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ORIGINAL ARTICLE

Early gallbladder carcinoma has a favorable outcome but Rokitansky–Aschoff sinus involvement is an adverse prognostic factor

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Abstract The general impression about gallbladder carcinomas is that they are uniformly fatal; however, for the early forms, an entirely different picture indicating a very good prognosis is evolving from the high-incidence regions. We subjected 190 early gallbladder carcinomas (EGBC), defined as carcinomas confined to and above the tunica muscularis (AJCC's Tis, T1a, and T1b), and identified in cholecystectomy specimens sampled entirely according to an established protocol, to detailed analysis. Average patient age was 57.9 years (29–95). In more than half of the cases (114/190; 60 %), the tumor was inapparent by gross examination. In 81 cases (42.6 %), carcinomatous epithelium abutted the muscularis, whereas 57.4 % ($n=109$) were qualified as intramucosal with no overt contiguity with muscularis. Intraepithelial extension into Rokitansky–Aschoff sinuses (RAS) was found in 34 cases (17.8 %). At the time of data analysis, 171 patients (90 %) were alive. Overall actuarial survival was 92.3 % at 5 years and 90.4 % at 10 years. The 5- and 10-year actuarial survival rates of the intramucosal group (93.2 and 92.1 %, respectively) were not statistically different from that of the muscle-abutting group (89.7 % and 88.2 % ; $p=0.334$). Patients with RAS involvement had a significantly shorter survival than those without ($p<0.001$). Of the 33 patients with RAS involvement, 13 (39 %) died of disease, whereas only 6 of the 154 patients (4 %) without RAS involvement died of disease. Disease-related mortality in these cases occurred relatively late (median 48 months). EGBC has a very good prognosis with a 90 % 10-year survival rate. It is seen on average in patients almost a decade younger than those with advanced cancers. RAS involvement is an independent prognostic factor, and additional surgery may have to be considered for such cases. Occasional recurrences are encountered several years later, which suggests a field-effect phenomenon and warrants long-term follow-up.

Keywords Gallbladder · Adenocarcinoma · Early stage

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Introduction

Gallbladder cancer (GBC) is the fifth most common gastrointestinal tract cancer [1, 26]. It has a very high incidence in certain parts of the world, in particular in Chile where the mortality rate exceeds 18 per 100,000 inhabitants [5], and where it is the leading cause of cancer deaths among women over the age of 40 (Fig. 1).

Most GBCs are *pancreatobiliary-type* adenocarcinomas and the general impression in the literature is that, akin to pancreatic cancer, GBCs are uniformly fatal [1, 26]. However, for early forms of this disease, an entirely different picture is evolving from high-incidence regions such as Chile and Southeast Asia [23, 35, 36], indicating a very good prognosis. This contrasts with the Western literature, which still records a high mortality rate even for the earliest stage tumors based on a fairly limited reports, typically representing a handful of cases [14, 17, 21, 27].

The growing experience in the high-incidence regions is leading to a revised definition of "early" gallbladder cancer, as has happened for early gastric cancer in Asia. Currently, worldwide, the most commonly used staging system is the TNM of International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) [15] (Table 1), in which the T-category parameters for GB were extrapolated directly from the other organs of the GI tract. In reality, the histologic layering of GB (Fig. 2) is such that there is no muscularis mucosa to delineate Tis from T1. Since the GB mucosa is highly irregular and often complex due to the abundance of metaplastic glands, there is no clear-cut definition of what constitutes Tis vs early invasion of the lamina propria. Furthermore, there is no clear demarcation of the lamina propria (T1a) from the tunica muscularis (T1b) because the muscularis of GB is irregular and lacunar, allowing brisk invaginations, and therefore, unlike the rest of the GI tract, lamina propria can be found within the muscularis in abundance. These distinctive aspects of GB render the T-category of AJCC/UICC less applicable for many cases, and as a result, authors from high-incidence regions have independently adopted the term "early gallbladder carcinoma" (EGBC) [9, 25, 28, 29, 32, 34] for carcinomas confined by (to and above) the tunica muscularis, a concept encompassing the spectrum of cases that were meant to be classified as Tis, T1a, or T1b in the AJCC/UICC (Fig. 3).

Another distinctive aspect of GB histology, also not accounted for in the current staging of GBC is that not only the lamina propria but also the epithelium itself commonly shows deep invaginations famously known as Rokitansky–Aschoff sinuses (RAS). In the setting of carcinomatous changes in the surface mucosa, the carcinoma cells often track along the mucosa into these sinuses (Fig. 4) [3, 24, 25, 37, 41]. The prognostic significance of this phenomenon has yet to be determined.

In terms of the management of EGBCs, different opinions have been presented in the literature [4, 6, 7, 10, 12, 14, 17, 19, 21, 22, 27, 30, 38, 39, 44]. For pT1a tumors, the prevailing approach is to regard simple cholecystectomy adequate. For, pT1b tumors, various degrees of additional surgery have been proposed, from liver wedge resection with lymph node dissection, to wide hepatic resections also including the hepatic duct. The benefits of adjuvant chemo/radiotherapy are not clear [4, 6, 7, 10, 12, 14, 17, 19, 21, 22, 27, 30, 38, 39, 44].

A factor contributing greatly to the conflicting impressions regarding outcome and management of EGBCs is undersampling of the specimen. GB carcinomas are highly insidious and difficult to visualize, not only at the clinical level (most patients present with inapparent carcinomas [11, 36]) but also in the gross room and at microscopic level. Therefore, random sampling, according to protocols employed in the USA and most of the Western World, often misses the deepest focus of the carcinomas and as a consequence they are commonly understaged [10, 32, 33].

The aim of this study was to investigate the clinicopathological characteristics of EGBC and determine the pathologic factors associated with outcome as well as those that may help in further stratification of EGBCs into more patient-centered

Fig. 1 While the overall global incidence of gallbladder carcinoma (GBC) is low, GBC is a common cancer type in certain parts of South America and Southeast Asia

Table 1 AJCC cancer staging for gallbladder and cystic duct cancers [15]

	Definition
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1a	Tumor invades lamina propria
T1b	Tumor invades muscle layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3	Tumor perforates serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Well-differentiated neuroendocrine neoplasms (carcinoid tumors) are not included

management protocols. For this purpose, 190 consecutive cases of well-characterized and thoroughly sampled EGBCs, the largest series reported to date, were analyzed as a concurrent cohort.

Materials and methods

Definition of EGBC

EGBC was defined by the criteria similar to the previous studies from high-incidence regions as carcinomas confined *by* (to and above) the tunica muscularis [35, 36, 43]. Accordingly, this category encompasses a spectrum of cases that would be regarded by the AJCC/UICC TNM as employed in the West as follows:

1. Carcinoma in situ (Tis) type cases, in which the intraepithelial carcinoma cells occur in noncomplex flat mucosa and thus can be unequivocally recognized as confined to the epithelium without any suspicion of invasion (Fig. 5), those that show complex glandular pattern and expand the mucosa (Fig. 6), creating the impression of or are definitive for lamina propria invasion (Tis/T1a). These cases were regarded as the *intramucosal* subset of EGBC.
2. Those with carcinomatous glands abutting the muscularis occurring in the crevices of the muscularis but are equivocal for definitive muscularis invasion (Fig. 7), which correspond to T1b in the AJCC/UICC TNM system. These were grouped as *muscle-abutting* subset of EGBC.

Cases with T2 and T3 invasive carcinomas were excluded from EGBC and classified as *advanced*. Those with extraserosal or remote extension outside the wall of the gallbladder as determined intraoperatively or microscopically were classified as exhibiting *extramural spread*.

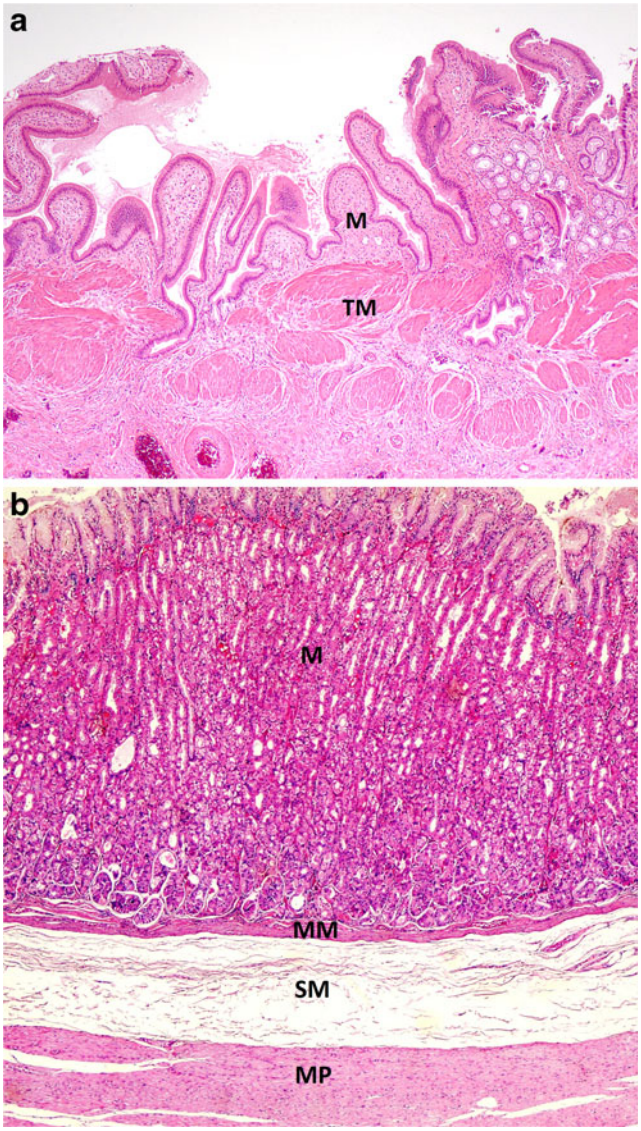

Fig. 2 Histologic layering of gallbladder (**a**) is significantly different than the GI tract (**b**), which renders the conventional T-staging parameters inapplicable for the gallbladder: while muscularis mucosa (*MM*) clearly demarcates the mucosa (*M*) in the GI tract, in the gallbladder there is no muscularis mucosa but only tunica muscularis (*TM*), which is highly porous, giving in to numerous invaginations of the mucosa which often abuts the muscle deep in the tissue (*SM*, submucosa; *MM*, muscularis propria)

Specimen sampling protocol

All the cholecystectomy specimens included in this study were processed thoroughly for microscopic examination according to an established sampling protocol (Fig. 8) [31]. After the GBs were opened from the free (ante-hepatic) surface, spread out, and fixed, they were examined carefully and also photographed (Fig. 8). If no visible gross lesions were

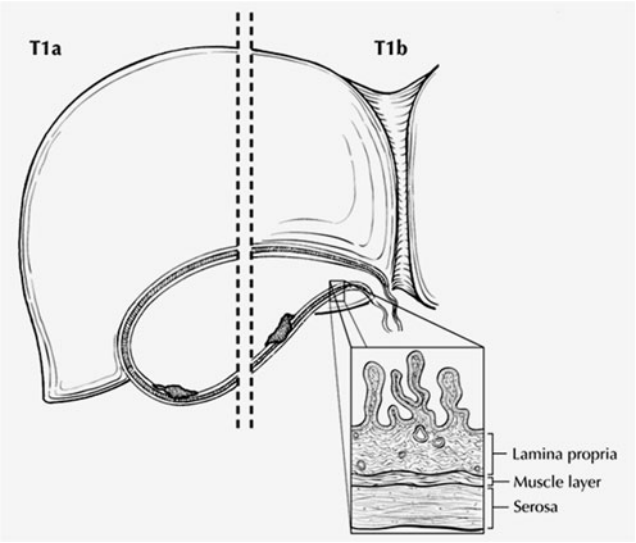

Fig. 3 The diagram in the College of American Pathologists' webpage regarding the AJCC/UICC staging protocol of gallbladder illustrates a well-formed mucosa that is clearly delineated by a "muscle-layer," although, in reality, gallbladder is not structured like this at all (see Fig. 2)

identified, a routine section composed of a full thickness slice going from the top of the fundus all the way to the cystic duct margin was obtained. This section was submitted for microscopic examination in as many cassettes as necessary (typically, one to three cassettes). If the microscopic examination of this initial set of slides revealed any suspicious findings, then the entire GB was submitted for microscopic examination by *mapping* according to the established protocol. This total sampling in neoplastic cases excluded the possibility of "missed" deeper aspects of the tumors not visible grossly, a common occurrence resulting from otherwise random examination methods widely employed in the Western World. This total examination approach not only confirmed that the case belonged to the EGBC category by effectively ruling out more advanced carcinomas but also allowed detailed documentation of various characteristics of EGBC, including the extent of the process, its three-dimensional patterns of spread, and the involvement of RAS, if present.

Study cohort

All 953 GB carcinoma cases at the Department of Pathology of the Hospital Hernán Henríquez Aravena in Temuco (Chile) that were processed according to the sampling protocol described above from 1988 to 2006 (non-probabilistic consecutive cases) were evaluated.

All 190 that fulfilled the criteria for EGBC as defined above and did not have perioperative mortality (within 1 month of the cholecystectomy) were subjected to detailed analysis. Also excluded were those patients who received a treatment in addition to the cholecystectomy.

Pathologic parameters evaluated

All the pathology material of these 190 cases was evaluated. Carcinomas that had not been detected by macroscopic (gross) examination of the specimen were classified as inapparent. The localization of the lesions was described as neck, body or fundus, or combination thereof. Additionally, the cases were classified into the muscle-abutting (Fig. 6) and intramucosal (Fig. 7) subcategories as best as possible, although this proved to be challenging in some cases, as described above. If the carcinomatous elements were clearly epithelium-confined or forming/involving glandular elements, which are often difficult to distinguish, they were classified as well-differentiated. If the carcinomatous cells were forming nonglandular and solid units, it was regarded as poorly differentiated. The extent of carcinoma was quantified as focal (involving <25 % of the mucosa), substantial (if 25–≤75 %), or diffuse (>75 % of the mucosa).

Extension to RAS was carefully evaluated. If there were less than three foci of RAS, it was arbitrarily regarded as rare,

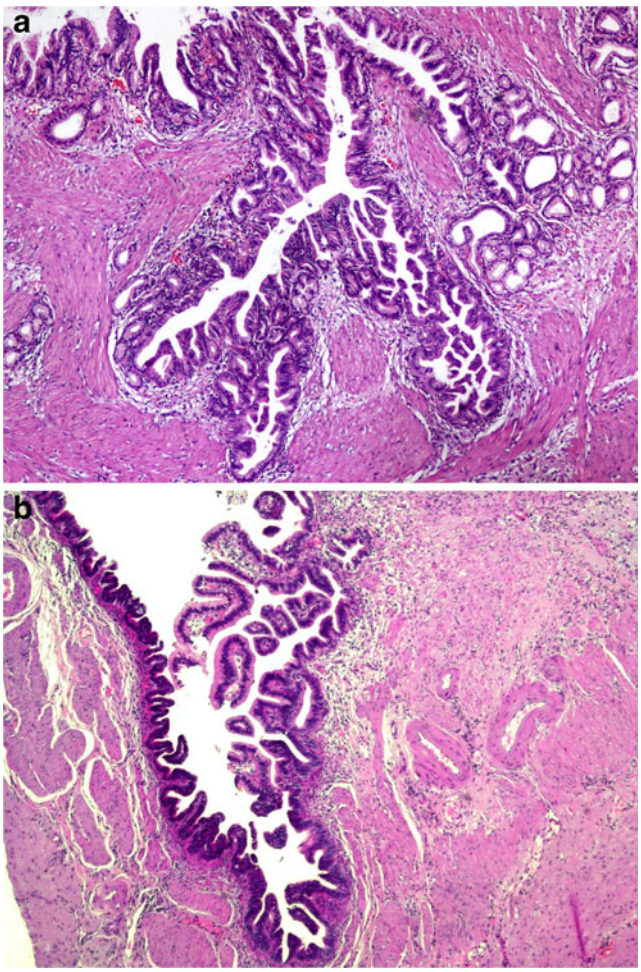

Fig. 4 In the setting of carcinomatous changes involving the epithelium, the in situ carcinoma cells often track along the mucosa into Rokitansky–Aschoff sinuses and extend deep into the gallbladder wall without being *invasive*

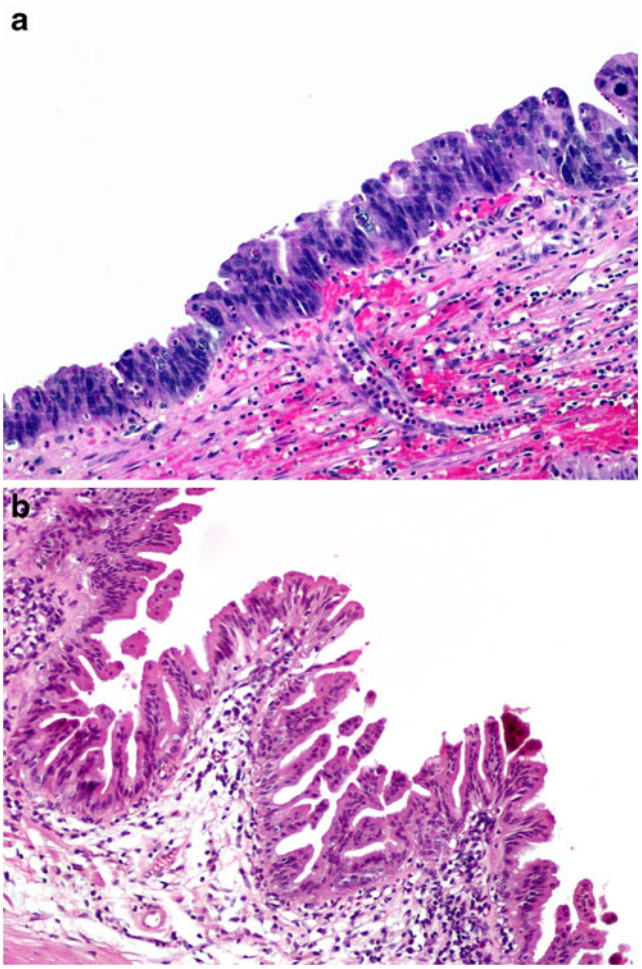

Fig. 5 "Carcinoma in situ (Tis)" type cases, in which the intraepithelial carcinoma cells occur in noncomplex flat mucosa and can be unequivocally recognized as confined to the epithelium without any suspicion of invasion

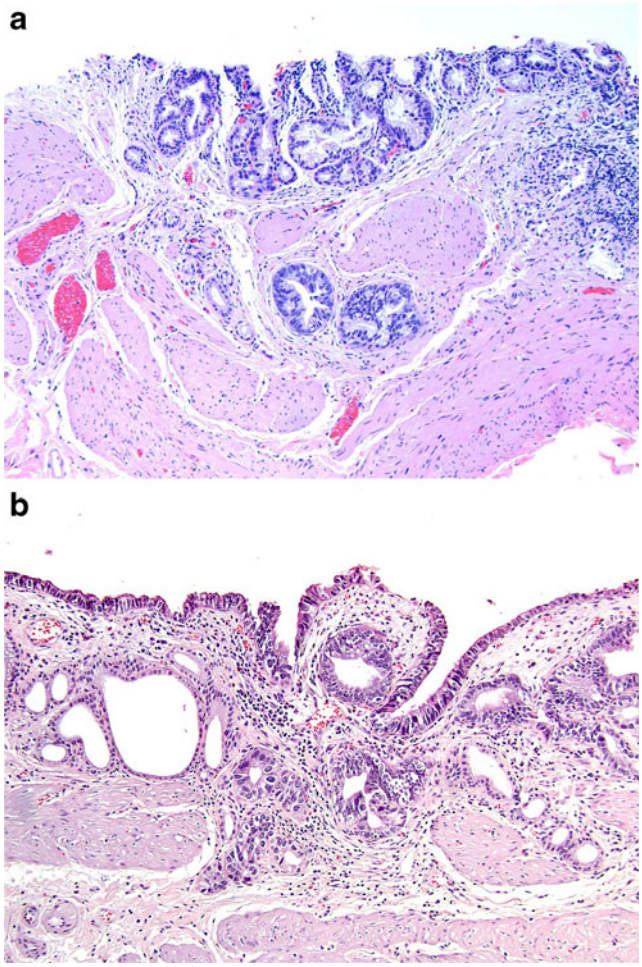

Fig. 6 In the gallbladder, due to injury, complex metaplastic glands commonly develop in the mucosa and often invaginate deep into tunica muscularis or beyond (Rokitansky–Aschoff sinuses). When these glands are involved by in situ carcinoma cells, they can be difficult, if not impossible, to distinguish from invasive carcinoma. These often abut the muscularis (**a**). In the examples depicted here, partial involvement of benign glands, smooth contours and the overall distribution of the glands allow the recognition of this process as noninvasive. However, this determination is often impossible, further justifying the concept of "early gallbladder cancer" for such cases

and if more than three foci, as substantial. The deepest level of extension of RAS as to muscular level or traversing into the subserosa was also recorded.

Clinical parameters evaluated

Information on the patients' gender, age, as well as clinical outcome was obtained through surgical pathology reports, patient's charts, patient's primary physicians, the Civil Registry, as well as from the databases of death certificates in the IT Department of the Head Office of the South Araucanía Health Service, in Chile. Patients who died within the first 30 days of the postoperative period were excluded from the survival analysis.

Survival analysis

The result or independent variable was "survival," determined in the months after surgery. The dependent variables were subtype of EGBC (intramucosal and muscle-abutting), RAS involvement, amount of EGBC, and its histologic differentiation. The associated variables studied were age, gender, and location. Patients who died within 1 month of the operation were regarded as perioperative mortality and disregarded from survival analysis.

Bias

Potential sources of bias were reduced by a complete follow-up of the patients of both cohorts. A blinded data collection and subsequent statistical adjustment-controlled confounding was obtained.

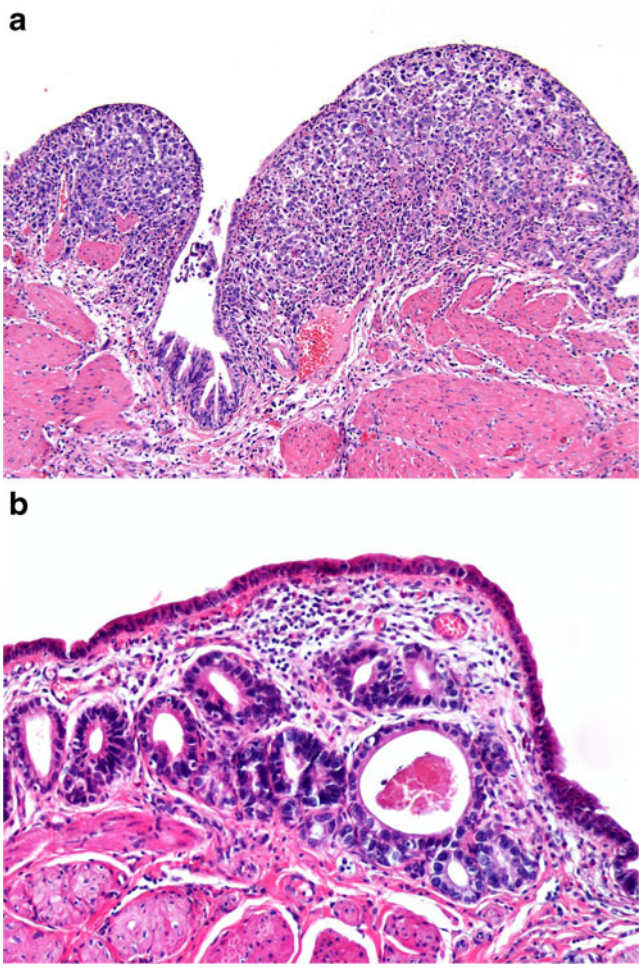

Fig. 7 Also included in early gallbladder carcinoma category are intramucosal adenocarcinomas that are presumably "invasive" and form poorly differentiated, i.e., nonglandular patterns (**a**) as opposed to well-differentiated examples characterized by glandular (tubular) pattern

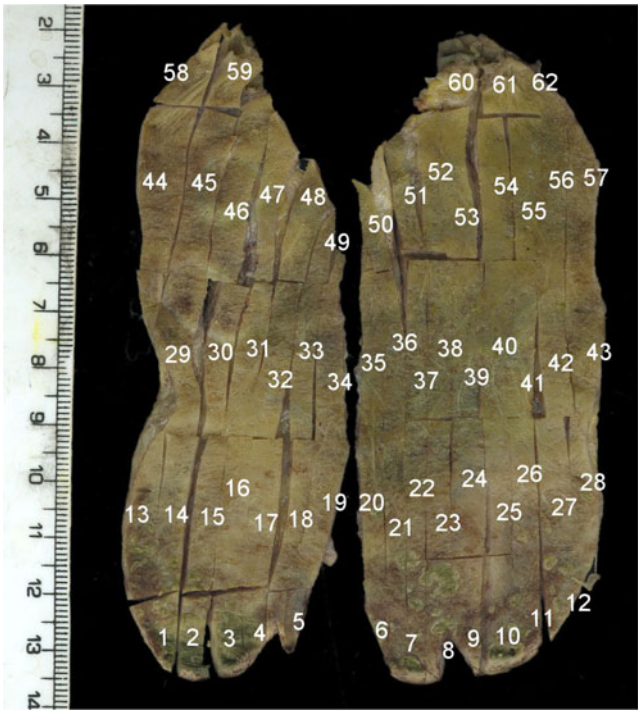

Fig. 8 Cholecystectomy specimens were processed thoroughly for microscopic examination according to an established sampling protocol

Study size

Given a power of 80 %, a confidence level of 95 %, a 1:1 exposed/non-exposed ratio, and an estimated difference of 18 % in survival at 5 years between the two cohorts (98 % for patients with intramucosal cancer and 80 % for those with cancer overtly invading the tunica muscularis), the sample needed to conduct this study was 104 cases (52 exposed and 52 non-exposed).

Statistical methods

Using the statistical software Epi Info 6.0 and Stata 9.0, an exploratory analysis of the data was performed and descriptive statistics subsequently applied with calculation of averages and standard deviations, medians and extreme values for continuous variables, calculation of percentages for categorical variables, and Kaplan–Meier actuarial survival curves. We then applied analytical statistics, using a *t* test and analysis of variance for continuous variables, Pearson's Chi squared and Fisher's exact tests for category variables, and a logrank test (Cox–Mantel) for comparison of survival curves. After statistical adjustment was made, applying logistic regression models, the relative risks (RR) and their respective 95 % CI were calculated.

Ethical aspects

In conduction of this study, Helsinki principles were observed. In addition, the confidentiality of each patient's data was assured via their codification. The studies were performed in accordance with the Institutional Review Board requirements.

Results

General characteristics

The average age of the 190 patients with EGBC was 57.9± 15.1 (29 to 95 years), as opposed to 65 for the advanced cancer group in the same database, confirming a progression phenomenon from *early* to *advanced* cancer. The vast majority of patients (157/190; 82.6 %) were females.

Pathologic findings

More than half of the patients (114/190; 60 %) had inapparent tumors by macroscopic examination in the gross room. Sixty-

one percent (116 patients) presented with symptoms interpreted as exacerbation of their "chronic condition."

Microscopically, 81 patients (42.6 %) revealed carcinomatous epithelium abutting the muscle, whereas 109 patients (57.4 %) were qualified as intramucosal with no overt contiguity with muscularis. Among intramucosal cases, 31 were complex, showing irregularities and involvement of metaplastic glandular elements in the lamina propria, and the remaining 78 were noncomplex. Carcinoma cells exhibited well-differentiated patterns in 64.2 % (122 patients). None of the cases had involvement of the lymph nodes.

Intraepithelial extension into the RAS by the carcinoma cells was found in 17.8 % of the cases (34 patients). Of the intramucosal-type cases, 23 (21.1 %) showed extension to RAS; 18 of these were limited to tunica muscularis and 5 reached deep into the subserosal level. Of the muscle-abutting-type cases, 11 (13.6 %) had RAS involvement, 10 of which extended to the subserosal level. None of these patients with RAS involvement had received additional treatment beyond the simple cholecystectomy.

Follow-up

The average follow-up was 139.9±65.6 (6 to 260 months). Eight patients (4.2 %) underwent additional surgery: a liver wedge resection and a regional lymphadenectomy. All these cases had muscle-abutting tumors. None of them were found to have carcinoma in the additional surgical specimens. They were all alive at the time of the study. These cases were not taken into consideration for the survival analysis.

Ninety percent of the cases (171 patients) were alive at the time of data analysis. Overall actuarial survival was 92.3 % at 5 years and 90.4 % at 10 years.

Correlation of pathologic parameters with survival

The 5- and 10-year actuarial survival rates of the intramucosal group (93.2 and 92.1 %, respectively) were not statistically different from those of the muscle-abutting group (89.7 and 88.2 %; $p=0.334$; with a RR of 0.84 [95 % CI of 0.28, 2.45]) (Fig. 9). Overall, there was no significant survival difference between noncomplex intramucosal (CIS type, $n=78$) or complex cases ($n=31$) and the muscle-abutting group ($n=81$; $p=0.4$).

The extent of carcinoma as to diffuse (>75 % of the entire GB mucosa; $n=72$) or substantial (25–75 %; $n=101$) or focal (<25 %; $n=17$)] was not significant ($p=0.3$).

In multivariate analysis using logistic regression models, it was confirmed that the degree of differentiation interacted in the association ($p=0.026$), which is why it was controlled by this association, obtaining an adjusted RR of 0.90 [95 % CI of 0.35, 2.32].

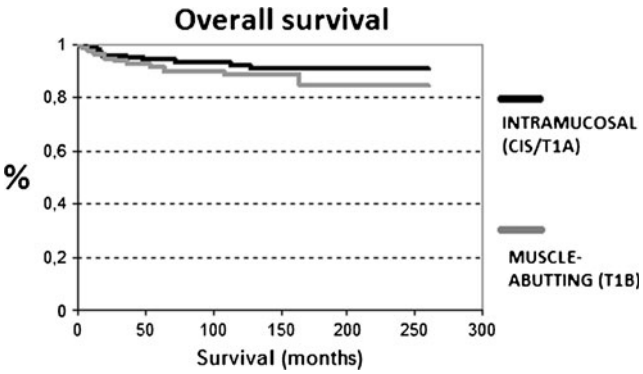

Fig. 9 Overall survival rates of intramucosal vs muscle-abutting EGBCs

All eight patients (4 %) who underwent additional surgery for lymphadenectomy and liver wedge resection had no residual disease present in the resection specimens, and all were alive at the time of the study. As mentioned earlier, these patients were not included in the survival analysis in order not to bias the results.

Characteristics and outcome of patients with RAS involvement

Patients with RAS involvement had a significantly shorter survival than those without ($p<0.001$) (Fig. 10). This was valid both for the intramucosal group ($p<0.001$) as well as the muscle-abutting group ($p=0.0004$) (Figs. 11 and 12). Patients with RAS involvement were much more likely to die of disease, with an odds ratio of 7.3. Of the 33 patients with RAS involvement, 13 (39 %) died of disease, whereas only 4 % (6/154) cases without RAS involvement had disease-related mortality. Six of the RAS-involving patients died within the first 2 years, and seven died between 2 and 5 years, with an overall median of 48 months.

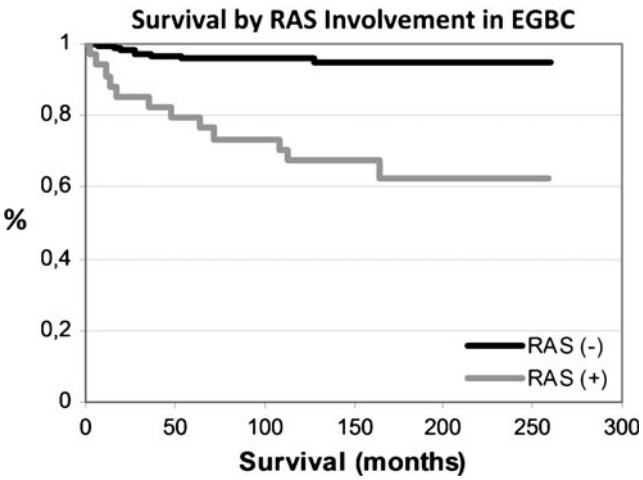

Fig. 10 Overall survival rates of EGBCs with or without RAS involvement

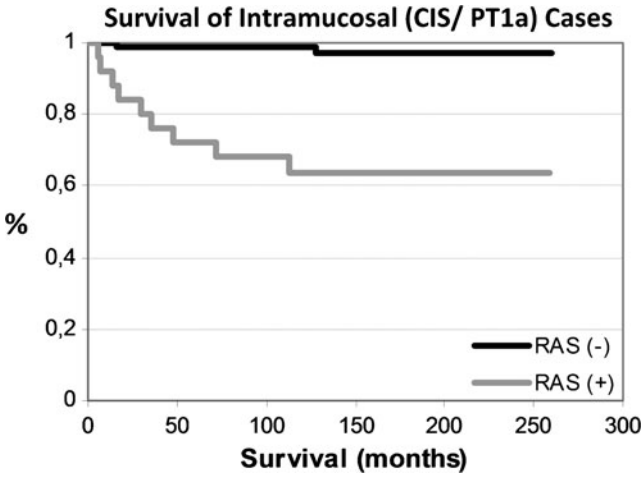

Fig. 11 Survival comparison of intramucosal EGBCs, with or without RAS involvement

When the RAS-positive cases were eliminated from the survival analysis, the survival at 10-year increased from 92 to 100 % for intramucosal-type cases, and from 88 to 93 % for muscle-abutting ones.

Discussion

In this study, a comprehensive clinicopathologic analysis of EGBC, defined as *confined to and above the tunica muscularis* (Tis, T1a, T1b), is performed in 190 entirely sampled cases, and several important characteristics of this rare but important category are elucidated.

First of all, while conducting this study, it became clear that it is often difficult, if not impossible, to make a distinction between the Tis, T1a, and T1b categories of AJCC/UICC. Contributing to this challenge is the absence of muscularis mucosa to delineate Tis from T1a, the frequency and abundance of metaplastic glandular elements, which imparts added complexity to the mucosa and thus blurs the distinction between Tis vs deep invaginations of the mucosa that often abut the muscularis, thus hindering the distinction between T1a and T1b. These factors preclude the application of AJCC/UICC T-category in many cases and warrant their collection under a unified category of EGBC as had occurred eventually for early cancers of colorectal region. Furthermore, even when we attempted to classify the cases as intramucosal vs muscle-abutting, albeit with questionable success due to the aforementioned challenges, the biologic behavior of these two subcategories of EGBC did not appear to be significantly different. Of note, this definition of EGBC is otherwise highly analogous to the principle employed in the colorectal region where, after decades of debates, both conventional in situ carcinomas and those invading the lamina propria of the mucosa as well as those invading the muscularis mucosae have all been collected under one stage category [15]. Also analogous are the concepts of "mucosal (M)" carcinoma and "early gastric carcinoma" developed in regions with high-incidence of early gastric cancers such as Japan.

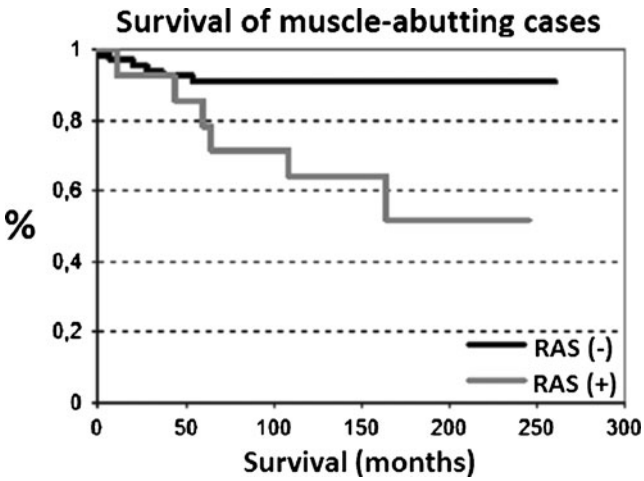

Fig. 12 Survival comparison of muscle-abutting EGBCs, with or without RAS involvement

This study also confirms the impression evolving in the high-incidence regions that the EGBC group has a very good prognosis, with a 10-year survival of 90 %, in contrast with the dismal outcome reported in the Western literature, based mostly on limited numbers of cases [13, 14, 16, 18, 21, 27]. Thus far, in the Western literature, for the cases that have been classified as CIS (Tis), virtually no reliable institutional-based data is in existence due to the rarity of these lesions and lack of their recognition. Thus, most of the impressions have been based on the questionable findings in the Surveillance Epidemiology End Results of the US Government (SEER) database [2]. In the SEER database, survival information recorded for CI cases indicated 70 % 10-year survival, significantly lower than the 90 % observed in our cases, attributable to the understaging phenomenon that occurs if GB is not examined entirely as done in this study. On the other hand, in terms of the delayed development of recurrences, our results are in accordance with the SEER database, which indicates that 5-year survival is 100 %, which then drops to 70 % at 10 years), reportedly due to biliary tract cancers. This leads us to speculate that GB CIS is a sign of field-effect in the entire biliary tract, and that some patients may later develop invasive carcinoma in the remaining biliary tract. For this reason, it is advisable to place these patients under long-term surveillance, although as yet this is easier said than done due to the limitations in the specificity of imaging modalities and lack of reliable screening methods for biliary tract tumors.

Our study also indicates that, if thorough sampling of the GB is performed and the possibility of more deeply invasive carcinoma has been ruled out definitively, the cases that qualify as T1a/T1b in the UICC/AJCC classification also have a very good prognosis. Even the cases we placed into the muscle-abutting category had a 10-year survival close to

90 %. This is in contrast to what is reported in the Western literature [20], which registers numbers as low as 48 % 5-year survival for T1a cancers and much lower for T1b. While one might speculate that this difference is population-related, it is our opinion that the most likely explanations are the very limited number of cases in the Western literature [14, 17, 21, 27] and, more importantly, the undersampling/understaging phenomenon, something those of us practicing in the USA witness on a regular basis. In addition, the few previous EGBC studies have been series of cases that contribute a type IV level of evidence. In contrast, our study is a concurrent or prospective cohort study that contributes a type Ib level of evidence [42] and is also the only protocol-based systematic study on EGBC conducted in a single center that includes complete mapping of the surgical specimen to specify the maximum level of tumor infiltration and analysis of the survival of the cohort in periods of up to 10 years (Fig. 13).

Various clinical and pathological characteristics of EGBC were elucidated in this study. First of all, EGBC occurs in patients on average 8 years younger than those with advanced cancers, confirming a continuum. Of importance, most cases were clinically unsuspected, and 60 % were invisible grossly as well, which further emphasizes the crucial role of the complete sampling protocol. In a median follow-up of 144 months (12 years), the actuarial survival was 92 % at 5 years and 90 % at 10 years. There was no significant survival difference between noncomplex (Tis type) cases and more complex ones that can be considered intramucosal adenocarcinoma or the muscle-abutting ones (T1b). The prognosis of well-differentiated/gland-forming EGBCs was better than those with solid patterns. EGBC often involved a substantial proportion of the mucosa and in 40 % of the cases it was diffuse, supporting the "wildfire" phenomenon, i.e., they spread rapidly once they develop. However, intriguingly, the lateral extent of the EGBC did not appear to correlate with outcome. In contrast, involvement of RAS proved to be an independent prognostic factor, with an odds ratio of 7.3. Along those lines, once the RAS-involving cases were eliminated from the analysis, the 10-year survival rates increased from 92.1 to 100 % for intramucosal tumors and 88.2 to 93 % for muscle-abutting ones.

The association of RAS involvement with adverse outcome is intriguing and brings up various questions, such as whether these cases may in fact have missed (unexamined) or misinterpreted foci of invasive carcinoma. Missed or unexamined does not seem to be the case since these GBs were examined entirely. Truly misinterpreted foci of invasion is also unlikely, as much of the disease related mortality in these RAS-involving cases occurred relatively late (median, 48 months), much later than would be expected from an advanced GBC, which would have been the diagnosis had there been invasion. An alternate and more plausible explanation is that RAS involvement may be surrogate evidence of the field-effect phenomenon discussed earlier, and thus predictor of adverse outcome. It is possible that the capacity of CIS cells for pagetoid extension into the RAS reflects a biologically different subset, prone to spread intramucosally to the remainder of the biliary tract as well, and thus prone to recurrences. Additionally, RAS involvement may be a manifestation of a more extensive CIS, although we did not find direct correlation with the extent of EGBC and outcome. This may be because most cases had substantial EGBC to begin with, suggesting that EGBC undergoes the wildfire phenomenon and involves the preserved epithelium extensively by the time it is diagnosed. Another question that this RAS outcome correlation brings up is that the gallbladders which develop RAS to begin with may be by their nature more vulnerable to recurrences of EGBC. In other words, the milieu or the fundamental defect that allow some gallbladders to develop RAS-type invaginations may in turn also render them more prone to

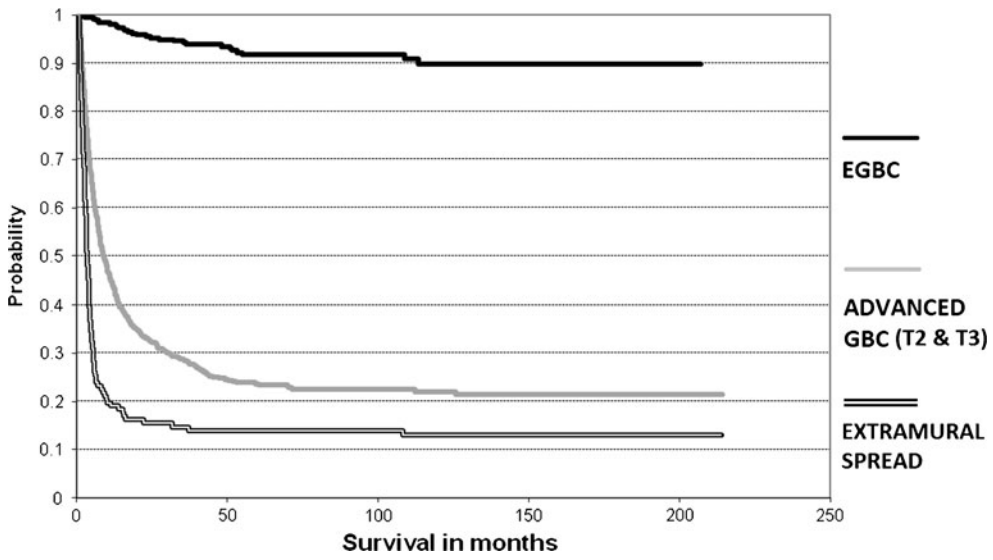

Fig. 13 Stage-dependent overall survival analysis of GBCs as EGBC, "advanced" and those with extramural spread

have recurrences. All of these possibilities warrant further analysis.

This study has major implications in the future management of GB neoplasia. First of all, the fact that EGBCs have a very good prognosis allows us to make extrapolations about the biological behavior of dysplasia. In our experience, focal/incidental dysplastic changes are detected in 2.5 % of cholecystectomies in the USA (and significantly more frequently in high-risk regions). Considering that there are more than a million cholecystectomies annually performed in the USA, this translates to more than 20,000 patients annually in this country alone being diagnosed with dysplasia of which the biological significance is unclear. With this study showing a very good prognosis for EGBC, it is safe to assume that focal/incidental dysplasia is clinically inconsequential and does not require any further treatment. Even for full-blown EGBCs, if there is no RAS involvement, cholecystectomy can be considered adequate, although a long-term surveillance of the patient is necessary, since approximately 10 % of patients with EGBC still experience progression. More importantly, if there is RAS involvement, additional radical surgery might have to be considered. This is a significant paradigm shift from the current impression in the Western literature, which was highly conflicted regarding the management of pT1b cases, owing to the aforementioned challenges in defining this stage as well as to the inadequacy of the data and the understaging phenomenon, mostly based on limited numbers of cases even in the experience of largest institutions in the USA [14, 27]. A variety of approaches have been employed in the past including radical cholecystectomy with resection of the liver bed and lymph node dissection in suspected cases of GBC pre- or intraoperatively, liver wedge resection and lymph node dissection in a second surgical intervention for incidental carcinomas, or in some cases, wider resections (right, central, or extended hepatectomy) because tumor extension into the liver bed through venous or lymphatic drainage directly from the GB has been demonstrated occasionally [7, 8, 19, 22, 30, 39, 40]. Our data indicates that these radical operations are justifiable for EGBCs with RAS involvement, but not for others, provided that "advanced" carcinoma has been ruled out through total sampling of the gallbladder. Even the muscle-abutting (T1b) cases can be managed conservatively, provided that the GB has been sampled entirely and the possibility of RAS involvement or more advanced carcinoma has been ruled out definitively, and of course, lon-term follow-up is warranted regardless.

That EGBCs have a very good prognosis also brings new hope to the management of GBC in the future. If new methods of identifying/imaging EGBC can be developed, for example, by tagging and highlighting the cancerous cells, then cholecystectomy can be performed even in asymptomatic cases, to halt its progression to more advanced forms of the disease. Along those lines, if involvement of RAS can be determined preoperatively with developing technology, then more radical surgical procedures can be planned ahead of time for such cases.

In summary, EGBC defined as carcinoma confined to and above the tunica muscularis confirmed by thorough sampling and careful examination of GB has a very good prognosis with a 10-year survival of 90 %. It is seen in patients on average almost a decade younger than those with advanced cancers. RAS involvement is an independent prognosticator of clinical outcome, and additional surgery may have to be considered for such cases.

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Conflict of interest We declare that we have no conflict of interest.

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