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Retrospective Cohort Study

Incidental gallbladder cancer diagnosis confers survival advantage irrespective of tumour stage and characteristics

IGBC survival advantage compared to NIGBC

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Abstract

BACKGROUND

Incidental gallbladder cancer (IGBC) represents 50-60% of gallbladder cancer cases. Data are conflicting on the role of IGBC diagnosis in oncological outcomes. Some studies suggest that IGBC diagnosis does not affect outcomes, while others that overall survival (OS) is longer in these cases compared to non-incidental diagnosis (NIGBC). Furthermore, some studies reported early tumour stages and histopathologic characteristics as possible confounders, while others not.

AIM

To investigate the role of IGBC diagnosis on patients' overall survival, especially after surgical treatment with curative intent.

METHODS

Retrospective analysis of all patient referrals with gallbladder cancer between 2008 and 2020 in a tertiary hepatobiliary centre. Statistical comparison of patient and tumour characteristics between IGBC and NIGBC subgroups was performed. Survival analysis for the whole cohort, surgical and non-surgical subgroups was done with the Kaplan-Meier method and the use of log rank test. Risk analysis was performed with univariable and multivariable Cox regression analysis.

RESULTS

The cohort included 261 patients with gallbladder cancer. 65% of cases had NIGBC and 35% had IGBC. A total of 90 patients received surgical treatment (66% of IGBC cases and 19% of NIGBC cases). NIGBC patients had more advanced T stage and required more extensive resections than IGBC ones. OS was longer in patients with IGBC in the whole cohort (29 *vs* 4 mo, p <0.001), as well as in the non-surgical (14 *vs* 2 mo, p<0.001) and surgical subgroups (29 *vs* 16.5 mo, P = 0.001). Disease free survival (DFS) after surgery was longer in patients with IGBC (21.5 mo *vs* 8.5 mo, P = 0.007). N stage and

resection margin status were identified as independent predictors of OS and DFS. NIGBC diagnosis was identified as an independent predictor of OS.

CONCLUSION

IGBC diagnosis may confer a survival advantage independently of the pathological stage and tumour characteristics. Prospective studies are required to further investigate this, including detailed pathological analysis and molecular gene expression.

Key Words: Gallbladder cancer; incidental gallbladder cancer; non-incidental gallbladder cancer; gallbladder cancer survival

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Core Tip: Data are conflicting on the role of incidental gallbladder cancer (IGBC) diagnosis in oncological outcomes. Some studies suggest that IGBC diagnosis does not affect outcomes, while others that overall survival (OS) is longer in these cases compared to non-incidental diagnosis (NIGBC). In our study, IGBC diagnosis conferred better OS in all patients with gallbladder cancer, as well as within the surgical and non-surgical groups. Similarly, disease free survival was significantly longer in patients with IGBC. NIGBC diagnosis was identified as an independent predictor of OS along with N stage and resection margin status.

INTRODUCTION

Gallbladder cancer (GBC) is associated with a poor prognosis even after treatment, with median overall survival (OS) ranging in the literature between 3 and 22 mo[1,2]. Incidental gallbladder cancer (IGBC) discovered on routine histological examination of

gallbladder specimens after cholecystectomy is more common than non-incidental gallbladder cancer (NIGBC) and represents 50-60% of all cases[3-5]. The prognostic implication of incidental or non-incidental diagnosis in oncological outcomes is still a matter of debate as is the effect of the timing of curative intent resection which is performed as a secondary operation in IGBC.

Published evidence are contradictory with some studies suggesting that incidental diagnosis does not affect survival[5-8], while others showed longer survival with IGBC[9-11]. Earlier tumour stages in the IGBC group have been suggested as a confounding factor for any potential survival benefit[5]. On the contrary, other studies identified a survival benefit in IGBC even after controlling for tumour stage and degree of differentiation[9,10].

4 The aim of this study was to investigate the role of IGBC diagnosis in patient OS and especially after surgical treatment with curative intent.

MATERIALS AND METHODS

This is a retrospective single tertiary centre cohort study between January 2008 and December 2020. The sample included all patients with a histological diagnosis of GBC obtained by surgery or biopsy. The management of all patients was discussed and agreed in the hepatobiliary multidisciplinary (MDT) meeting. IGBC diagnosis was established after histopathological examination of specimens following cholecystectomy for benign aetiology. This was followed by complete staging with a computerized tomography scan of the thorax, abdomen and pelvis (CT-TAP) with subsequent curative intent resection if appropriate. NIGBC diagnosis was made based on imaging and/or biopsy after MDT discussion of referred patients. All patients had staging with CT-TAP, followed by surgery if clinically appropriate. In patients with locally advanced disease, neoadjuvant chemotherapy (NAC) was administered and resection was contemplated after restaging. Liver magnetic resonance imaging (MRI) and positron emission tomography (PET) scans were used selectively in both groups if liver

metastases or extrahepatic disease was suspected on CT. Following surgical resection all patients were referred to oncology for assessment of adjuvant chemotherapy (AC).

Data were collected and recorded for patient's demographics, American society of anesthesiology (ASA) score, extent of surgical resection, histology, chemotherapy, recurrence and survival. The extent of surgery was defined as minor if radical cholecystectomy, gallbladder (GB) bed resection or liver segments IVb/V resection with or without bile duct resection was performed. It also included patients who only had bile duct resection. The resection was defined as major if a major hepatectomy (three or more liver segments) or multi-visceral resection was performed. Recurrence was defined as local/regional (GB bed, hilar lymph nodes), distant or both.

The primary outcome of the study was difference in OS between IGBC and NIGBC and the secondary outcome was difference in disease-free survival (DFS).

T-test, Chi-Square, Fisher's Exact and Mann-Whitney U tests were used as appropriate to compare variables and outcomes between the two groups, with statistical significance set at $p<0.05$. Survival analysis was performed with the Kaplan-Meier method and log rank test was used to compare survival curves between the study groups. Univariable and multivariable time to event analyses were performed using the Cox proportional hazard model to determine risk factors for OS and DFS. Variables were subjected to a univariable analysis first and those with $p<0.2$ were introduced into a multivariable model. Hazard ratios (HR) and associated 95% confidence intervals (CI) were calculated. A two-tailed p value <0.05 was considered statistically significant. All statistical analyses were performed using the software package SPSS Statistics for Windows (version 25.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Cohort characteristics and management pathway

The study cohort comprised of 261 patients, with 35% presenting as IGBC and 65% had non incidental presentation (NIGBC) at the time of diagnosis (Figure 1). Median age was 69 years (interquartile range (IQR) 61-77) and male to female ratio was 1:3. Eighty-

one percent of NIGBC and 34% of IGBC patients did not undergo resection. For the majority of these (82%) locally advanced or metastatic disease was the main reason. Other causes included patient's choice, poor medical status and pathological stage <1b (where resection is not indicated) (Table 1). Reasons for not having AC after resection were patients' choice or comorbidities and early tumour stages (CIS, T1/T2, N0) with negative resection margins.

Patient and tumour characteristics of surgical patients

A total of 90 patients had curative intent resection. The type of resection depended on IGBC *vs* NIGBC diagnosis, pre-operative staging, intra-operative findings, cystic duct margin status and the T stage of IGBC patients. Hepatoduodenal (portal) lymphadenectomy was performed in all patients. For IGBC cases, the median time from the time of the index cholecystectomy to the curative resection was 13.5 wk (IQR: 11-16 wk).

Patient and tumour characteristics are shown on Table 2. Patients with NIGBC had more advanced T stage and underwent more extensive resections compared to those with IGBC. Similarly, N stage approached but did not reach significance. The types of procedures performed are shown on Table 3.

Survival analysis

For the whole cohort, median OS was longer in patients with IGBC diagnosis, (29 *vs* 4 mo, p <0.001). OS of IGBC patients was significantly longer compared to NIGBC patients in the non-surgical group (14 *vs* 2 mo, p<0.001), as well as the surgical group (29 *vs* 16.5 mo, $P = 0.001$). Similarly, DFS was significantly longer in patients with IGBC (21.5 mo *vs* 8.5 mo, $P = 0.007$) (Figure 2).

Risk analysis

Univariable Cox regression analysis (Table 4) identified that age, ASA, T stage, N stage, resection margin status and NIGBC diagnosis were significantly related to OS ($p<0.05$). On multivariable analysis, N stage, resection margin status and NIGBC diagnosis were identified as independent predictors of survival, increasing the risk of mortality by 3, 5 and 2 times respectively (Table 4).

Similarly, T stage, N stage, resection margin status and NIGBC diagnosis were identified to be associated with worse DFS on univariable analysis, however only N stage and resection margin status were found to be independent predictors on multivariable analysis (Table 5).

In an effort to statistically investigate if NIGBC diagnosis acted as a confounding factor for the T stage of the disease despite the use of time-dependent regression analysis, models without this parameter were produced. Again, only N stage and margin status were identified as independent prognostic factors for OS and DFS, while T stage was not (Tables 4 and 5).

DISCUSSION

GBC is a rare malignancy with unfavorable prognosis despite the advances in oncological treatments [1, 2, 12]. The timing of GBC diagnosis, whether incidental after cholecystectomy for benign causes or pre-operative on imaging and/or biopsy, has been previously under investigation for the potential effect in outcomes, however evidence is scarce. Violation of the anatomical planes around the tumour and incomplete clearance during the index laparoscopic cholecystectomy with residual disease in 35-46% of the patients have been proposed as factors responsible for adverse oncological outcomes in IGBC patients.[13-15]. Furthermore, inadvertent GB perforation during cholecystectomy has been reported in up to 22% [16, 17], and this could theoretically lead to tumour seeding and metastatic disease. Interestingly, the site of invasion of local disease has also been shown to play an important role in T2 disease [15]. Nonetheless, some published evidence suggested that IGBC diagnosis confers favourable survival, regardless of the stage or degree of differentiation of the disease [9-

[11]. On the other hand, in other studies, NIGBC diagnosis did not adversely affect survival [5-8]. In a meta-analysis of 51 studies by Pyo *et al*, IGBC patients had favorable survival in comparison to NIGBC. However, not all studies included in this meta-analysis were able to show the same difference between both groups[18].

Sixty five percent of referred patients in our cohort had a preoperative radiological diagnosis of GBC. Sixty six percent of all patients did not proceed to an oncological resection (81% of NIGBC and 36% of IGBC patients), 16% of these due to locally advanced disease (all NIGBC patients) and 38% due to metastatic disease on staging imaging (23% of IGBC and 46% of NIGBC patients). Only 3% of IGBC were stage T1a or below and therefore, no further resection was indicated. Of note only 7% of patients were deemed unfit for surgical treatment. It is clear that the majority of the patients that did not proceed to management with curative intent were due to the late presentation of the disease, a fact that is well described for GBC [19]. The percentage of patients who had AC after curative intent surgery was low (22%). This is comparable with the published literature of around 24% [20]. The reasons for this may include patients' choice and comorbidities, however, may also be attributed to the change in recommended best practice over the years of the study. According to a previously published expert consensus statement, AC was considered only in patients with high risk pathologic features: T3-T4 stages, metastatic lymph nodes and positive resection margins [21]. However, after the BILCAP trial showing improved survival with capecitabine (36.4 mo to 51.1 mo; $P = 0.028$), it is currently recommended that all patients with resected biliary tract malignancy, including GB cancer, receive 6 mo of adjuvant capecitabine [22]. The results of the currently ongoing ACTICCA-1 trial are eagerly awaited and will provide further evidence if the combination chemotherapy of gemcitabine and cisplatin is superior to capecitabine monotherapy in the adjuvant setting.

Our data suggests that NIGBC diagnosis adversely affected oncological outcomes. NIGBC patients were more likely to have higher stages of the disease (T3/4), consequently undergoing more extensive resections. The range of oncological

procedures for selected cases included multi-visceral resections and major hepatectomies to achieve histologically clear resection margins. Routine performance of such procedures is not associated with survival benefit and has high morbidity rates; however, it is still indicated when the vascular inflow or resection margins are/may be compromised [23-25]. Positive lymph node status was more common in patients with NIGBC with the difference approaching statistical significance. OS of all patients with NIGBC diagnosis was substantially worse than those with IGBC and this was also noted in both surgical and non-surgical subgroups. Furthermore, in the surgical subgroup, NIGBC diagnosis was identified as an independent predictor of OS; doubling the risk of mortality. Stronger predictors were pN stage and margin status, increasing the risk by 3 and 5 times respectively. These findings persisted when models computed that accounted for the possibility of NIGBC diagnosis acting as a confounding factor for T stage (by not including this parameter in the analysis), indicating that it is not true. This seemingly paradoxical observation may be explained by the presence of micro-metastases in early stages of GBC [26], which would affect and in the end dictate OS and DFS, rather than pT stage. Similar were the results for DFS, with N stage and margin status conferring higher relative risk of recurrence, while NIGBC diagnosis approached but did not reach significance.

Lymph node status is an important prognostic factor in GBC. Bernhard *et al* in a meta-analysis of 18 observational studies which included more than 27,000 patients, has shown that lymph node involvement has significant effect on OS and DFS [27]. Lymphadenectomy also was associated with better OS and DFS in patients with T1b, T2 and T3 disease. This was not clearly demonstrated with T4 disease due to the low number of cases undergoing curative resection in this stage. Lymph node micrometastases, defined as disease detected on immune-histochemical staining, have also been described to correlate with the pathologic N stage of the disease and disease prognosis [28]. Nonetheless, the significance of the extent of lymphadenectomy and lymph node yield is controversial in the published literature, with data from two studies suggesting that harvesting more than four lymph nodes during surgery is

associated with improved survival[29,30], whilst a third study concluded that lymph node yield does not correlate with improved survival[31]. These differences may be explained by the differences in pathological reporting (higher lymph node yield may result in more accurate pN staging) and/or variations in the non-surgical part of the patients' management, such differences in the administration of neoadjuvant and adjuvant chemotherapy, regimens, duration *etc.*

Overall, our data suggest that the timing of diagnosis of GBC may play a significant role in the oncological outcomes. Due to the retrospective nature of the study and the long study period, data on the site of invasion (hepatic *vs* peritoneal) were not available, hence this could not be investigated as a possible explanation[32,33]. Another possibility is a difference in the genetic profile of the tumours which could account for different behavior, such as early micrometastases, that cannot be captured by the common radiological investigations and standard pathological parameters of stage and differentiation [34]. However, this cannot be investigated by the current study and would require a prospective molecular study design.

The limitations of the study include its single centre retrospective methodology. The long study period also included differences and evolution in the surgical approach during the oncological resection, with more bile duct resections done during the early study period to achieve a negative margin and a greater lymph node yield. In the later years, bile duct resection was only performed in the presence of a positive cystic duct margin. Nonetheless, this is the first study to include all patients referred for GBC to a tertiary regional centre, rather than only the ones receiving surgical treatment, therefore providing outcome data in an intention to treat basis over the whole referral cohort including the patients that did not receive surgical treatment. It is also one of few studies to demonstrate the effect of non-incidental diagnosis on the oncological outcomes.

CONCLUSION

Conclusively, the presented data suggest that IGBC diagnosis may confer a survival advantage, including patients that received surgical treatment, independently of the pathological stage and tumour characteristics. Prospective studies are required to investigate the reasons behind this, including detailed pathological analysis and molecular gene expression.

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