Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: Well documented retrospective study.

The authors appreciate the reviewer's comments and have nothing to add.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade D (Rejection)
Conclusion: Rejection
Specific Comments to Authors: The authors investigated the difference between incidental gallbladder cancer (IGBC) and non-incidental diagnosis (NIGBC) for overall survival (OS) and disease-free survival (DFS). This manuscript is interesting study, however, there is not enough information and analysis to publish it. Comments are as follows:

Major comments;

1. There has been a lot of published studies about this theme, so novelty of this study seems to be nothing. After of all, only analyses of prognostic factor for OS and DFS were performed, however, the mechanisms and reasons for this have not been analyzed and are poorly discussed.

Despite the number of published studies on gallbladder cancer, there are only a few that have demonstrated the effect of incidental or not diagnosis on the oncological outcomes. The authors have mentioned and discussed the relevant evidence extensively. These are contradicting and inconclusive and therefore more data on the topic provided by this study will increase the body of evidence and may provide the background for future studies. Furthermore, **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.**

The study has investigated a comprehensive panel of parameters that may affect oncological outcomes and the statistical investigation with unavailable and multivariable analysis was detailed and thorough. Similar to all studies of similar design, the results can identify significant associations. The mechanisms and reasons can only be hypothesized and in order for them to be investigated, prospective trials and cancer molecular studies are required. This has been discussed and clearly addressed in the discussion section of the manuscript, which has also been expanded for this reason.

2. The factors in the Cox proportional hazard analysis for OS and DFS seems to be small. If patient background and oncological factors are included, surgical factors including complication must be included for a valid analysis at least. As mentioned in the discussion, the authors should analysis the bile leak during the operation in hazard analysis

We have collected data regarding the surgical complications post oncological resection. We have added these on the table comparing IGBC versus NIGBC. We have also included the presence of post-operative complications in our risk analysis. There was no significant difference between both groups in the frequency of complications. On univariable analysis, there was no significant association between surgical complications and survival and therefore the parameter was not included in multivariable analysis.

The fact that bile leak during index cholecystectomy may play a role in the prognosis of ICGB cancer patients is a theory that has not be proved by any study yet. The retrospective data on bile leak during index cholecystectomy are heavily biased (in most cases this is not mentioned in the operation notes as the cholecystectomy is performed for benign pathology) and therefore of no use in the current study.

3. In the Result 4, Risk analysis, the authors mentioned as follows: In the resulting model as well, only N stage and margin status were identified as independent prognostic factors for OS and DFS, while T stage was not. I am sorry for not understanding this analysis. Please explain and show the Table.

In the risk analysis, all parameters were investigated to identify independent predictors of OS and DFS. Each parameter was initially investigated with univariable Cox regression analysis and subsequently those with a $p<0.200$ were investigated further with multivariable Cox regression. With regards to the pathological T stage, even though it was significant in the univariable analysis, on the multivariable analysis this significance was lost. As NIGBC had significantly higher T stage than IGBC, the timing of diagnosis may have been a confounding factor for differences observed in OS and DFS, masking the effect of pT despite the multivariable analysis. In an effort to exclude this confounding issue, a multivariable investigation was performed by omitting the parameter of the incidental or not diagnosis (IGBC vs NIGBC), however pT remained non significant in these models as well.

The additional tables can be found below. The multivariable model has been added as additional two columns on Tables 4 and 5.

Cox regression analysis for overall survival

Variable	**p value**	**HR (95% CI)**	**p value**	**HR (95% CI)**
	Univariable analysis		*Multivariable analysis*	
Age	**0.011**	1.04 (1.01-1.07)	0.153	1.04 (0.99-1.10)
Gender	0.960	1.01 (0.706-1.44)	-	-
Race	0.853	1.05 (0.611-1.81)	-	-
BMI	0.601	0.983 (0.92-1.05)	-	-
ASA score	**0.024**	1.96 (1.09-3.52)	0.061	2.53 (0.96-6.66)
CCI score	0.064	1.19 (0.99-1.42)	0.269	0.78 (0.50-1.21)
T stage	**<0.001**	2.73 (1.72-4.34)	0.088	1.62 (0.93-2.81)

N stage	**<0.001**	5.65 (2.84-11.25)	**0.001**	3.59 (1.72-7.49)
R status	**<0.001**	7.35 (3.38-15.95)	**0.012**	3.00 (1.27-7.07)
Degree of Differentiation	0.443	1.40 (0.61-3.21)	-	-
Adjuvant chemotherapy	0.870	1.07 (0.47-2.44)	-	-

Cox regression analysis for disease-free survival

Variable	**p value**	**HR (95% CI)**	**p value**	**HR (95% CI)**
	Univariable analysis		*Multivariable analysis*	
Age	0.275	1.02 (0.98-1.06)	-	-
Gender	0.732	0.85 (0.34-2.13)	-	-
Race	0.997	1.13 (0.15-8.51)	-	-
BMI	0.782	0.99 (0.91-1.07)	-	-
ASA score	0.817	0.91 (0.42-1.98)	-	-
CCI score	0.842	0.98 (0.76-1.26)	-	-
T stage	**0.021**	2.06 (1.12-3.82)	0.210	1.53 (0.79-2.97)
N stage	**0.001**	4.08 (1.83-9.08)	**0.008**	3.08 (1.35-7.06)
R status	**<0.001**	11.05 (3.31-36.94)	**0.002**	6.95 (1.98-24.34)
Degree of Differentiation	**0.011**	0.65 (0.33-1.28)	-	-
Adjuvant chemotherapy	**0.211**	1.42 (0.56-3.58)	-	-

4. In the discussion, adjuvant chemotherapy including BILCAP was mentioned, however, those did not seem to correlated to the author's manuscript. Please delete.

The percentage of patients receiving adjuvant chemotherapy in this study was low (22%) and comparable to other published studies. The authors mentioned the change in the chemotherapy practice in order to explain for this. In the initial phase of the study the recommendations were for only patients with advanced disease to have adjuvant chemotherapy, while in the latter stage and due to the BILCAP trial the recommendation has changed in favour of all patients receiving adjuvant chemotherapy. Since the study is looking into oncological outcomes that are clearly affected by systemic treatment, explaining this change in practice is relevant and important. Minor changes have been made in this paragraph of the discussion to make this more clear to the reader.

5. T factor has no effect on prognostic factors (in multivariate analysis), however, what if the analysis is divided into factors below T2 and above T3? Usually, the difference in prognosis between IGBC and NIGBC would correlate with the degree of tumor progression, because there is no difference in tumor factors except for tumor progression at the time of surgery. Therefore, there can be no difference in genetic mutations, as the authors pointed out. Even if there is, it is not a difference between IGBC and NIGBC.

T stage is a categorical variable with 4 categories that has been statistically investigated by univariable and multivariable regression. Converting this to a binary categorical variable may be considered a statistical trick to yield significance. Nonetheless, as per the reviewers comment, the authors have performed this analysis, ie created models in which T stage was grouped as T1/T2 and T3/T4. However pT group was not significant in multivariable analysis (results below). In the interest of space and relevance to publication and as the result was not significant, this was not included in the revised version of the manuscript.

Furthermore, the reviewer comments that there is no difference in genetic mutations but only in tumour progression. The authors understand and respect this personal opinion that is however not backed by any evidence. First of all, as explained in the manuscript, several studies have already provided clinical evidence for the opposite in GBC, ie oncological outcomes are different between IGBC and NIGBC despite tumour differentiation and stage. More importantly there is a large number of evidence from genetic studies on the differences with regards to the genetic signatures (alleles and mutations) in malignancies of the same organ (ex colon cancer, lung cancer, pancreatic cancer) that affect survival. Based on these studies, trials on individualised systemic chemotherapy have been launched around the world. It is therefore logical to hypothesise that this may also be the case in GBC and future trials will be required to prove or dismiss it.

Cox regression analysis when T stage is group into T1/T2 and T3/T4 without non-incidental diagnosis included in the analysis

Variable	P value	HR (95% CI)	P value	HR (95% CI)
	Univariate analysis		*Multivariate analysis*	
Age	**0.011**	1.04 (1.01-1.07)	0.229	1.03 (.98-1.09)
Gender	0.960	1.01 (0.706-1.44)	-	-
Race	0.853	1.05 (0.611-1.81)	-	-
BMI	0.601	0.983 (0.92-1.05)	-	-
ASA score	**0.024**	1.96 (1.09-3.52)	**0.047**	2.69 (1.02-7.13)
CCI score	**0.064**	1.19 (0.99-1.42)	0.316	0.798 (0.51-1.24)
T group	**<0.001**	3.32 (1.78-6.21)	0.204	1.66 (0.76-3.65)
N stage	**<0.001**	5.65 (2.84-11.25)	**<0.001**	4.03 (1.96-8.32)
R status	**<0.001**	7.35 (3.38-15.95)	**0.018**	3.03 (1.21-7.58)

Degree of differentiation	0.443	1.40 (0.61-3.21)	-	-
Adjuvant chemotherapy	0.870	1.07 (0.47-2.44)	-	-

Cox regression analysis when T stage is group into T1/T2 and T3/T4 with non-incidental diagnosis included in the analysis

Variable	P value	HR (95% CI)	P value	HR (95% CI)
	Univariate analysis		*Multivariate analysis*	
Age	**0.011**	1.04 (1.01-1.07)	0.333	1.03 (0.97-1.08)
Gender	0.960	1.01 (0.706-1.44)	-	-
Race	0.853	1.05 (0.611-1.81)	-	-
BMI	0.601	0.983 (0.92-1.05)	-	-
ASA score	**0.024**	1.96 (1.09-3.52)	0.58	2.56 (0.97-6.79)
CCI score	**0.064**	1.19 (0.99-1.42)	0.439	0.84 (0.54-1.31)
T group	**<0.001**	3.32 (1.78-6.21)	0.613	1.22 (0.57-2.62)
N stage	**<0.001**	5.65 (2.84-11.25)	**<0.001**	4.37 (2.09-9.14)
R status	**<0.001**	7.35 (3.38-15.95)	**0.002**	4.06 (1.66-9.97)
Non-incidental diagnosis	**0.004**	2.41 (1.32-4.38)	**0.022**	2.16 (1.12-4.16)
Degree of differentiation	0.443	1.40 (0.61-3.21)	-	-
Adjuvant chemotherapy	0.870	1.07 (0.47-2.44)	-	-

Minor comments;

1. In Abstract, Aim, please change the sentence “to” to “To”.

2. In Abstract, Methods, “subgroupds” is a typo.

3. Only in Table 3, the positions of NIGBC and IGBC are swapped, which confuses the reader.

All minor comments were dealt with as per the reviewer’s recommendation.

Reviewer #3:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: This is a well written manuscript. My observations are as follows:

The authors appreciate the reviewer's feedback and comments. Please notice that all of the reviewer's comments have been addressed in the manuscript.

1. What was the work-up protocol for the patients who presented with IGBC. Did they undergo PET-CT or CECT for reassessment?

All patients who were found to have gallbladder cancer after routine laparoscopic cholecystectomy had a formal staging which included chest, abdomen and pelvis CT scan with contrast. PET -CT scans and occasionally MRI were done only in selective cases. This has been clarified in the methods section of the manuscript.

2. Please comment upon the median time from first surgery to completion surgery in patients with IGBC.

Median time from the index cholecystectomy to the cancer surgery was 13.5 weeks (IQR: 11-16 weeks). This was included in the results section of the paper.

3. How many of the patients with IGBC had positive cystic duct margin after first surgery?

6/58 patients with IGBC had positive cystic duct margin on histologic examination of the gallbladder after the index cholecystectomy. This has been included on Table 2.

4. Please comment upon the extent of regional lymphadenopathy.

Hepatoduodenal (portal) lymphadenectomy was the standard practice in our unit during the study period. This is mentioned in the results section of the manuscript.

5. As per table 3, please define minor/major resection.

This has been clarified in the methods section: "Extent of surgery was defined as minor resection if radical cholecystectomy, GB bed resection or liver segments IVb/V resection with or without bile duct excision was performed. It also included patients who only had bile duct excision. Surgery was defined as major resection if major hepatectomy (three or more liver segments) or multi-visceral resection was performed"

6. Why almost one fourth of the patients did not receive adjuvant chemotherapy? Please comment.

Only 22% of the patients in our cohort received adjuvant chemo, which is comparable to the percentage found in the literature (reference no. 20). This has been further clarified and

analysed in the discussion section of the manuscript: "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 months to 51.1 months; p=0.028), it is currently recommended that all patients with resected biliary tract malignancy, including GB cancer, receive 6 months of adjuvant capecitabine"

Reviewer #4:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: The authors statistically compared the surgical outcomes between incidental gallbladder cancer (IGBC) and non-incidental gallbladder cancer (NIGBC). In their results, IGBC series showed significantly better OS, and IGBC status was independent predictor of better OS in multivariate analysis. Although design, procedure, and statistical analyses are appropriate, the most limitations of this study are small sample size and its retrospective nature. Therefore, the clinical impact of this paper is not so strong and the issue of IGBC and surgical outcomes still remains controversial. The paper is relatively well-written. It is the matter of the editor's decision that whether clinical and academic impact of this paper is enough for publication in WJG.

The authors appreciate the reviewer's comments and feedback. They also acknowledged the limitations in the discussion section of the manuscript.