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Tumor characteristics and survival analysis of incidental versus suspected gallbladder carcinoma

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Tumor characteristics and survival analysis of incidental versus suspected gallbladder carcinoma

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An abstract of a thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Master of Science in Clinical Research

2011

ABSTRACT:

Tumor characteristics and survival analysis of incidental versus suspected gallbladder carcinoma

By Laura M. Mazer

Introduction**:** Gallbladder cancer (GBC) is a rare malignancy with a poor prognosis. Over half of all GBC, however, is discovered incidentally after cholecystectomy for benign disease. There are scant data comparing presentation and outcome for patients with incidental versus suspected GBC. The goal of this study is to examine the presentation and prognosis of these two entities.
Study Design: Patients with GBC were identified retrospectively from medical records at academic healthcare institutions in Temuco, Chile; Atlanta, GA; and Rochester, MN between 1984 and 2008. Overall survival was compared for patients with and without preoperative suspicion using stratified Kaplan-Meier curves and a multivariate Cox Proportional Hazards model.
Results: Of 571 patients from three centers, 128 (22.4%) had preoperative suspicion of malignancy and 443 (77.6%) were discovered incidentally. Incidental tumors were lower stage, better differentiated, and with lower rates of nodal metastases and local invasion. Median survival time for incidentally discovered GBC was 32.3 months versus 5.8 months for suspected GBC (p<0.0001). In a Cox Proportional Hazards model controlling for extent of operation, T-stage, degree of differentiation, and other factors, preoperative suspicion remains a strong risk factor (OR 2.0, CI 1.5-2.9, p<0.0001).
Conclusions: Tumor characteristics differed significantly between patients with incidentally discovered GBC and those with preoperative suspicion on imaging. Incidental GBC has a significantly better median survival, even when controlling for tumor stage and degree of differentiation. More research is needed to understand the underlying cause of the improved prognosis for patients with incidental GBC.

Tumor characteristics and survival analysis of incidental versus suspected gallbladder carcinoma

By

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TABLES AND FIGURES:

INTRODUCTION:

Gallbladder carcinoma (GBC) is the 5th most common gastrointestinal malignancy in Western countries, with approximately 5000 new cases diagnosed annually in the United States[1]. Five-year survival is extremely low, and many patients present with late-stage, unresectable disease. However, up to 61% of GBC are diagnosed incidentally, during surgery for benign disease or on post-operative histology[2, 3]. In these cases, patients are diagnosed preoperatively with cholelithiasis or cholecystitis, and have no clinical or radiographic indications of cancer. During or after the cholecystectomy, a tumor is discovered and an incidental diagnosis of GBC is made. Depending on regional prevalence, between 0.1-6% of all patients undergoing cholecystectomy will have an incidental discovery of GBC [1, 4, 5]

Incidental GBC may represent early stage cancer that would eventually present symptomatically with a correspondingly poor prognosis. Alternatively, it may represent a unique clinical entity with a different biology and prognosis when compared with symptomatic GBC. Without understanding the characteristics and implications of incidental GBC, it is extremely difficult for the surgeon to counsel his patient on the unexpected diagnosis or provide appropriate management.

To address this problem, multi-center data on all patients with GBC from three centers in the United States and Chile has been compiled. The current study examined the characteristics of patients and tumors in this dataset to understand the clinical differences between incidental and suspected GBC. Additionally, survival analysis examined the impact of time of diagnosis on survival in patients with GBC when considering the interaction with other known prognostic factors.

BACKGROUND:

Several retrospective studies have examined prognostic factors for patients with GBC. Tumor stage, according to the AJCC staging system, is the strongest overall predictor of patient survival[2, 6]. Other prognostic factors include the operative procedure, lymph node status, age, and sex[6, 7]. Overall, five-year survival for patients with GBC remains dismal and in most studies is less than 10%[1, 7].

The management of incidental GBC has been described previously[8]. There are scant data, however, on the importance of incidental discovery of GBC as a prognostic indicator of patient survival. Incidental GBC may represent early-stage cancer that would eventually progress to symptomatic disease, or it may represent a unique histological entity with a different prognosis.

METHODS:

Hypothesis and Study Design:

There is no significant difference in survival between patients who present with symptoms of GBC and those who are diagnosed incidentally, when controlling for other factors. This hypothesis will be tested in a retrospective cohort study.

Patient Population:

Patients were identified from the prospectively maintained surgical records of three healthcare centers with academic affiliation in Atlanta, GA, Rochester, MN, and Temuco, Chile. Records were reviewed for 571 patients with histologically confirmed GBC who underwent surgical resection for between 1984 and 2008.

A manual retrospective chart review was performed to record age at operation, gender, presence of associated cholelithiasis, stage at presentation, and histologic characteristics. Operative characteristics were also recorded, including the extent of surgical resection. For the purpose of the analysis, this was dichotomized to cholecystectomy alone or cholecystectomy with liver resection. Suspicion of malignancy prior to operation was ascertained based on preoperative records. Patients were considered to have preoperative suspicion of cancer if either the surgeon's notes or the radiologist's interpretation of a preoperative imaging study contained any suspicion of non-benign gallbladder disease. The types of imaging studies obtained prior to the operation leading to the were also recorded. The amount of time between the operation and the date of last follow-up were recorded along with status (alive or deceased) at last follow-up.

Stage at presentation is recorded in accordance with the American Joint Committee on Cancer (AJCC) Staging Manual, 6th edition, as data collection was performed prior to the release of the AJCC 7th edition. Although the recent edition includes changes to staging of GBC, the definition of primary T- stage is identical between the two editions[9, 10].

To validate the multi-center data, pathologists at the Temuco and Atlanta centers randomly reviewed histologic features of a selected portion of the dataset. The sample group demonstrated over 90% agreement between centers.

Statistical Analysis:

Patient and tumor characteristics were compared using either Chi square test of independence or Fisher's Exact Test for categorical variables and two-sample *t* test for continuous variables.

Survival analysis was performed using the Kaplan-Meier method[11]. Differences in observed survival distributions among patient groups were compared by two-sided log-rank test. Survival time was measured from the date of operation until the date of last follow-up or the date of death from any cause. For multivariate survival analysis, a Cox proportional hazards model was carried out[12]. To select the predictor variables, the patient and tumor characteristics were analyzed in a univariate fashion for their impact on the outcome of mortality at one year. All variables found on univariate analysis to be significant predictors of mortality were included in the final proportional hazards model.

The predictive value of the covariates was analyzed using a multivariate logistic regression model with one-year mortality as the outcome variable. The same candidate covariates used in the Cox model were considered in a stepwise fashion for the final logistic regression ($p \leq 0.10$ for entry, $p \leq 0.05$ to remain in the model). Forward and backward selection

procedures were used to validate the stability of the model; the same covariates were selected regardless of selection procedure.

All statistical tests were performed using the SAS 9.2 statistical software package for Windows (SAS Institute Inc, Cary, NC, USA).

RESULTS:

Study Population:

Of 571 patients identified on chart review following surgery for adenocarcinoma of the gallbladder, 443 were discovered incidentally and 128 were suspected on preoperative imaging. Patient characteristics are compared in Table 1. The two cohorts were similar in age and gender, but tumor characteristics differed significantly. Only 13% of suspected tumors were well-differentiated, versus 28% of incidentally discovered tumors (p=0.0013). Rates of nodal metastases (p=0.0001) and perineural (p<0.0001), perilymphatic (p<0.0001), and perivascular invasion (p<0.0001) were also significantly higher in tumors suspected preoperatively. T-stage also differed, with significantly more T0 cancers in the incidental group (17% vs 3%, p=0.0002) (see Table 1).

Tumor characteristics also differed significantly depending on geography, and are compared in Table 2. The three centers had similar distributions of gender (83% female in Chile versus 71% in Atlanta and 75% in Rochester, p=0.0922) and age (mean age 62, 64, and 65 years, p=0.1752). The types of GBC seen at each center, however, differed significantly. In Chile, 11% of cancers are suspected preoperatively, compared with 50% in the Atlanta cohort and 76% in the Rochester cohort. In Chile, 98% of patients were diagnosed with cholelithiasis, compared with 78% in Atlanta and 77% in Rochester (p<0.0001). No patients in Rochester or Atlanta had T0 cancer, but 16% of tumors in Chile were stage T0 (p<0.0001). Indications of aggressive disease, including nodal metastasis and perineural, perivascular, and perilymphatic invasion are all significantly more common in the American centers (p<0.0001, see Table 2).

The type of preoperative imaging also differed between the different patient groups. The majority of patients with incidentally discovered cancer were evaluated with ultrasound

alone (408, 89%). For the remaining patients, 6 (1.4%) had no preoperative imaging, 16 (4%) were evaluated with MRI, and 8 (2%) received more than one imaging study prior to operation. In comparison, 52 patients (43%) with preoperative suspicion of cancer were evaluated with ultrasound alone, while 35 (29%) received MRI studies and 33 (27%) were evaluated with more than one imaging modality.

Survival data:

The median survival time for incidentally discovered GBC was 32.3 months. Suspected GBC had a median survival time of 5.8 months. The difference in survival was statistically significant (log rank test $p<0.0001$; Figure 1). The patients were then stratified based on AJCC T-stage. Separate Kaplan-Meier curves were created to assess the effect of preoperative suspicion in patients with stage T0-T1 and patients with stage T2-T4 cancers. In both cohorts the survival difference remained statistically significant ($p=0.0097$, Figure 2, and $p<0.0001$, Figure 3).

Patients were also stratified based on country of origin to address the different tumor characteristics seen in each population (Table 2). In both cohorts, preoperative suspicion remained a strong predictor of mortality ($p<0.0001$, Figures 4 and 5).

The patient and operative characteristics were analyzed in a univariate logistic regression model with mortality at one year as the outcome. The variables with a significant (defined as $p<0.05$) correlation in a univariate analysis were: preoperative suspicion of cancer, age, t-stage (dichotomized as T0/T1 vs T2-T4), degree of differentiation, extent of resection (cholecystectomy alone vs with liver resection), gender, presence of cholelithiasis, and country of origin. These variables were included in a multivariate Cox model (Table 3). Preoperative suspicion remained a significant predictor of survival when controlling for other risk factors ($p<0.0001$, HR 2.042). In a multivariate logistic regression analysis, the same variables were

considered in a stepwise fashion with $p<0.10$ with one-year mortality as the dependent variable. Age at surgery, T-stage, degree of differentiation, and preoperative suspicion were found to be significant predictors of mortality. In this final model, preoperative suspicion remained a strong predictor (OR 4.86, 95% CI 2.34-10.08, $p<0.0001$; Table 4).

DISCUSSION:

Over 50% of GBC are detected incidentally after surgery for benign disease. Approximately 0.2% of patients undergoing cholecystectomy will have an incidental discovery of GBC[13, 14]. As the number of cholecystectomy operations increase, it is likely that the number of incidentally discovered GBC will also increase. An incidentally discovered GBC forces a rapid decision on the surgeon during the initial operation, and presents an unexpected challenge to patients postoperatively. In order to effectively manage the disease and counsel patients regarding the diagnosis, it is necessary to understand the prognosis of incidental GBC.

Many studies designed to analyze prognostic factors for survival with GBC do not consider preoperative suspicion of cancer[6, 7]. In one of the few studies attempting to stratify patients on the basis of preoperative suspicion, Lohe et al performed a retrospective analysis of 152 patients with GBC to assess the effect of time of diagnosis on patient survival. Although time of diagnosis was strongly predictive of survival in a univariate analysis, the association disappeared when patients were stratified by stage. They conclude that only tumor stage and extension of resection are significant predictors of patient survival[2].

The current study, in a larger sample, finds that incidental GBC carries a significantly improved prognosis in both univariate and multivariate analyses. When patients are stratified by T-stage, early T0-T1 cancer (Figure 2) and late stage T2-T4 disease (Figure 3) still differ significantly on the basis of preoperative suspicion ($p<0.01$ in both groups). It has been theorized that the survival difference seen with incidental GBC is an example of lead-time bias, and that the incidentally discovered tumors are simply earlier stage than those that present clinically. To assess this explanation, we performed multivariate analyses controlling for T-stage and degree of differentiation. In these models, the association between preoperative suspicion

and survival remains (Tables 2 and 3, $p<0.0001$). Although incidentally discovered cancer does tend to be earlier stage with better differentiation (Table 1), these factors do not sufficiently explain the survival benefit conferred by an incidental diagnosis.

The current study also presents data from three separate institutions. This is both a strength and a potential weakness of our data. The frequency of GBC differs significantly in different geographic regions[15]. The disease is endemic in Chile when compared to the rates in American centers. Additionally, the frequency and type of preoperative imaging in Chile differs when compared to Atlanta or Rochester. A significantly larger proportion of GBC is detected incidentally in Chile, likely reflecting a difference both in prevalence and hospital protocol or access to care. Even within American centers, 50% of GBC is detected incidentally in Atlanta versus 24% in Rochester. This difference likely represents the different specializations of the two centers, and the likelihood of a patient being referred to each center after receiving a diagnosis of GBC on imaging elsewhere.

The multi-center patient population also allows for a larger sample size. In a Kaplan Meier plot looking at survival as a function of preoperative suspicion in the Chilean cohort separate from the American cohort (Figures 4 and 5), preoperatively suspected cancers continue to have a significantly shorter mean survival. The multiple centers remain as a potential confounder, however, as patient, tumor, and institutional characteristics in each country are significantly different. More extensive data is needed to fully examine the potential effect of geographic, genetic, and procedural factors.

Early stage diagnosis and treatment, as well as varying pre- and intraoperative techniques, certainly impact survival with GBC, but they do not adequately explain the significance of incidental diagnosis. Controlling for age, extent of surgery, the presence of gallstone disease, country of origin, and stage of tumor are unable to explain the association

(Table 3). We hypothesize that these data may suggest a previously unrecognized histological difference between cancer that becomes symptomatic, and that which is detected only incidentally. It is possible that the growth patterns in these two situations differ biologically, and carry different prognoses for the patient.

Further research is warranted to fully understand the implications of the current study. In univariate and multivariate analyses, controlling for known risk factors and stratifying by presumed confounders, preoperative suspicion remains one of the strongest predictors of survival for patients with gallbladder cancer. Whether this represents an unknown biologic difference between incidental and suspected cancer is not yet clear. The current implications of our data lie in allowing surgeons to better counsel patients regarding an unexpected diagnosis of gallbladder cancer. This disease continues to carry a very poor prognosis, and the current study may help in defining expectations for this patient population.

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TABLES AND FIGURES:

Table I: Patient and tumor characteristics between gallbladder cancer from patients with and without preoperative suspicion on imaging, presented as N (%)[1] or mean ± SD:

Variable	Preop suspicion (n=128)	No preop suspicion (n=443)	P-value*
Female gender	97 (76%)	365 (82%)	0.0936
Age	63 ± 12	63 ± 13	0.8373
Cholelithiasis	86 (76%)	432 (98%)	*<0.0001*
AJCC[2] T0	3 (3%)	65 (17%)	*0.0002*
AJCC T1	8 (7%)	1 (<1%)	*<0.0001*[+]
AJCC T2-T5	101 (90%)	327 (83%)	0.0712
Well-differentiated	17 (14%)	116 (28%)	*0.0013*
Nodal metastasis	35 (40%)	62 (16%)	*0.0001*
Vascular invasion	28 (30%)	44 (10%)	*<0.0001*
Perineural invasion	25 (29%)	26 (6%)	*<0.0001*
Lymphatic invasion	44 (44%)	38 (9%)	*<0.0001*
Chile	50 (39%)	410 (93%)	*<0.0001*

[1]Percentages reflect the percentage of patients in each cohort with complete data available for the given variable.

[2]American Joint Committee on Cancer Staging system

* P-values obtained from chi square test of independence for categorical variables and t-test for continuous variables.

[+] P-value obtained from 2-sided Fisher's Exact test

Table 2: Patient and tumor characteristics between gallbladder cancer comparing patients from three centers, presented as N (%)[1] or mean ± SD:

Variable	**Temuco, Chile (n=460)**	**Atlanta, GA (n=24)**	**Rochester, MN (n=87)**	**P-value***
Preoperative suspicion	50 (11%)	12 (50%)	66 (76%)	<0.001
Female gender	380 (83%)	17 (71%)	65 (75%)	0.0922
Age	62 ± 13	64 ± 11	65 ± 12	0.1752
Cholelithiasis	448 (98%)	18 (78%)	52 (74%)	<0.0001
AJCC[2] T0	68 (16%)	0	0	<0.0001
AJCC T1	0	6 (25%)	3 (4%)	<0.0001
AJCC T2-T4	335 (78%)	18 (75%)	75 (96%)	<0.0001
AJCC T5	28 (7%)	0	0	0.0130
Well-differentiated	129 (29%)	3 (14%)	1 (1%)	<0.0001
Nodal metastasis	57 (15%)	10 (45%)	30 (50%)	<0.0001
Vascular invasion	51 (11%)	13 (57%)	8 (16%)	<0.0001
Perineural invasion	32 (7%)	15 (79%)	4 (9%)	<0.0001
Lymphatic invasion	43 (10%)	13 (57%)	26 (46%)	<0.0001

[1]Percentages reflect the percentage of patients in each cohort with complete data available for the given variable.

[2]American Joint Committee on Cancer Staging system

* P-values obtained from chi square test of independence for categorical variables and ANOVA for continuous variables.

Table 3: Multivariate Cox proportional hazards model for prognostic variables with univariate significance for survival:

Variable*	**P-value**	**Hazards Ratio (95% CI)**
Preoperative suspicion	*<0.0001*	2.042 (1.458-2.860)
Age	0.3652	1.005 (0.995-1.015)
Cholecystectomy with liver resection[1]	0.0376	0.581 (0.349-0.969)
Lithiasis	0.8009	0.930 (0.527-1.640)
Chile[2]	0.3531	0.780 (0.462-1.317)
T-stage[3]	*<0.0001*	7.682 (3.778-15.619)
Degree of differentiation	*<0.0001*	1.756 (1.469-2.099)

*Variables represent all possible covariates with significant univariate association with survival, excluding those missing for >10% of the dataset

[1]Versus cholecystectomy only

[2] Versus Atlanta or Rochester clinic

[3] AJCC stage T0 or T1 versus T2-T4

Table 4: Multivariate Logistic Regression model for one-year mortality:

Variable*	**P-value**	**Odds Ratio (95% CI)**
Preoperative suspicion	*<0.0001*	4.857 (2.339-10.084)
Age	0.0180	1.021 (1.004 -1.039)
T-stage[1]	*<0.0001*	10.894 (5.213-22.768)
Degree of differentiation	*<0.0001*	2.179 (1.598-2.972)

*Variables represent all possible covariates with significant univariate association with survival, excluding those missing for >10% of the dataset

[1] AJCC stage T0 or T1 versus T2-T4

Figure I: Kaplan-Meier analysis of postoperative survival time in patients with GBC discovered incidentally (median survival 32.3 months) versus GBC suspected on pre-operative imaging (median survival 5.8 months), log rank test p<0.0001

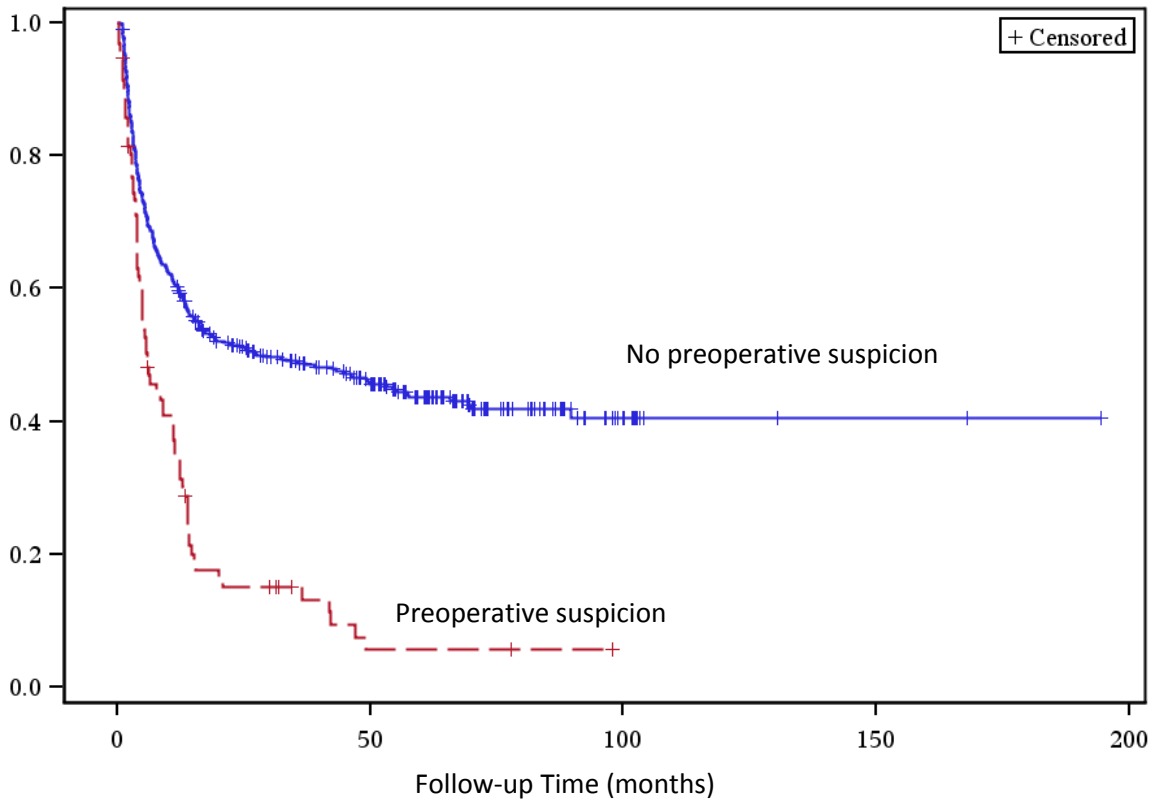

Figure 2: Post-operative survival time in patients with stage T0-T1 GBC comparing incidental versus suspected disease, log rank test p=0.0097

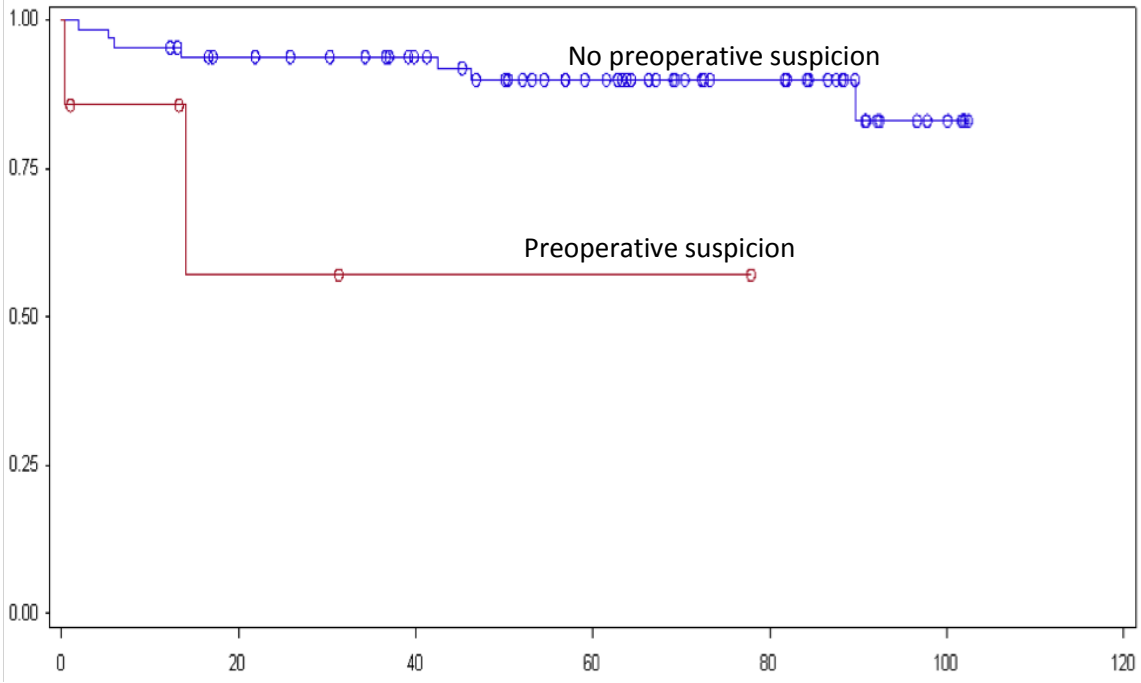

Figure 3: Post-operative survival time in patients with stage T2-T4 GBC comparing incidental versus suspected disease, log rank test p<0.0001

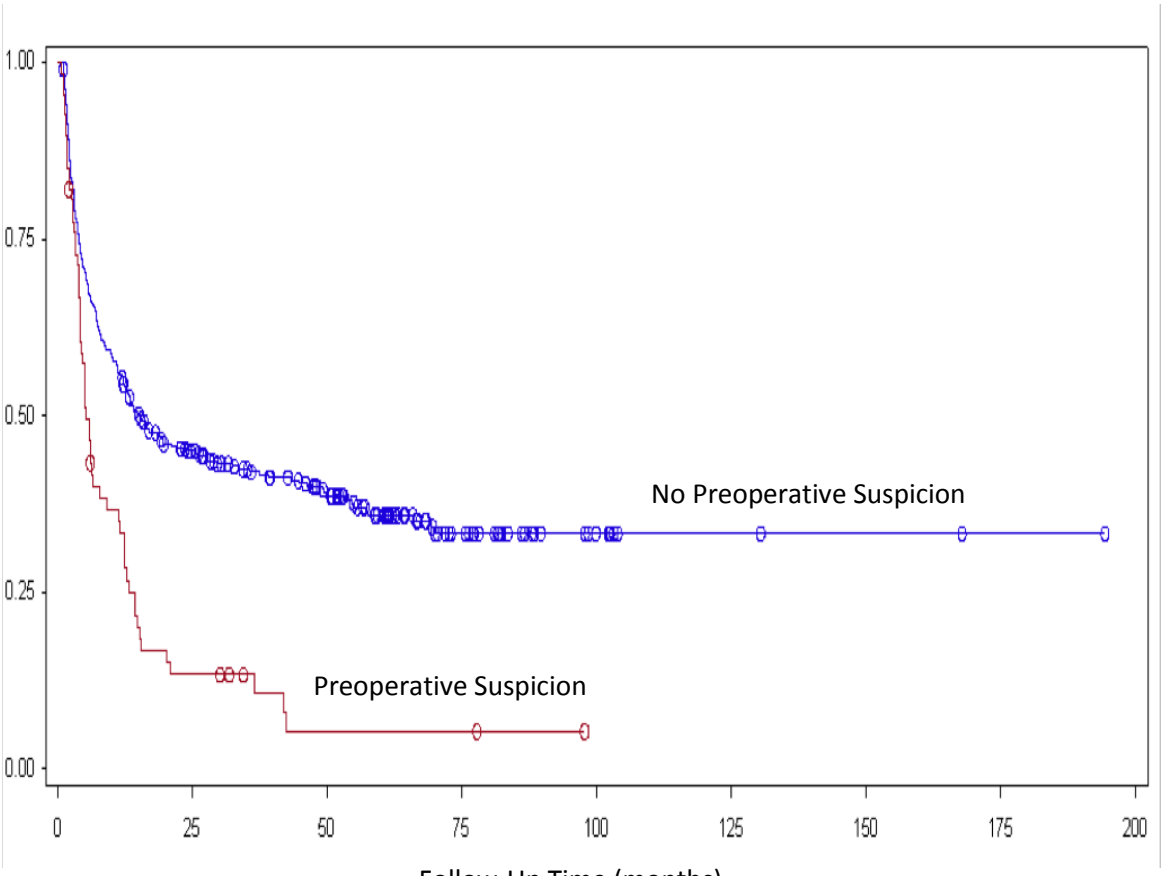

Figure 4: Post-operative survival time in patients from Temuco, Chile comparing incidental versus suspected disease, log rank test p<0.0001

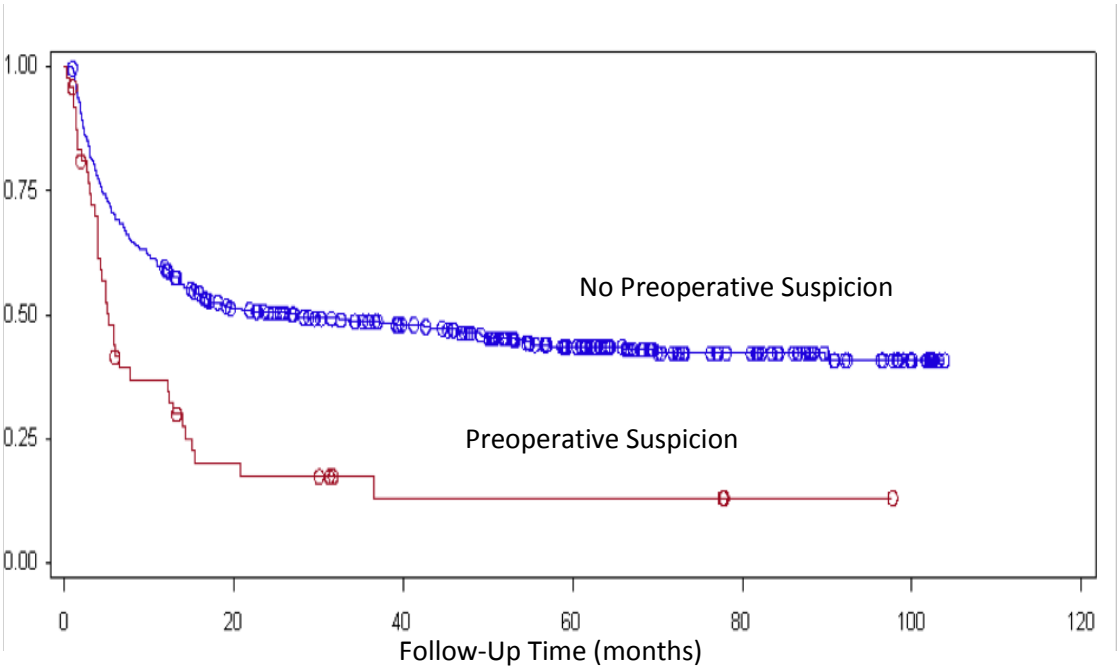

Figure 5: Post-operative survival time in patients from American centers (Rochester, MN and Atlanta, GA) comparing incidental versus suspected disease, log rank test p<0.0001