) were found to have invasive carcinoma while 124 were classified as non-invasive (pTis). Using the criteria employed in the West (AJCC/UICC TNM classification), invasive carcinoma confined to the muscularis and above (pT1) was identified in only 24 cases. In 5 of these, no definitive involvement of the muscularis was identified. These cases were classified as pT1a. In the remaining 19 (including 3 consults), the invasive carcinoma cells in the mucosa/lamina propria were either abutting the muscle or lying in between the muscle bundles without clear-cut deeper penetration into perimuscular soft tissues. These cases were classified as pT1b. Thus, the true proportion of pT1b tumors among all GBC cases in this series was 5%.

There were 24 cases that had been designated as pT1b in the original reports, and 7 (29%) of these proved to be pT2 upon review. In the US group, of the 10 cases classified as pT1b in the original pathology reports, 3 showed subtle areas of tumor penetration through the tunica muscularis into the perimuscular tissue (Fig. 1) and were thus re-classified as pT2 and excluded. In the Chilean group, 51 cases were initially classified as "early GBC" (corresponding to pTis/T1 of AJCC). Of these, 18 qualified as pT1 (4 pT1a and 14 pT1b) upon review, and 33 were determined to lack definitive invasion (i.e., classified as pTis by Western criteria). In 4 cases, carcinoma originally designated "early GBC with muscle involvement" (i.e., corresponding to pT1b in AJCC/UICC) was found to be infiltrating into the perimuscular tissue; these were upstaged to pT2 and excluded. In most cases, there was no suspicion of a neoplasm or malignancy at the time of the operation or during the grossing, and therefore, the adequacy of the cystic duct margin section was in question.

Carcinomas that were qualified as pT1b (confined to the muscularis) were miniscule in size. The overall distribution, size, and appearance were very similar to those of "intramucosal adenocarcinomas" seen in the rest of the gastrointestinal tract (Fig. 2). The mean size of invasion was a fraction of a millimeter, and most cases were composed of few clusters of carcinoma cells (Fig. 3). In the rare cases that showed relatively wide intramucosal carcinoma involving the full thickness of the mucosa and the muscle (Fig. 4), the carcinoma typically proved to be less than 1 mm in thickness.

Of the 19 patients with pT1b-GBC, 17 were female. The median age was 66 years (range, 47–94 years). Except for five cases who had polypoid lesions, the patients had undergone cholecystectomy for gallstone disease or cholecystitis, unsuspected of having any malignancy. In 5 patients, an acute attack of cholecystitis was noted. One US patient had a gallbladder removed during liver transplantation. The five cases with polypoid lesions proved to be intracholecystic papillary tubular neoplasm with high-grade dysplasia along with a focus on muscle-invasive carcinoma [58]. RAS involvement by in situ carcinoma was present in 5. None of the Chilean pT1b cases had post-cholecystectomy surgery or any additional therapy. One patient from the USA, with initially negative cystic duct margin and negative pericholecystic lymph nodes, underwent bisegmentectomy of the liver. Because the cases were not suspected to have malignancy in the initial gross evaluation, cystic duct margin had not been submitted in an oncologic manner or had been obtained only

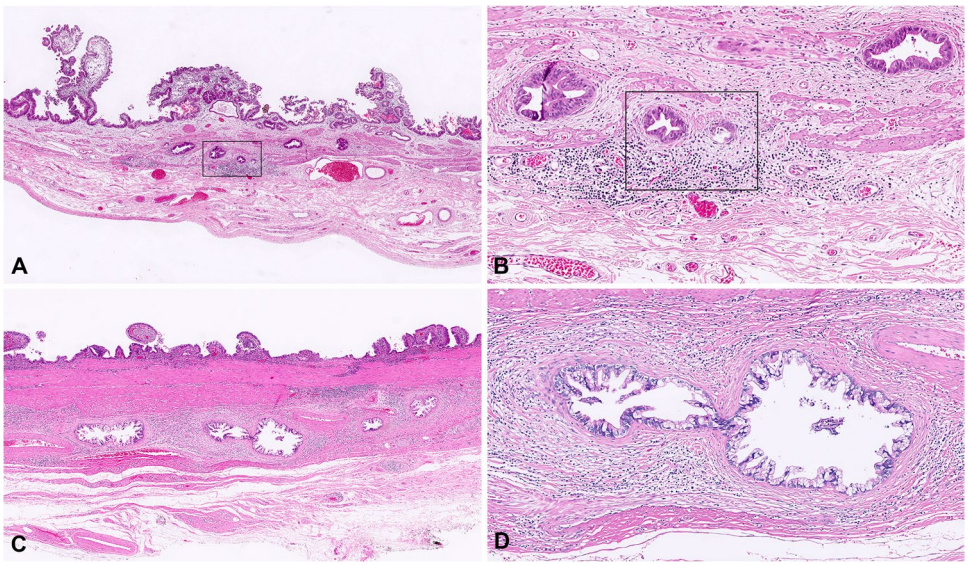

Fig. 1 Subtle examples of pT2 misinterpreted as pT1. Overall, 29% of the cases which had been defined as pT1b in the original reports proved to be pT2 upon review due to the presence of subtle areas of tumor penetration through the tunica muscularis into the perimuscular tissue. While some were overt pT2s, others were more challenging. Two subtle examples are illustrated here. In the first example case (**A**–**B**), dispersed neoplastic glands dissect the muscle bundles, and while most are separated by a muscle layer from the subserosal tissues, in one focus (box) no muscle layer is observed under the invasive glands indicating that this is in fact a very early T2. In the second example case (**C**–**D**), on low power examination, the invasive glands give the erroneous impression of being confined by the tunica muscularis although the adjacent large vascular structures indicate that they are in fact in the peri-muscular tissue. In the high-power view, the pink band underneath the invasive glands prove to be fibrous tissue rather than muscle confirming that they are indeed at pT2 level, not pT1b

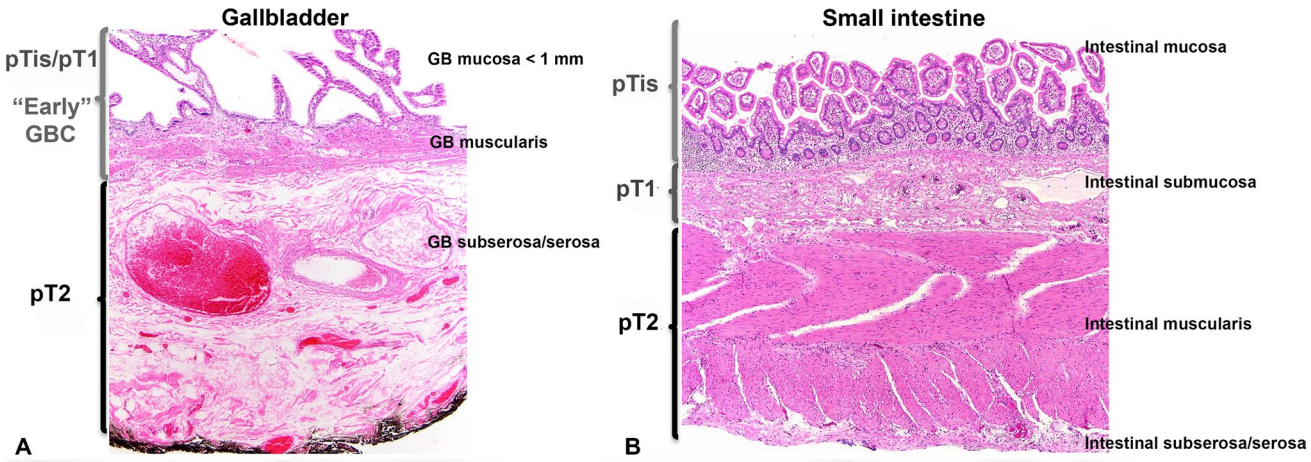

Fig. 2 pT1 of gallbladder (GB) (**A**) essentially corresponds to intramucosal carcinoma in other gastrointestinal organs (**B**). The tunica muscularis of the gallbladder is very superficial (like muscularis mucosae). Thus, it is very uncommon to catch a convincing invasion in this small zone

after the diagnosis of carcinoma was discovered by microscopy, and thus, assessment could not be conducted reliably in the majority. However, in the only case that died of carcinoma in 27 months, in situ carcinoma overtly extended to the cystic duct margin but the pT1b focus was away from the margin. Two out of eleven patients with a lymph node available in the cholecystectomy specimen showed metastasis in the lymph node. Of the 2 cases with lymph node metastasis, 1 also had terminal colorectal carcinoma, and the other patient was still alive at the last follow-up (162.2 months).

Median follow-up was 69.9 months (range, 4.8–179 months). Of the 19 pT1b cases, 2 died perioperatively, 2 died of other causes, and 1 died of tumor at 27 months (this patient also had extensive pTis

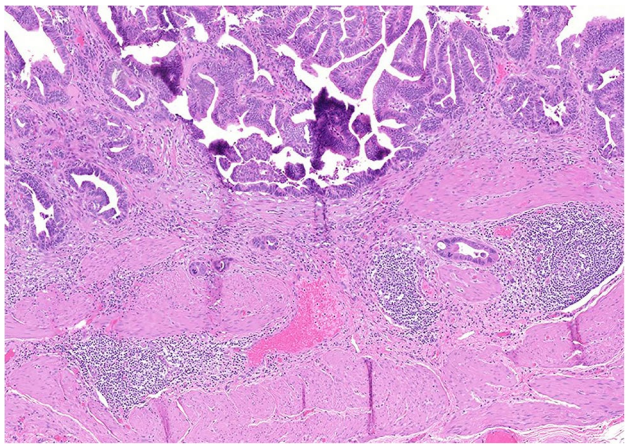

Fig. 3 pT1b gallbladder adenocarcinoma. A more typical example composed of a handful of glands invading into the muscle bundles. Some of the invasive glands show paradoxical acidophilia that creates a contrast with the surface in-situ carcinoma (high-grade dysplasia) component and allows their recognition as invasion, not invagination. In this case, muscularis is more compact and thicker and invasion is confined to the upper segment of the muscularis

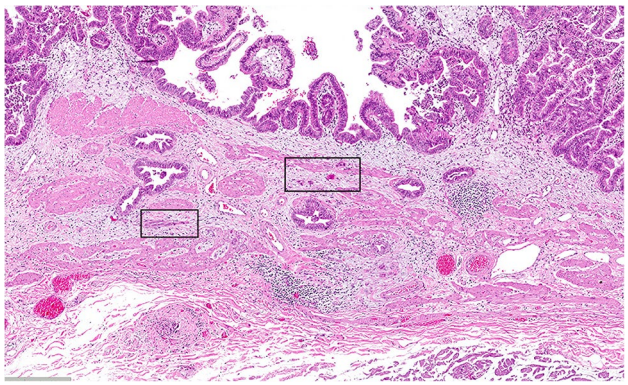

Fig. 4 An example of a pT1b gallbladder carcinoma arising in an intracholecystic papillary neoplasm with high-grade dysplasia/carcinoma in situ. This is a relatively larger example of pT1b composed mostly of exceedingly well-differentiated adenocarcinoma units, that resemble Rokitansky-Aschoff sinus involvement with pagetoid spread. However, there are also less differentiated smaller units (shown in squares). The carcinoma units are abutting the muscle in multiple foci, and thus qualify as pT1b. This case also has relatively thick but patchy muscularis and thus illustrates the zonal variability in its distribution. However, it is also clear that in this case, the carcinoma is indeed confined entirely to this layer

throughout the gallbladder extending to the margins), and the remaining 14 were alive without disease; thus, the overall 5-year survival was 83% and disease-specific 5-year survival was 92% (Table 1).

Critical review of the literature (Tables 2 and 3)

In the West, a substantial proportion of publications on pT1b GBCs was a retrospective analysis of the SEER or similar registries, which comprised data based on non-standardized reports collected from many hospitals, using the random sampling approach that is routine in the West. These registry-based studies reported the relative frequency of pT1b among invasive GBCs as 10–19% [15, 17, 19, 20, 24, 27, 28], and the 5-year survival rate at about 50% or lower (between 34 and 50%) [17, 19, 20, 28, 39, 40, 51]. However, in stark contrast with SEER-based publications, the studies based on institutional databases from tertiary care centers in the West including Memorial Sloan-Kettering and Massachusetts General Hospital placed the frequency much lower typically less than 8% [1, 5, 6, 9, 10]. More importantly, although the survival information was very limited, the behavior did not seem to be as aggressive [1, 6, 59, 60]. In one institution-based study of 6 pT1b GBC cases, no disease-specific death was reported [11].

Most cited guidelines and consensus statements in the West [42–45] were based on the article by Principe et al. [59] quoted as "Principe and colleagues have reported only 50% 1-year survival rate with simple cholecystectomy; therefore, in fit patients, it seems reasonable to proceed with a more radical operation involving portions of segments IVb and V of the liver as well as performing a portal lymphadenectomy." However, when the article by Principe et al. was carefully analyzed [59], there were only 2 patients with pT1b GBC, one of whom died on the postoperative day 95, and the other one died of natural causes at 4 years. Evidently, in the articles evaluating this paper, the stage "IB" cases of this study were mistaken as "pT1b".

In the East, analyses based on the institutional databases of experienced institutions also reported a low frequency of pT1b similar to those in the West, and a very good behavior with a 10-year survival of over 85% [3, 4, 35]. However, similar to the situation in the Western studies based on country-wide databases like SEER or consortia in the Far East also reported a high frequency of pT1b among invasive GBCs (11–29%) [12, 21, 26, 29, 30, 32, 36]. Some of these also reported a somewhat poorer 5-year overall survival of 75% [13, 18, 61].

Discussion

The results of this study, combined with the critical review of the literature, bring major clarifications to the identity of pT1b-GBC and warrant a paradigm shift in the current guidelines in the West: (1) Only a small percentage

Table 1 Follow-up information of the patients with pT1b GBC in our series

Case #	Age	Sex	Survival (months)	Status	Cause of death
1	66	Male	4.8	Alive	
2	80	Female	9.5	Alive	
3	75	Male	16	Alive	
4	94	F	110.8	Alive	
5	70	F	11.2	Alive	
6	80	F	28.2	Alive	
7	63	F	12.9	Alive	
8	67	F	37.8	Died of another cause	Colorectal cancer
9	78	F	69.9	Died of another cause	Cardiac failure
10	**47**	**F**	**27.0**	**Died of disease +**	Gallbladder Cancer
11	60	F	0	Perioperative mortality*	Acute toxic cholangitis
12	65	F	0.8	Perioperative mortality*	Acute toxic cholangitis
13	63	F	132.7	Alive	
14	55	F	135.0	Alive	
15	47	F	146.4	Alive	
16	81	F	151.5	Alive	
17	52	F	157.0	Alive	
18	67	F	162.2	Alive	
19	54	F	179.0	Alive	

+ This patient had extensive pTis throughout the gallbladder extending to the margins (written in bold)

*Patients who died perioperatively were not included in the survival analysis

(5%) of the GBCs qualify for this stage in well-sampled cases using Western invasiveness criteria. (2) pT1b-GBC is fundamentally an "intramucosal adenocarcinoma" that is typically very small and thus, not surprisingly, has a very good prognosis (5-year disease-specific survival, 92%) and may not warrant major resection. (3) The major discrepancies in the literature are attributable to pathologic under-sampling/under-staging and differential application of pathologic criteria as well as misinterpretation of the literature. Below, these issues are discussed individually in further detail.

This study elucidates that pT1b-GBC is actually the gallbladder counterpart of "intramucosal adenocarcinoma." In the gallbladder, the mucosa is thin (typically less than a 1 mm in thickness, Fig. 2). Moreover, the tunica muscularis also serves like a muscularis *mucosa* in this organ. Therefore, as disclosed in this study, any carcinoma that achieves the size of more than a millimeter or so is already infiltrative through the muscularis into perimuscular tissue and thus would have to be qualified as pT2, not pT1b. Such small carcinomas within the mucosa are typically regarded as "intramucosal adenocarcinoma" in the remainder of the gastrointestinal tract, or as "microcarcinoma" in solid organs, and they mostly display very good prognosis, close to in situ carcinomas, and are often cured by complete removal. Therefore, it is not surprising that, both in our series as well as the other studies from tertiary care centers (see Table 2) with proper documentation of the cases, pT1b-GBC is rare and has a good prognosis [1, 5–11, 59, 60].

Unfortunately, the current guidelines in the Western literature are mostly based on the SEER database and other similar registries that report a much higher frequency, typically 10–19% [15, 17, 19, 20, 24, 27, 28], and shockingly poorer survival results, which are starkly different than our results as well as those of other institutional-data based analyses also from the West [1, 5, 6, 9, 10]. Naturally, it is impossible to ascertain the nature of this discrepancy; however, based on some of the findings in our study as well as what we observe in our consultation practice regularly, a few speculations are in order. For example, even in our cohort of GBCs from our tertiary care centers, 29% of the cases that had been originally classified as pT1b had to be re-classified as pT2 upon our re-review. This is something we also observe routinely in our consultation practice as well; most cases brought to us as pT1 prove to be pT2 with further sampling and sectioning. Furthermore, in our international consensus study in Santiago, Chile, in 2014, we observed that even experts sometimes interpret pT2 carcinoma as CIS extension into RAS, and vice versa. Therefore, we believe the erroneous impression in the West based on SEER data (which places the frequency of pT1b at 10–20% and its 5-year survival at < 50%) is very likely due to under-sampling/under-diagnosis (deeper cancers classified as pT1) as a result of

Table 2 Comparison of our findings with Western literature

Authors	*Country*	*Source*	*Follow-up*	*Info on pathologic sampling adequacy or re-verification*	*pT1b % (n)*	*5-yr DSS %*	*5-yr OS %*
This study	USA and Chile	Institutional	1 DOD, 14 Alive	Extensive sampling Re-evaluation of tumor depth	5 (19)	92	83
Registry based studies (presumably inflated significantly due to under-sampling)							
Goetze and Paolucci [17]	Germany	German Registry	N/A	N/A	13 (84)	-	SC: 34 Re-res: 75
Goetze and Paolucci [20]	Germany	German Registry	N/A	N/A	14 (72)	-	SC: 42 Re-res: 79
Goetze and Paolucci [39]	Germany	German Registry	N/A	N/A	N/A	-	45 (pT1a + pT1b)
de Savornin Lohman et al. [15]	Netherlands	Cancer Registry	Median OS: 56 months	N/A	12 (57)	N/A	N/A
Glauser et al. [24]	Switzerland	SALTS	N/A	N/A	17 (12)	N/A	N/A
Steffen et al. [27]	Switzerland	SEER	N/A	N/A	19 (390)	N/A	N/A
Downing et al. [67]	USA	SEER	Median OS: 33 months	N/A	-	N/A	N/A
Hari et al. [28]	USA	SEER	N/A	N/A	19 (536)	56	39
Mayo et al. [19]	USA	SEER	N/A	N/A	13 (381)	-	< 40
Vo et al. [40]	USA	NCDB	N/A	N/A	-	-	SC: 48 RC: 58
Institutional Studies (These studies have very limited data)							
Puhalla et al. [11]	Austria	Two-hospitals	No DOD	N/A	10 (6)	-	40
Schauer et al. [63]	Germany	Institutional	Median OS: 63 months	N/A	9 (T1a + T1b)	N/A	N/A
Cangemi et al. [6]	Italy	Institutional	5 DOD	"Detailed histopathologic examination"	6 (11)	-	SC: 38 EC: 100
Cucinotta et al. [41]	Italy	Institutional	6 DOD, 1 Alive	N/A	44 (7)	N/A	N/A
Principe et al. [59]	Italy	Institutional	1 DOD, 1 DOC	N/A	6 (2)	-	50
Butte et al. [5]	USA	Institutional	N/A	N/A	5 (7)	N/A	N/A
Butte et al. [14]	USA	Institutional	N/A	N/A	12 (14)	N/A	N/A
Duffy et al. [1]	USA	Institutional	4 T1 cases, All Alive	N/A	2 (3)	N/A	N/A
Foster et al. [60]	USA	Institutional	1 DOD, 1 Alive	N/A	4 (2)	-	67 (pT1a + pT1b)
Ito et al. [10]	USA	Institutional	N/A	N/A	8 (10)	N/A	N/A
Leigh et al. [16]	USA	Institutional	N/A	N/A	12 (11)	N/A	N/A
Maker et al. [9]	USA	Institutional	N/A	N/A	7 (12)	N/A	N/A
Multicenter/Survey Based Studies							
Benoist et al. [31]	France	Nationwide survey	6 DOD	N/A	27 (23)	-	44
Cupertafond et al. [68]	France	Multinational survey	Median OS: 24 months	N/A	3 (pT1a + pT1b)	-	20 (pT1a + pT1b)
Fuks et al. [8]	France	Multicenter	N/A	N/A	7 (11)	N/A	N/A
Ethun et al. [7]	USA	Multicenter	N/A	N/A	6 (14)	N/A	N/A

DOD, died of disease; *DOC*, died of other causes; *DSS*, disease-specific survival; *N/A*, not available; *OS*, overall survival; *SC*, simple cholecystectomy; *RC*, radical cholecystectomy; *Re-res*, re-resection

Table 3 Comparison of our findings with Far Eastern[#] and Chilean* literature

Authors	*Country*	*Source*	*Follow-up*	*Info on pathologic sampling adequacy or re-verification*	*pT1b % (n)*	*5-yr DSS %*	*5-yr OS %*
This study	USA and Chile	Institutional	1 DOD, 2 DOC, 14 Alive	Extensive sampling Re-evaluation of tumor depth	5 (19)	92	83
Bertran et al. [69]	Chile	Cancer registry	N/A	N/A	7 (22)	-	85
Roa et al. [38]	Chile	Institutional	N/A	Established sampling/mapping protocol	10 (132)	-	89
Aretxabala et al. [70]	Chile	Institutional	4 DOD, 6 DOC	Microscopic re-evaluation	- (*n* = 50)	-	RAI+: 67 RAI-: 89
Roa et al. [37]	Chile	Institutional	N/A	Established sampling/mapping protocol	- (n = 81)	-	90
Chan et al. [71]	China	Institutional	2 with recurrence	N/A	13 (3)	N/A	N/A
Tian et al. [29]	China	Institutional	N/A	N/A	23 (16)	-	94
Shukla et al. [33]	India	Institutional	N/A	N/A	30 (23)	N/A	N/A
Wagholikar et al. [2]	India	Institutional	6 alive, recurrence in 5	N/A	9 (12)	-	68 (pT1a + pT1b)
Kim et al. [35]	International	Korea-Japan-Chile-USA	N/A	Established sampling/mapping protocol	- (*n* = 237)	95	89
Ouchi et al. [61]	Japan	Institutional	2 DOD, 2 Alive	N/A	13 (4)	-	75
Yamaguchi et al. [25]	Japan	Institutional	1 DOD, others unknown	N/A	18 (5)	N/A	N/A
Wakai et al. [3]	Japan	Institutional	2 DOD, 3 DOC	Established sampling protocol	4 (25)	N/A	N/A (10-yr: 87)
Yuza et al. [4]	Japan	Institutional	2 DOD, 20 DOC	Established sampling/mapping protocol	5 (47)	97	81
Ouchi et al. [22]	Japan	Nation-wide Survey	N/A	N/A	14 (67)	95	-
Kang et al. [13]	Korea	Institutional	No DOD	N/A	11 (8)	-	75
Yoon et al. [12]	Korea	Institutional	3 DOD, 3 DOC	N/A	11 (85)	-	90
Kim et al. [18]	Korea	Institutional	3 DOD, 19 Alive	N/A	13 (22)	SC: 73% EC: 57	-
Sung et al. [21]	Korea	Institutional	N/A	Microscopic re-evaluation	14 (48)	82	85
Sun et al. [36]	Korea	Institutional	All alive w/o disease	N/A	17 (5)	-	100
Yoon et al. [26]	Korea	Institutional	No DOD	N/A	19 (8)	100	-
Chong and Lee [30]	Korea	Institutional	N/A	N/A	24 (26)	94	-
Kim et al. [32]	Korea	Institutional	2 recurrences	N/A	29 (9)	-	100
Jang et al. [34]	Korea	Multicenter	N/A	Established sampling/mapping protocol	- (*n* = 72)	-	96
Lee et al. [72]	Korea	Nation-wide survey	18 recurrences	N/A	- (*n* = 141)	85	-

DOD, died of disease; *DOC*, died of other causes; *DSS*, disease-specific survival; *N/A*, not available; *OS*, overall survival; *SC*, simple cholecystectomy; *RC*, radical cholecystectomy; *Re-res*, re-resection

[#]Asian cases: includes complex pTis cases classified as pT1

*pTis/T1 cases are classified as early GBC

the non-standardized reports collected in these multicenter registries that include primary care facilities. Considering more than half of GBCs are "clinically unapparent" and grossly unrecognizable as cancer (which was also the case in our series), and therefore processed in pathology laboratories without due attention to tumor characteristics, this discrepancy is actually not at all surprising. Along those lines, the cystic duct margin is also not properly processed. Of note, some of the studies that cite an aggressive course for pT1b cases also record very large carcinomas [12, 62], possibly due to the inclusion of under-staged pT2-GBCs, whereas, as was found in our study, most cases that truly qualify as pT1b are actually fairly small. We believe all these observations point to the sampling phenomenon as the potential reason for these discrepancies; however, naturally, there is no way to ascertain this impression.

Another Western dataset that forms the basis of the current guidelines (and consensus documents) recommending major surgery for pT1b-GBC [42–44] is an article by Principe et al. [59]. The main texts on the topic cite this article as "pT1b cases have only 50% 1-year survival rate." However, when this, article was carefully reviewed, there were only 2 patients with pT1b-GBCs, one who died within 100 postoperative days (close to the 90 days limit of perioperative mortality) and the other one who died of natural causes at 4 years [59]. When the guideline texts that cite this reference are critically reviewed, it becomes clear that this is a misinterpretation of "Stage-IB" cases as "pT1b" [42, 43]. In contrast, most of the publications analyzing institutional databases (Table 2) show no signs of aggressive behavior for pT1b although most included only a handful of cases [1, 5, 6, 9–11, 14, 16, 41, 59, 60, 63].

Our analysis of 19 pT1b cases identified among 473 GBCs using Western invasiveness criteria, which is the largest to date, fully supports the findings in the East that these tumors have a very good prognosis. Defined by the Western invasiveness criteria carcinomas qualified as pT1b by careful examination and extensive sampling account for only a small percentage of GBCs (5%), and they are very small in size. Considering that they are delimited by muscularis (i.e., they are a form of intramucosal adenocarcinoma) and are relatively distant from external surfaces (being several mm by definition), it is not at all surprising that it has a very good survival rate (5-year disease-specific survival > 90%). Therefore, it does not seem justifiable to recommend major surgery in every pT1b patient; however, this issue needs to be further analyzed with a more standardized approach to sampling and diagnosis. In a critical reappraisal of the literature, analyses based on the institutional cohorts from experienced centers in the West also point to this direction [1, 11, 31, 41, 59, 60]. Therefore, Western guidelines recommending major post-cholecystectomy radical operation for pT1b cancers may have to be re-visited.

It should also be reiterated here that before a case can be classified as pT1b and placed into any management protocol, pT2-GBC ought to be ruled out definitively. There are also other considerations in devising the management of a proven pT1b patient.

Considering that all examples of pT1 in this study also had in situ carcinoma, the literature on CIS would also be applicable to these cases. For example, for patients with extensive pTis or RAS involvement, positive cystic duct margin, or associated pancreatobiliary maljunction, the remainder of the biliary tract has also been shown in some studies to be at risk for de novo carcinoma [37, 64–66]. These concerns are presumed to be also valid for pT1 cases although this issue was not specifically investigated in this analysis. Perhaps more importantly, the two pT1b cases that had lymph node metastasis in this study (out of 11 that had lymph node available in the simple cholecystectomy) also raise concern for local progression potential and may be viewed as justification by itself for additional surgery in pT1-GBC cases. Accordingly, although our study elucidates a very good prognosis for pT1b-GBCs (incomparably better than what has been reported in the Western literature), nevertheless, additional surgery remains an important consideration for these patients. At minimum, very close and long-term follow-up is warranted especially for those with additional risk factors that render the biliary tract at risk [37, 64–66].

In conclusion, based on these observations and critical appraisal of the literature including the evolving data regarding the GB CIS, the following recommendations should be considered for guidelines and daily management of pT1b-GBC patients.

1. A case should not be classified as pT1b (or pTis or pT1a) unless the gallbladder is submitted entirely for microscopic examination to exclude pT2 carcinoma. Considering these lesions are typically not discernable grossly, simply relying on "random" or "selective" sections is not adequate to exclude a small pT2.
2. Studies focusing on pTis or pT1 analysis should document the pathologic sampling status, and if not totally sampled, then a number of submitted blocks should be reported.
3. Studies investigating pT1b cancer in registries such as SEER database should be evaluated critically in this regard.
4. International pathology consensus is needed to bridge the philosophical differences between continents in qualifying a case as pTis vs. pT1b based on microscopic examination [57].
5. Even if there is no clinical or gross suspicion of malignancy, it is advisable to sample the cystic duct margin in all cholecystectomy specimens at the initial examination

so that if carcinoma is detected incidentally later on, the margin status can still be documented reliably.

6. At the time being, an additional surgery may be justifiable despite the very good prognosis of pT1b-GBC (estimated 5-year disease-specific survival > 90%) because of the potential risk and occurrence of lymph node metastasis in some patients although whether it is really needed in every patient or not needs to be further evaluated.
7. Further studies are warranted, and protocols need to be devised to manage the biliary tract mucosal risk in pT1b patients with widespread mucosal carcinoma, positive cystic duct margin, RAS involvement, and/or pancreatobiliary maljunction.

Author contribution All authors agreed with the content and gave explicit consent to submit this work. All authors made substantial contributions to the conception, design, case acquisition, analysis, and interpretation of data, and assisted with drafting and revising the work, and approving the version to be published. The authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Each investigator contributed significantly in multiple ways as outlined below:

VA, JCR, MDR, and OB conceived the study and designed the approach and analytic methods along with MG and JHK. Case procurement for study, case organization, and collection of clinical information including survival data were performed by JS, SKM, and SB from the USA, JCR, HL, JCA, and OTE from Chile. The initial histopathologic review was conducted by VA, GA, BM, MDR, SB, and OB for cases from the USA, and JCA, and JCR for Chilean cases. The second histopathologic review was performed by VA, BP, GA, BM, and MDR. BP, GA, BM, BS, PB, SB, OB, and VA conducted the literature analysis and organization of the manuscript. Statistical analysis was performed by MG, JHK, and BP. BP, GA, OB, MDR, JCR, and VA prepared the manuscript draft. All authors of this paper have critically reviewed the intellectual content and approved the final version submitted.

Data availability The data reported in this manuscript are available from the corresponding author upon reasonable request.

Declarations

Ethics approval The study was conducted in accordance with the Institutional Review Board requirements.

Conflict of interest The authors declare no competing interests.

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