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Cecilia G. Ethun Date

Surgical Management of Incidental Gallbladder Cancer:
Who, When, and How?

By

Cecilia G. Ethun, M.D.
Master of Science

Clinical Research

_____

Shishir K. Maithel, MD
Advisor

_____

John F. Sweeney, MD
Advisor

_____

Amita Manatunga, PhD
Committee Member

_____

Mitchel Klein, PhD
Committee Member

# Surgical Management of Incidental Gallbladder Cancer: Who, When, and How?

By

Cecilia G. Ethun
M.D., Baylor College of Medicine, 2013

Advisors: Shishir K. Maithel, M.D. and John F. Sweeney, M.D.

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
2017

## ABSTRACT

Surgical Management of Incidental Gallbladder Cancer:
Who, When, and How?

By Cecilia G. Ethun

Current recommendation is to perform re-resection for select patients with incidentally-discovered gallbladder cancer (IGBC), based on T-stage alone. Residual disease at re-resection, however, is the most important factor in predicting outcomes, and the optimal time-interval to re-resection is not known. Furthermore, current data on the utility of port-site resection during re-resection in the US are conflicting and limited to single-institution series. The purpose of this study was to utilize a large, U.S.-based, multi-institutional database to: 1) develop an association model to estimate the risk of finding locoregional residual (LRD) and/or distant disease (DD) at the time of re-resection, and to estimate survival in patients with IGBC; 2) assess the association between time-interval from initial cholecystectomy to reoperation with overall survival (OS) and identify a time-interval that yields the best overall survival; and 3) compare practice patterns of port-site management over time and assess the association of port-site resection with OS. All patients with IGBC who underwent reoperation at 10 institutions from 2000-2015 were evaluated by retrospective chart review (n=266). Advanced T-stage, grade, lymphovascular and perineural invasion were associated with increased LRD and DD, and decreased OS. Each characteristic was assigned a value, which added to a total score from 3-10, and were separated into 3 risk-groups (Low:3-4; Intermediate:5-7; High:8-10). Each progressive group was associated with increased incidence of LRD and DD, and reduced OS. Patients underwent re-operation at 3 different time-intervals: Group A:<4wks; B: 4-8wks; C: >8wks. Patients who underwent reoperation between 4-8 weeks had the longest median OS compared to those who underwent early or late reoperation. Group A (HR 2.63) and Group C (HR 2.07) time-intervals (vs Group B) were associated with decreased OS on multivariable Cox regression analysis. The rate of port-site resection remained similar over time. On multivariable Cox regression, port-site resection was not associated with improved OS. In conclusion, by accounting for variations within each T-stage, the proposed risk score better stratifies patients with IGBC. Between 4 and 8 weeks appears to be the optimal time-interval to reoperation. Port-site resection is not independently associated with improved survival, and is not routinely recommended.

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# INTRODUCTION

Gallbladder carcinoma is a rare disease with a poor prognosis and an estimated 5-year survival of 5-13% (1-3). Despite advances in medical therapies for gallbladder cancer, surgery remains the only potentially curative treatment option (1, 4, 5). In 50-70% of patients, gallbladder carcinoma is found incidentally following elective cholecystectomy for presumed benign disease (6, 7). Current management of incidental gallbladder cancer (IGBC) is largely dictated by T-stage alone, with guidelines recommending re-resection for T1b, T2, and T3 lesions, unless contraindicated by advanced disease or poor performance status (6, 8).

The rationale for this recommendation is based on the observation that patients with T1b, T2, and T3 disease who undergo re-resection have better survival than those who do not (6, 7, 9-11). Furthermore, up to 60% of patients have residual disease at the time of re-resection, indicating inadequate tumor clearance by cholecystectomy alone (6, 7, 12, 13). Although the incidence of finding residual disease on re-resection has been shown to increase with advancing T-stage, there is some evidence that it is the presence of residual disease, and not T-stage, that ultimately dictates outcomes (7, 13). Indeed, patients with residual disease have worse survival than those who do not have residual disease, regardless of T-stage (13). Approximately 15% of patients have disseminated disease at the time of reoperation, which is a contraindication to further resection (7, 14). Thus, identifying patients at highest risk of having residual and disseminated disease before surgery is of particular interest for patient selection and operative planning.

Tumor grade, lymphovascular invasion (LVI), and perineural invasion (PNI) are important factors associated with survival in other biliary and gastrointestinal

malignancies (15-19). In IGBC, grade, LVI, and PNI have been shown in some studies to be associated with the presence of residual and/or disseminated disease at the time of re-resection, and predictive of survival (13, 14, 20, 21). Currently, however, no studies have assessed the combined value of T-stage, grade, LVI, and PNI in predicting outcomes in patients with IGBC.

Beyond patient selection for surgery, there are little data to guide the timing of re-resection, which currently can vary from 1 day to over 2 years following the initial cholecystectomy (13). In the benign setting, most surgeons generally elect to re-operate either within the first 7-10 days, before the inflammatory processes has peaked, or after approximately 4-6 weeks, when these processes have begun to subside. In malignancy, tumor biology, in addition to technical considerations, plays an important role in defining the optimal timing of reoperation. In several other cancers, such as esophageal and rectal cancer, the timing of definitive surgery following initial treatment has been studied in detail, yet has primarily focused on timing of surgery following neoadjuvant radiation (22, 23). In IGBC, no study has examined the effect of timing of reoperation after initial cholecystectomy on outcomes.

Once patients are taken back to the operating room for re-resection, the majority of those with residual disease will be found to have microscopic tumor cells in and around the gallbladder fossa (6, 7, 13). Thus, re-resection with partial hepatectomy of liver segments IVb/V and portal lymph node dissection removes the area most likely to contain residual tumor, as well any local lymph node metastases (6, 7, 10). Whether there is a benefit to routine excision of areas outside the gallbladder fossa and portal lymph

node basin, such as the peritoneum and abdominal wall fascia surrounding the laparoscopic port sites from the prior cholecystectomy, is questionable.

Some surgeons advocate for routine port-site excision during reoperation for IGBC because, in theory, it may lower the incidence of port-site recurrence due to potential contamination from occult tumor seeding during the initial laparoscopic cholecystectomy (24, 25). Other investigators have questioned this claim, citing a low incidence of disease in port site specimens, an increased morbidity, and no difference in survival following the procedure (26, 27).

Due to the rarity of this disease, data on IGBC have been largely limited to small cohorts of patients, and in the U.S., studies are primarily based on single-institution analyses. The purpose of this study was to utilize a large, U.S.-based, multi-institutional database to: 1) develop an association model using pathology data that is readily available from the initial cholecystectomy to estimate the risk of finding locoregional residual (LRD) and/or distant disease (DD) at the time of re-resection, and to predict survival in patients with IGBC; 2) assess the association between time-interval from initial cholecystectomy to reoperation with overall survival and identify a time-interval that yields the best overall survival; and 3) compare practice patterns of port-site management over time and assess the association of port-site resection with overall survival.

## METHODS

The U.S. Extrahepatic Biliary Malignancy Consortium (USEBMC) is a collaboration of 10 high-volume, academic institutions: Emory University, Johns Hopkins University, New York University, The Ohio State University, Stanford University, University of Louisville, University of Wisconsin, Vanderbilt University, Wake Forest University, and Washington University in St. Louis. The USEBMC database contains all patients taken to the operating room from January 2000 to March 2015 with a diagnosis of either hilar cholangiocarcinoma, gallbladder cancer, or distal cholangiocarcinoma. Institutional Review Board approval was obtained at each institution prior to data collection. Baseline demographic, preoperative, intraoperative, pathologic, and post-operative outcome data were collected retrospectively based on a review of the medical records for all patients. Pathologic review was performed at each institution by experienced GI pathologists. Pathologic staging and the extent of lymph node dissection were defined as per American Joint Committee on Cancer (AJCC) $7^{th}$ edition guidelines (28). Data regarding neoadjuvant and adjuvant therapy, disease recurrence, and survival were additionally recorded. Survival information was verified with the Social Security Death Index, when appropriate.

All statistical analysis was conducted using SPSS 22.0 software (IBM Inc., Armonk, NY). Statistical significance for each endpoint was predefined as $p<0.05$. In order to better estimate oncologic-specific survival, all 30-day mortalities were excluded from survival analyses.

## AIM 1

We aimed to develop a practical and more robust model, beyond T-stage alone, for estimating LRD and DD at the time of reoperation for incidental gallbladder cancer. Secondarily, we aimed to assess the value of the association model to estimate overall survival (OS).

### Methods

#### *Study Population*

All patients with IGBC who underwent reoperation from January 2000 to March 2015 were evaluated. Only patients with IGBC and information regarding the presence of LRD and/or DD on re-exploration were included. Descriptive and comparative analyses were performed on the entire cohort. Only patients with complete data for T-stage, tumor grade, LVI, and PNI were included in descriptive and survival analyses for the proposed Gallbladder Cancer Risk Score.

#### *Gallbladder Cancer Risk Score (GBRS)*

The Gallbladder Cancer Risk Score was developed using T-stage, tumor grade, and the presence of LVI and PNI. Each factor was assigned a value, which was added to obtain a total risk score ranging from 3-10. The scores were then separated into 3 risk groups—low (3-4), intermediate (5-7), and high (8-10)—based on their overlapping associations with the outcomes (Figure 1).

#### *Outcome Measures*

The primary objective was to assess the association of the GBRS with LRD and/or DD at the time of re-resection for IGBC. ‘Locoregional residual disease’ was

defined as the presence of tumor at the bile duct, regional lymph nodes, and the gallbladder fossa at the time of re-resection. 'Distant disease' was defined as the presence of tumor in the liver outside the gallbladder fossa, in the peritoneum, and other distant locations. The secondary outcome was overall survival (OS), which was defined as time from reoperation to death from any cause.

*Statistical Analysis*

Chi-square analysis was used to compare categorical variables, and Student's *t*-test or one-way ANOVA was used for continuous variables, where indicated. Univariable regression analyses were performed to assess the association of individual pathologic factors and GBRS with LRD and DD. Log-rank tests and Kaplan-Meier survival plots were performed for OS. Univariable Cox regression analysis was performed to assess the effect of individual pathologic features and GBRS on OS. Due to co-linearity between the individual pathologic factors and GBRS, no multivariable analyses were performed.

## Results

Of 449 patients with gallbladder cancer, 266 (59%) were discovered incidentally. Four patients did not have information regarding the presence of LRD or DD at reoperation and were excluded, leaving 262 patients (58%) for analysis. Baseline demographics and clinicopathologic features are summarized in Table 1.1. LRD was identified in 129 patients (49%). DD was identified in 45 patients (17%). In 48 patients (18%), the procedure was aborted due to the presence of distant and/or locally-advanced disease. The majority of patients underwent a partial hepatectomy (segments IVb/V) with portal lymph node dissection (n=182, 82%). Most patients had T2 disease (50%),

negative margins (75%), and moderately differentiated tumors (58%). Forty-six percent of patients were positive for LVI and 53% for PNI. Positive lymph nodes were found in 44%. Eight patients (3%) received neoadjuvant chemotherapy, and all had T3/T4 disease. Half of the patients (n=99) received adjuvant chemotherapy.

The associations between T-stage and grade, LVI, and PNI are shown in Table 1.2. All patients with Tis/T1a disease had either well- or moderately differentiated tumors, and were LVI and PNI negative. Patients with T1b, T2, and T3/T4 disease showed greater heterogeneity and an increased association with more adverse pathologic factors, such as poor differentiation, and LVI and PNI positivity.

*Gallbladder Cancer Risk Score*

The GBRS is detailed in Figure 1. Eighty-eight patients had complete data regarding T-stage, grade, LVI, and PNI, and were included in subsequent GBRS analysis. After adding the assigned values for each pathologic factor, 4 patients (4%) were in the low-risk group, 42 (48%) in the intermediate-risk group, and 42 (48%) were in the high-risk group. Based on the additional pathologic factors, T1b patients were redistributed across low- and intermediate-risk groups, and T2 and T3/T4 patients were redistributed across intermediate- and high-risk groups (Table 1.3).

*Locoregional Residual Disease*

The prevalence of LRD at the time of reoperation increased with advancing T-stage and grade, and was higher in LVI and PNI positive patients (Table 1.4). Each progressive GBRS group was associated with an increased prevalence of LRD at the time of reoperation (Figure 1.1). On univariable logistic regression, the odds ratio (OR) for finding LRD comparing T3/T4 to T2 disease was 3.5 (95% CI, 1.9–6.3; $p<0.001$). The

OR for finding LRD comparing high to intermediate GBRS groups was 4.5 (95% CI, 1.7–11.6; p=0.002) (Table 1.5).

*Distant Disease*

The prevalence of DD at the time of reoperation increased with advancing T-stage and grade, and was higher in patients with LVI and PNI compared to those without (Table 1.4). Each progressive GBRS group was associated with an increased prevalence of DD at the time of reoperation (p=0.006; Figure 1.1). On univariable logistic regression, the OR for finding DD comparing T3/T4 to T2 disease was 3.0 (95% CI, 1.3–7.0; p=0.01). The OR for finding DD comparing high to intermediate GBRS groups was 12.2 (95% CI, 1.5–100.0; p=0.02) (Table 1.5).

*Survival Analyses*

Median follow-up for survivors was 15.2 months (IQR, 5.1–30.0). Median OS among the whole cohort was 24.8 months. Patients with DD at the time of re-resection had a median OS of 11.1 months, compared to 20.7 months in those with isolated LRD, and 59.5 months in those with no additional disease (p<0.001).

Advancing T-stage and grade, and positive LVI and PNI were each associated with worse OS (Figure 1.2a-d). Each progressive GBRS group was associated with decreased OS (Figure 1.3a). On univariable Cox regression analysis, the hazard ratio (HR) comparing T3/T4 to T2 disease was 2.2 (95% CI, 1.5–3.3; p<0.001). The HR comparing high to intermediate GBRS groups was 4.6 (95% CI, 2.0–10.3; p<0.001) (Table 1.5).

Median OS for T1b patients was not reached in either low- or intermediate-risk groups. Patients with T2 disease in the high-risk group had worse OS compared to T2

patients in the intermediate GBRS group (26.4 months versus 66.5 months; p=0.03) (Figure 1.3b). Among T3/T4 disease, patients in the high-risk group tended to have worse OS (14.2 months) compared to T3/T4 patients in the intermediate GBRS group (23.6 months; p=0.22).

## Discussion

Current guidelines for re-resection of IGBC are based solely on T-stage, with radical re-resection recommended for T1b, T2, and T3 disease (8). These recommendations are largely driven by the observation that patients in these T-stage cohorts who undergo re-resection have improved survival compared to those who do not, and patients without residual disease have improved survival compared to those with residual disease (6, 7, 9-13). While T-stage has been shown to be associated with both the presence of residual disease and survival in IGBC, the predictive value of T-stage alone is somewhat controversial (6, 7, 13, 29). Contrary to prior reports, Fuks *et al.* found no correlation between T-stage and residual disease, although both factors were prognostic for survival (6). Butte *et al.* found that, although T-stage was associated with the presence of residual disease at re-resection, only residual disease, and not T-stage, was predictive of survival. Furthermore, T1b and T2 patients with residual disease had significantly worse disease-free survival than T2 and T3 patients without residual disease (13). Thus, the presence of residual disease appears to be one of the most important prognostic factors in patients with IGBC, and identifying patients at risk for residual disease is critical.

The current study represents one of the largest multi-institutional series to date of patients with IGBC who underwent reoperation. Of 262 patients, half had T2 disease, which is in line with the general T-stage distribution among IGBC patients worldwide (12). LRD was identified in 49% and DD in 17% of patients at the time of reoperation, findings that mirror several previous reports (6, 7, 13). As expected, patients with DD at the time of reoperation fared the worst, followed by patients with isolated LRD. Patients with neither LRD nor DD had the best outcome.

Unlike Fuks *et al.*, we found that T-stage was associated with the presence of LRD and DD at the time of re-resection, and was predictive of survival. Other factors, however, may also play a role. Tumor grade, LVI, and PNI are important pathologic factors associated with outcomes in other biliary and GI malignancies, such as hilar and intrahepatic cholangiocarcinoma, and pancreatic, gastric, appendiceal, and colorectal cancers (15-17, 19, 30-33). In gallbladder cancer, tumor grade, LVI, and PNI, in addition to T stage, have all been implicated as important prognostic factors (13, 14, 20, 21). Ouchi *et al.* observed that patients with gallbladder cancer surviving less than 5 years more frequently had moderate or poorly-differentiated tumors, and were LVI and PNI positive, compared to those surviving more than 5 years (21). Butte *et al.* found that IGBC patients with residual disease were more likely to have tumors with advanced T-stage and be PNI positive than those without residual disease, and tended to have higher grade tumors and be LVI positive. However, histologic grade was the strongest predictor of survival in their study (13). In an earlier series from Butte and colleagues, high grade was also shown to be the strongest predictor of DD at the time of re-resection, although

advanced T-stage, and positive LVI and PNI tended to be more frequent among patients with DD, as well (14).

In the current series, advancing T-stage and grade, and the presence of LVI and PNI were each associated with LRD and DD at reoperation. With this in mind, the proposed GBRS incorporates T-stage, histologic grade, LVI, and PNI, which are all routinely reported on pathologic analysis of initial cholecystectomy specimens and are readily available prior to re-resection, in order to better risk-stratify patients with IGBC. To our knowledge, this is the largest series of patients with IGBC undergoing reoperation, and the only series that examines the combined value of these pathologic factors for predicting outcomes. Each progressive GBRS group was associated with a significantly increased risk of finding LRD and DD, and decreased OS. While this pattern was also seen with T-stage alone, GBRS was a stronger predictor of LRD and DD on logistic regression, and OS on Cox regression.

When assessing each T-stage individually, we found that by taking into account grade, LVI, and PNI, subtle pathologic variations emerged and lead to a redistribution of each T-stage across GBRS groups. Among patients with T1b disease, 78% were in the intermediate GBRS group, a finding that falls in line with the current recommendations for re-resection in these patients. However, 22% had well-differentiated, and LVI- and PNI-negative tumors, classifying them as low-risk. For these patients with no other poor prognostic features and zero risk of finding LRD or DD, surveillance instead of re-resection may be a reasonable option.

Among patients with T2 disease, 68% fell in the intermediate-risk, and 32% in the high-risk GBRS group. These high-risk T2 patients, who had higher grade tumors and

were nearly all LVI and PNI positive, had significantly worse survival compared to the intermediate-risk T2 patients, suggesting more aggressive tumor biology that would go unaccounted for using T-stage alone. Indeed, 62% of high-risk T2 patients had LRD and 23% had DD at re-resection, compared to only 32% and 0%, respectively, among intermediate-risk T2 patients. Thus, it may be prudent in high-risk T2 patients to consider additional high-quality imaging, staging laparoscopy, or neoadjuvant or adjuvant therapy. Conversely, the vast majority of T3/T4 patients fell in the high-risk group. For the 19% with more favorable pathologic features who were classified as intermediate-risk, however, an upfront surgical approach may be appropriate.

## Conclusion

In conclusion, by accounting for subtle pathologic variations that may influence tumor biology within each T-stage, the Gallbladder Cancer Risk Score combines T-stage with grade, LVI, and PNI to better stratify patients with incidental gallbladder cancer. Compared to T-stage alone, it more accurately identifies those at risk for locoregional residual and distant disease, and better predicts long-term survival. This novel risk-score may help guide treatment strategy regarding patient selection for reoperation, staging laparoscopy, and neoadjuvant or adjuvant therapy, and external validation using a separate retrospective dataset or in the setting of a prospective clinical trial should be performed.

## AIM 2

We aimed to assess the association between time-interval from initial cholecystectomy to reoperation with overall survival and identify a time-interval that yields the best OS. We hypothesized that patients undergoing reoperation between 4 and 8 weeks will have improved overall survival compared to those undergoing reoperation before 4 weeks or after 8 weeks.

### Methods

#### *Study Population*

All patients with IGBC who underwent reoperation from January 1, 2000 to December 31, 2014 were assessed. Only patients with IGBC who had information regarding the dates of initial cholecystectomy and reoperation were included. Cases in which the diagnosis of IGBC was made intra-operatively and the definitive resection was performed under the same anesthesia were excluded.

#### *Time-Interval Groups*

The time-interval from the date of original cholecystectomy to the date of reoperation was calculated for all patients. Patients were then separated into 3 groups according to their time-interval to reoperation: group A (< 4 weeks), B (4 – 8 weeks), and C (>8 weeks).

#### *Outcome Measures*

The primary objective was to assess the difference in OS between groups in order to identify the optimal timing for reoperation and re-resection in patients with IGBC. Overall survival was calculated from date of reoperation to date of death from any cause.

To account for potential length-time bias between groups, OS was also calculated from date of initial cholecystectomy to date of death from any cause.

*Statistical Analysis*

One-way ANOVA was used to compare continuous variables, and Chi-square analyses were used for categorical variables, where indicated. Log-rank tests and Kaplan-Meier survival plots were performed for OS comparing time-interval groups. Univariable and multivariable Cox regression analyses were performed to assess the effect of time-interval group on OS in the context of other clinically relevant clinicopathologic features.

## Results

Of 449 patients with gallbladder cancer, 266 (59%) were discovered incidentally. The date of initial cholecystectomy was not available for 33 patients, and in 26 patients the definitive resection was performed at the time of incidental discovery, leaving 207 (46%) for inclusion in analysis. Among the entire cohort, the median time to reoperation was 7.4 weeks (IQR, 5.0 – 10.7). Twenty-five patients (12%) underwent reoperation less than 4 weeks (Group A), 91 (44%) between 4 weeks and 8 weeks (Group B), and 91 (44%) underwent reoperation greater than 8 weeks (Group C) after initial cholecystectomy. Comparative analyses of clinicopathologic factors across groups are shown in Table 2.1. There was no difference in baseline demographics or underlying comorbidities between groups.

Patients in group A tended to be more likely to have undergone the initial cholecystectomy at their respective participating institution (24%), while patients in groups B and C tended to have undergone the initial cholecystectomy at outside hospitals

(91% and 90%, respectively), although this was not statistically significant (p=0.09). A similar proportion of patients in each group had locoregional residual or distant disease at the time of reoperation, and underwent completed resections. There was no difference in the extent of resection performed, with the majority of patients undergoing the recommended partial hepatectomy (segments IVb and V) with portal lymph node dissection in all groups (96%, 87%, and 93%, respectively; p=0.29). There was no difference between groups in margin status, T-stage distribution, histologic grade, lymphovascular invasion, perineural invasion, or the presence of positive lymph nodes.

There was no difference in the incidence of major post-operative complications between groups (p=0.24). Seven patients (8%) in group C received neoadjuvant therapy, compared to zero patients in groups A and B (p=0.01). A similar proportion of patients received adjuvant therapy in all groups.

Median follow-up was 13.9 months (IQR, 2.7–37.5). Median overall survival for the entire cohort was 27.6 months (95% CI, 21.4–33.8). Reoperation between 4 and 8 weeks (Group B) was associated with improved OS (40.4 months; 95% CI, 16.4–64.4) compared to reoperation less than 4 weeks (Group A; 17.4 months; 95% CI, 11.1–23.7) or greater than 8 weeks (Group C; 22.4 months; 95% CI, 18.2–26.6) following initial cholecystectomy (p=0.03; Figure 2.1A). Group B was still associated with improved OS compared to Groups A and C when excluding R2 resections (110.3 months versus 33.5 and 24.3 months, respectively; p=0.01; Figure 2.1B). When calculating survival from date of initial cholecystectomy, Group B was similarly associated with improved OS compared to Groups A and C (41.5 months vs 17.4 and 25.9 months, respectively; p=0.04; Figure 2.1C).

Univariable and multivariable Cox regression analyses for OS calculated from date of reoperation are shown in Table 2.2. Time-interval group (A and C versus B), advanced T-stage (T3/4 versus T2), margin positivity, the presence of residual disease at reoperation, and LN positivity were all associated with worse survival on univariable analysis. Only time-interval group, R2 resection, and advanced T-stage were associated with worse survival on multivariable analysis. On multivariable Cox regression analysis calculating OS from date of initial cholecystectomy, Group A (HR 2.82; 95% CI, 1.33–5.97; p=0.007) and Group C (HR 1.89; 95% CI, 1.07–3.33; p=0.03) were still associated with worse survival compared to Group B, as were advanced T-stage and R2 resection.

## Discussion

Gallbladder cancer is a rare and aggressive malignancy with a poor prognosis. Resection is the only potentially curative treatment option, and the timing of resection has been shown to be an important factor in determining outcomes—patients diagnosed incidentally, which account for the majority of cases, have better survival than those diagnosed only after the signs and symptoms of malignancy become apparent (7). Once IGBC is discovered, re-resection is the recommended treatment strategy for patients with T1b, T2, and T3 tumors (8). The choice of timing for reoperation is largely dictated by the waxing and waning of the inflammatory process in order to minimize complications and maximize patient safety. However, just as the timing of diagnosis of gallbladder cancer can translate to survival, so too may the timing of re-resection be an important, and heretofore underappreciated, determinant of outcomes in patients with IGBC. Indeed,

the optimal timing of re-resection in IGBC that balances both technical considerations and tumor biology is currently not known.

In the current study, 207 patients underwent reoperation for IGBC. Baseline demographics, clinicopathologic characteristics, and outcomes of the entire cohort were similar to those in previous studies on IGBC (6, 7, 12-14, 29). Overall, the median time to reoperation was 7.4 weeks (IQR, 5.0 – 10.7). This is in line with the general global practice patterns for this disease (7, 13, 14, 29, 34). Twenty-five patients (12%) underwent reoperation within 4 weeks (Group A), 91 (44%) between 4 weeks and 8 weeks (Group B), and 93 patients (44%) beyond 8 weeks (Group C) after the initial cholecystectomy.

The groups were very similar with regards to baseline demographics and clinicopathologic characteristics. There were no differences in the presence of locoregional residual or distant disease at the time of reoperation, the percentage of aborted procedures and R2 resections, or the incidence of major complications between groups. Important prognostic factors other than margin status, such as T-stage, grade, lymphovascular invasion, perineural invasion, and lymph node status, were also similar between groups.

Based on data from the current study, it appears that reoperation between 4 and 8 weeks (Group B) is the optimal time-interval for re-resection in patients with IGBC. Group B had significantly better survival than Groups A and C on Kaplan-Meier analysis, univariable Cox regression, and multivariable Cox regression analyses. Even when excluding patients with aborted procedures and R2 resections, and calculating OS from the date of the original cholecystectomy, Group B patients still did better than both A and

C. The possible reasons for this are many. First, re-operating earlier than 4 weeks may not allow for complete tumor evaluation and staging. Preliminary results based on frozen section analysis can be difficult to interpret and may be unreliable in the setting of acute inflammation. Furthermore, inflammation in the operative field can make visualization of important structures on cross-sectional imaging near-impossible in the early post-operative period. Thus, it may take several weeks for adequate TNM and clinical staging to be completed, and rushing to the operating room may be doing so without all the information.

Second, re-operating outside the 4 to 8 week window may be suboptimal from a tumor biology standpoint. The goal of re-resection in IGBC is to remove all visible and microscopic tumor cells before disease progresses beyond surgical salvage—either due to locally advanced disease or distant spread. Disease progression itself can be thought of in 3 stages: clinically apparent pre-operatively, in which disease is clearly visible on cross-sectional imaging; clinically apparent intra-operatively, in which disease is only appreciated on visual or tactile inspection; and subclinical, in which disease progression has occurred, but is neither apparent on pre-operative evaluation nor on operative inspection. While this may seem obvious, it is important to note that subclinical disease progression is the most difficult to predict and manage, particularly in malignancies, such as gallbladder cancer, that do not have the safety net of effective systemic therapy. Thus, reoperation too early (before 4 weeks) may not allow sufficient time for subclinical disease, which was likely already present at the time of diagnosis, to be appreciated. Conversely, reoperation too late (after 8 weeks) may allow too much time for disease dissemination. Although the percentage of patients with locoregional or distant disease at

the time of reoperation was similar between Groups B and C, this finding likely reflects selection bias and should be interpreted with caution—only patients who survived long enough, without evidence of locally advanced or distant disease pre-operatively, underwent reoperation and were included in this study. Given this, one might expect patients in Group C, who represent the 'hearty survivors,' to have better survival than Groups A and B; yet Group B still had better outcomes than Group C, which may reflect more advanced subclinical disease in the latter group that might have been prevented had these patients been re-operated on sooner.

## Conclusion

In conclusion, this is one of the largest series that examines patients who underwent reoperation for incidental gallbladder cancer and, to our knowledge, the only study that assesses the effect of time from initial cholecystectomy to reoperation on survival in these patients. Between 4 and 8 weeks appears to be the optimal time-interval to re-resection that balances both technical considerations and tumor biology in patients with incidental gallbladder cancer.

## AIM 3

We aimed to compare the practice patterns of port-site management over three time periods: 2000-2004, 2005-2009, and 2010-2015, and to assess the association of port-site resection with overall survival. We hypothesized that the incidence of port-site resection will decrease over time, and there would be no difference in overall survival between patients who underwent port-site resection and those who did not.

### Methods

#### *Study Population*

All patients with IGBC who underwent reoperation from January 2000 to March 2015 were assessed. Only patients with IGBC who underwent curative-intent re-resection and had information regarding port site excision were included for analysis.

#### *Outcome Measures*

The primary objective was to assess the association of port site resection with OS. Overall survival was calculated from the date of re-resection to the date of death or last follow-up. All 30-day mortalities were excluded from survival analyses. The secondary objective was to assess the incidence of port site resection over three time periods: 2000-2004, 2005-2009, and 2010-2015.

#### *Statistical Analysis*

Patients with and without port site resection were compared. Chi-square analysis was used to compare categorical variables, and Student's t-test was used for continuous variables. Univariable and multivariable Cox regression analyses were performed to assess the association of individual pathologic factors and port site excision with OS.

Log-rank tests and Kaplan-Meier survival plots for OS were performed to compare port site and no port site excision groups.

## Results

Of 449 patients with gallbladder cancer, 266 (59%) were incidentally discovered. Information regarding port site resection was missing in 31 patients, and 42 patients underwent palliative or R2 resections, leaving 193 (73%) patients for inclusion in analysis: 47 (24%) who underwent port site resection, and 146 (76%) who did not. The incidence of port site resection was 33% from years 2000 to 2004, 22% from 2005-2009, and 22% from 2010 to 2015 (p=0.36; Figure 3.1).

Comparative analyses of baseline demographics and clinicopathologic factors between port site and no port site groups are shown in Table 3.1. There was no difference in baseline demographics or underlying comorbidities between the two groups. There was also no difference between groups in the incidence or location of locoregional residual disease at the time of re-resection, the type of resection performed, the incidence of major complications (> Clavien-Dindo grade IIIa), or in pathologic factors, including margin status, T-stage, grade, lymphovascular invasion, perineural invasion, and lymph node status (Table 3.1). Receipt of adjuvant therapy was similar between port site and no port site patients (57% vs 46%, p=0.35), as was the incidence of overall disease recurrence (28% vs 37%, p=0.38) and, specifically, distant disease recurrence (80% vs 81%, p=1.00).

Median follow-up was 17.6 months (IQR, 7.0–33.6). Median OS for the entire cohort was 32.4 months (95% CI, 23.3–41.4). Port site resection was not associated with

improved median OS (88.9 months; 95% CI, 11.3–166.5) compared to no port site resection (30.1 months; 95% CI, 24.5–35.8; p=0.06; Figure 3.2). When examining only patients who had residual disease at the time of reoperation, port site resection was still not associated with improved median OS (31.4 months; 95% CI, 3.8–59.0) compared to no port site resection (20.1 months; 95% CI, 14.9–25.3; p=0.44; Figure 3.3).

Univariable and multivariable Cox regression analyses for OS are shown in Table 3.2. Advanced T-stage (T3/T4), high grade, margin positivity, and residual disease were associated with worse OS on univariable analysis, which persisted on multivariable analysis only for advanced T-stage, high grade, and margin positivity. Port site resection was not associated with improved OS on either univariable (HR 0.60; 95% CI, 0.35–1.03; p=0.07) or multivariable analysis (HR 0.64; 95% CI, 0.33–1.22; p=0.18).

## Discussion

Incidental gallbladder cancer is a rare malignancy that carries a poor prognosis. Although survival following re-resection of IGBC is improved, it can be highly variable, depending on the stage of disease and extent of resection (7, 29). Current management guidelines for IGBC recommend a partial hepatectomy of liver segments IVb/V and portal lymphadenectomy, with more extensive resections, such as a major hepatectomy and/or bile duct resection, reserved for cases where necessary to achieve an R0 margin (8). However, the role of additional resection, such as port site resection, is controversial. In this study, we utilized a large, U.S.-based, multi-institutional database to assess the practice patterns of port site management over time, and investigate the association of port site resection with OS. We found that the rate of port site resection did not change

over time, and that port site resection was not associated with improved survival compared with no port site resection, when accounting for other adverse pathologic factors.

Citing high rates of disease recurrence at laparoscopic port sites, some surgeons advocate for routine port site resection (24). Lundberg *et al.*(35) found port site recurrences in 16% of patients, and in their review of 409 IGBC cases, Paolucci *et al.*(25) discovered port site recurrences in 17% of patients. Importantly, neither the use of a plastic retrieval bag nor the absence of gallbladder perforation excluded the risk of disease recurrence at port sites. Thus, some argue that port site resection may lower wound recurrence rates by removing potential subclinical tumor seeding that may have occurred at the time of the initial laparoscopic cholecystectomy.

Although other more contemporary studies cite a low incidence of port site metastases, even among patients who are at high risk, the utility of port site resection remains debated (26, 27). In a single-institution review of 69 patients with IGBC who underwent port site resection at Memorial Sloan Kettering Cancer Center, Maker *et al.*(27) reported that 19% had port-site involvement, though only 11% had it among patients with R0 resections. Regardless of margins status, all patients with port site involvement had T2 or T3 disease, and 77% had generalized peritoneal carcinomatosis either at the time of reoperation or shortly thereafter. These data suggest that, rather than mere localized tumor seeding, port site metastases represent a more disseminated problem that may not benefit from operative management. Indeed, when compared to stage-matched patients who did not get port site resections, those who did showed no difference in overall survival, even among only R0 patients (27). Fuks *et al.*(26)

examined 54 patients who underwent port site resection, among whom only one (2%) had port site involvement. This patient developed generalized peritoneal carcinomatosis 7 months after reoperation and died of disease 8 months later. Not only was there no difference in overall survival among patients who underwent port site resection and those patients who did not, the authors reported a 15% incidence of port site incisional hernia associated with port site resection, underscoring the potential morbidity of this procedure (26).

Of the 193 patients included in the current study, 47 (24%) underwent port site resection and 146 (76%) did not. Over the 15-year time period, the rate of port site resections remained constant, ranging from 22% to 33%, despite more recent data suggesting a lack of benefit associated with the procedure. In our cohort, the groups were well-matched with regards to baseline demographics, operative details, postoperative complications, and pathologic characteristics. In addition, there was no difference between groups in the incidence of finding residual disease at the time of reoperation, the overall recurrence rate, or in the distant disease recurrence rate, the latter representing 80% of the recurrences in both groups. Similar to the studies by Maker *et al.*(27) and Fuks *et al.*(26), port site resection was not associated with improved OS on univariable or multivariable analysis in our cohort. Although data on specific port site pathology were not available for this study, all patients with disease recurrence at the port sites were categorized as having residual disease at the time of reoperation. When examining only these patients with residual disease at the time of reoperation, still no association between port site resection and survival was seen. Given that the presence of disease in resected port-site specimens has been associated with distant disease recurrence and generalized

peritoneal carcinomatosis, surgical resection of the port sites likely carries very little benefit.

## Conclusion

In conclusion, despite current literature, the practice of routine port site resection during reoperation for incidental gallbladder cancer has not changed over time. Port site resection is not associated with improved overall survival or lower distant disease recurrence. Thus, routine port site resection is not recommended.

## LIMITATIONS

This study has several limitations. First, the retrospective nature of this study makes disease recurrence and survival data difficult to capture, and makes it challenging to draw definitive conclusions from our results. In addition, the small number of patients with complete pathologic data limited our ability to perform thorough subset analyses. However, this study includes data from 10 geographically-diverse, academic institutions, which eliminates single-institution bias, and more closely represents the disease characteristics and general practice patterns of the U.S. In addition, given the aggressive nature of and poor prognosis associated with gallbladder cancer, overall survival is a good surrogate for disease-specific survival in most cases. Although multi-center studies are often additionally subject to poor data quality and control, a standardized database was used, data collection was monitored and interactive, and each completed institutional database was carefully vetted prior to inclusion for analysis. Still, further validation of study results, particularly the GBRS, is needed.

Second, by including only patients who underwent reoperation, there is an inherent selection bias in this study, as previously discussed. There may have also been a selection bias for patients undergoing reoperation during different time-intervals, as well as for patients who underwent port-site excision compared to those who did not. Regarding the former, this is not uncommon in studies examining the effect of surgery timing on patient outcomes, particularly in a tertiary care setting where the majority of patients are referred from outside facilities after diagnosis, as was the case in this study. Despite these biases, time-interval groups and port-site resection groups were still well-matched for most baseline and clinicopathologic factors.

Finally, although analysis of initial cholecystectomy specimens was often performed at facilities outside the involved institutions, which may have led to inconsistencies and inaccuracies of pathologic assessment, most were re-reviewed by experienced pathologist at the participating institution. Still, details regarding certain pathologic factors, such as margin status of the original cholecystectomy specimen, were difficult to ascertain and were not included in the USEBMC dataset. In addition, the database utilized for this study lacked information regarding specific port site pathology. Still, our findings mirror those of other more contemporary studies on this topic, and confirm that port site resection is not independently associated with improved survival, regardless of port site pathology.

## CONCLUSION

This study includes one of the largest cohorts of surgical patients with incidental gallbladder cancer in the literature. To our knowledge, it is the first study to examine the utility of T-stage, grade, lymphovascular invasion, and perineural invasion in combination to predict residual disease and survival, and it is the first study to assess the association between time-interval from initial cholecystectomy to reoperation with survival. In addition, it is the only U.S.-based, multi-institutional study to examine the association between port-site excision and survival.

By accounting for subtle pathologic variations within each T-stage, the Gallbladder Cancer Risk Score better stratified patients with incidental gallbladder cancer, and may help optimize patient selection and treatment strategies for this disease. Between 4 and 8 weeks appears to be the optimal time-interval to reoperation that balances both technical considerations and tumor biology. Port-site resection is not independently associated with improved survival, and is not routinely recommended.

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# TABLES

Table 1.1

Baseline Demographics and Clinicopathologic Variables of Patients with Incidental Gallbladder Cancer undergoing Reoperation

| Variable | All pts (n=262) |
|---|---|
| Age (yrs), mean ± SD | 65 ± 11.6 |
| BMI, mean ± SD | 30 ± 6.9 |
| Race, n (%) | |
| White | 190 (73) |
| African-American | 27 (10) |
| Latino | 15 (6) |
| Asian | 5 (2) |
| Other/unknown | 25 (9) |
| ASA class, n (%) | |
| 1 | 2 (1) |
| 2 | 63 (35) |
| 3 | 107 (60) |
| 4 | 6 (3) |
| Preoperative biliary drainage, n (%) | 21 (8) |
| Location of original cholecystectomy, n (%) | |
| Participating Institution | 45 (17) |
| Time to reoperation (wks), mean ± SD | 9.3 ± 14.3 |
| Staging laparoscopy at reoperation, n (%) | 52 (20) |
| Residual disease at reoperation, n (%) | 129 (49) |
| Location of residual disease, n (%) | |
| Bile duct | 21 (19) |
| Liver | 54 (48) |
| Lymph node | 45 (40) |
| Distant disease at reoperation, n (%) | 45 (17) |
| Location of distant disease, n (%) | |
| Liver | 8 (19) |
| Peritoneum | 20 (47) |
| Both | 6 (14) |
| Other | 9 (21) |
| Attempted re-resection, n (%) | 231 (88) |
| Completed re-resection, n (%) | 214 (82) |
| Type of Resection, n (%) (n=222) | |
| Bile duct only | 8 (4) |
| Cholecystectomy only | 20 (9) |
| Partial hepatectomy† + Portal LND | 182 (82) |
| Major hepatectomy | 9 (4) |
| Common bile duct resection, n (%) | 73 (28) |
| Port sites excised, n (%) | 87 (33) |
| EBL (mL), mean ± SD | 340 ± 346 |
| Final margin status, n (%) (n=260) | |
| R0 | 196 (75) |

| | |
|---|---|
| R1 | 15 (6) |
| R2 | 49 (19) |
| AJCC T-Stage, n (%) (n=226) | |
| T1a/Tis | 8 (4) |
| T1b | 14 (6) |
| T2 | 113 (50) |
| T3/T4 | 91 (40) |
| Grade, n (%) (n=195) | |
| Well | 24 (12) |
| Moderate | 115 (58) |
| Poor/Undifferentiated | 56 (30) |
| Lymphovascular invasion present, n (%) (n=113) | 52 (46) |
| Perineural invasion present, n (%) (n=117) | 62 (53) |
| Lymph node (LN) retrieved, n (%) (n=236) | |
| Any | 197 (83) |
| N1 | 197 (83) |
| N2 | 53 (23) |
| Total LN retrieved, mean $\pm$ SD | 4.9 $\pm$ 5.5 |
| Lymph node (LN) positive, n (%) (n=197) | |
| Any | 86 (44) |
| N1 | 82 (42) |
| N2 | 14 (7) |
| # Positive LN, mean $\pm$ SD | 0.9 $\pm$ 1.4 |
| Neoadjuvant chemotherapy, n (%) | 8 (3) |
| Adjuvant chemotherapy, n (%) (n=199) | 99 (50) |

[†]Resection of liver segments IVb and V

BMI, body mass index; ASA, American Society of Anesthesiologists; LND, lymph node dissection; EBL, estimated blood loss; AJCC, American Joint Committee on Cancer

Table 1.2

Association of T-stage with Grade, Lymphovascular Invasion, and Perineural Invasion

| | AJCC T-Stage | | | |
|---|---|---|---|---|
| **Pathology Data** | T1a/Tis | T1b | T2 | T3/T4 |
| Grade, n (%) | | | | |
| Well | 2 (40) | 6 (43) | 9 (10) | 6 (8) |
| Moderate | 3 (60) | 7 (50) | 54 (58) | 42 (55) |
| Poor/Undifferentiated | 0 (0) | 1 (7) | 30 (32) | 28 (37) |
| Lymphovascular invasion, n (%) | | | | |
| Negative | 4 (100) | 7 (70) | 31 (61) | 17 (40) |
| Positive | 0 (0) | 3 (30) | 20 (40) | 26 (60) |
| Perineural invasion, n (%) | | | | |
| Negative | 4 (100) | 5 (56) | 29 (57) | 12 (27) |
| Positive | 0 (0) | 4 (44) | 22 (43) | 33 (73) |

AJCC, American Joint Committee on Cancer

Table 1.3

Association of T-stage with GBRS Group

| | GBRS Group | | |
|---|---|---|---|
| **AJCC T-Stage** | Low | Intermediate | High |
| Tis/T1a, n (%) | 2 (100) | 0 (0) | 0 (0) |
| T1b, n (%) | 2 (22) | 7 (78) | 0 (0) |
| T2, n (%) | 0 (0) | 28 (68) | 13 (32) |
| T3/T4, n (%) | 0 (0) | 7 (19) | 29 (81) |

AJCC, American Joint Committee on Cancer; GBRS, Gallbladder Cancer Risk Score

Table 1.4

Association of Predictive Factors with Locoregional Residual and Distant Disease

| **Predictive Factors** | **LRD** | p-value | **DD** | p-value |
|---|---|---|---|---|
| AJCC T-Stage, n (%) | | **<0.001** | | **0.005** |
| T1a/Tis | 0 (0) | | 0 (0) | |
| T1b | 2 (17) | | 0 (0) | |
| T2 | 42 (40) | | 9 (8) | |
| T3/T4 | 60 (70) | | 19 (21) | |
| Grade, n (%) | | **0.02** | | **0.05** |
| Well | 7 (32) | | 1 (4) | |
| Moderate | 53 (51) | | 13 (11) | |
| Poor | 37 (65) | | 13 (22) | |
| Lymphovascular invasion, n (%) | | **0.004** | | **0.01** |
| Negative | 18 (33) | | 2 (3) | |
| Positive | 31 (63) | | 10 (19) | |
| Perineural invasion, n (%) | | **0.04** | | **0.006** |
| Negative | 19 (40) | | 1 (2) | |
| Positive | 37 (63) | | 12 (19) | |

LRD, Locoregional residual disease; DD, Distant disease; AJCC, American Joint Committee on Cancer

Table 1.5

The Predictive Value of GBRS versus T-Stage Alone for Locoregional Residual and Distant Disease, and Overall Survival

| | **Locoregional Disease** | | **Distant Disease** | | **Overall Survival** | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value | HR (95% CI) | p-value |
| **GBRS** | | | | | | |
| **High vs Intermediate** | **4.5** (1.7–11.6) | **0.002** | **12.2** (1.5–100.0) | **0.02** | **4.6** (2.0–10.3) | **<0.001** |
| T-stage | | | | | | |
| T3/T4 vs T2 | 3.5 (1.9–6.3) | <0.001 | 3.0 (1.3 – 7.0) | 0.01 | 2.2 (1.5–3.3) | <0.001 |

GBRS, Gallbladder Cancer Risk Score; OR, odds ratio; CI, confidence interval; HR, hazard ratio

Table 2.1

Clinicopathologic Features of Incidental Gallbladder Patients by Time-Interval Group

| **Variable** | **Group A** (<4 weeks) | **Group B** (4-8 weeks) | **Group C** (>8 weeks) | **p-value** |
|---|---|---|---|---|
| Total n (%)[◊] | 25 (12) | 91 (44) | 91 (44) | |
| Time to re-operation (wks), median (range) | 2.9 (0.4-3.9) | 5.9 (4.1-8.0) | 11.4 (8.1-179.6) | |
| Age (yrs), mean ± SD | 65 ± 9 | 64 ± 11 | 66 ± 12 | 0.75 |
| Male gender, n (%) | 10 (40) | 34 (37) | 33 (36) | 0.94 |
| BMI, mean ± SD | 28.7 ± 6.5 | 29.0 ± 6.9 | 30.3 ± 7.0 | 0.40 |
| Race, n (%) | | | | 0.81 |
| White | 21 (88) | 67 (77) | 68 (76) | |
| African-American | 0 (0) | 11 (13) | 12 (13) | |
| Latino | 2 (8) | 5 (6) | 6 (7) | |
| Asian | 1 (4) | 2 (2) | 2 (2) | |
| Other | 0 (0) | 2 (2) | 2 (2) | |
| ASA class, n (%) | | | | 0.22 |
| 1 | 0 (0) | 1 (2) | 1 (2) | |
| 2 | 13 (62) | 19 (29) | 25 (37) | |
| 3 | 8 (38) | 44 (67) | 39 (57) | |
| 4 | 0 (0) | 2 (3) | 3 (4) | |
| Comorbidities[±], n (%) | | | | 0.16 |
| 0 | 4 (17) | 32 (37) | 25 (28) | |
| 1 | 15 (65) | 34 (39) | 37 (42) | |
| ≥2 | 4 (17) | 21 (24) | 26 (30) | |
| Clinical Jaundice, n (%) | 2 (8) | 9 (11) | 4 (5) | 0.34 |
| Location of original cholecystectomy | | | | 0.09 |
| Participating institution | 6 (24) | 8 (9) | 9 (10) | |
| Locoregional residual disease, n (%) | 14 (56) | 42 (47) | 42 (48) | 0.71 |
| Distant disease, n (%) | 2 (8) | 18 (20) | 16 (18) | 0.38 |
| Attempted resection, n (%) | 22 (88) | 79 (87) | 77 (85) | 0.87 |
| Completed resection, n (%) | 22 (88) | 74 (81) | 72 (79) | 0.60 |
| Extent of resection, n (%) | | | | 0.29 |
| Partial hepatectomy + Portal LN | 21 (96) | 66 (87) | 69 (93) | |
| Major hepatectomy | 1 (5) | 10 (13) | 5 (7) | |
| Operative Approach | | | | 0.67 |
| Open | 23 (100) | 84 (97) | 85 (97) | |
| Laparoscopic | 0 (0) | 3 (3) | 3 (3) | |
| Common bile duct resection, n (%) | 9 (41) | 29 (37) | 23 (30) | 0.54 |
| EBL (mL), mean ± SD | 428 ± 318 | 294 ± 292 | 352 ± 396 | 0.26 |
| Final margin status, n (%) | | | | 0.10 |
| R0 | 19 (76) | 72 (79) | 69 (76) | |
| R1 | 3 (12) | 1 (1) | 3 (3) | |
| R2 | 3 (12) | 18 (20) | 19 (21) | |
| Tumor size (mm), mean ± SD | 38.9 ± 18.1 | 28.4 ± 25.4 | 30.2 ± 19.9 | 0.31 |
| AJCC T-Stage, n (%) | | | | 0.11 |
| T1a/b | 1 (5) | 5 (6) | 10 (12) | |
| T2 | 11 (50) | 50 (63) | 35 (43) | |

| | | | | |
|---|---|---|---|---|
| T3/4 | 10 (46) | 24 (30) | 36 (44) | |
| Grade, n (%) | | | | 0.45 |
| Well/Moderate | 13 (62) | 51 (71) | 56 (76) | |
| Poor/Undifferentiated | 8 (38) | 21 (29) | 18 (24) | |
| Lymphovascular invasion, n (%) | 5 (46) | 20 (50) | 17 (41) | 0.69 |
| Perineural invasion, n (%) | 8 (73) | 19 (46) | 25 (58) | 0.25 |
| Lymph node (LN) positive, n (%) | 9 (39) | 31 (47) | 30 (40) | 0.63 |
| Total LN retrieved, mean $\pm$ SD | 5.8 $\pm$ 5.5 | 5.2 $\pm$ 5.4 | 4.7 $\pm$ 4.9 | 0.63 |
| Major complication, n (%) | 3 (13) | 8 (9) | 16 (18) | 0.24 |
| **Neoadjuvant chemotherapy, n (%)** | **0 (0)** | **0 (0)** | **7 (8)** | **0.01** |
| Adjuvant chemotherapy, n (%) | 8 (44) | 41 (54) | 40 (52) | 0.77 |

[◊] Total n varies depending on availability of data for each variable

[‡] Includes hypertension, diabetes, prior cardiac event, end-stage renal disease

ASA, American Society of Anesthesiology; EBL, estimated blood loss; LN, lymph node

Table 2.2

Univariable and Multivariable Cox Regression Analyses for Overall Survival from Date of Reoperation

| | **Univariable Analysis** | | **Multivariable Analysis** | |
|---|---|---|---|---|
| **Variable** | HR (95% CI) | p-value | HR (95% CI) | p-value |
| **Time-Interval** | | | | |
| Group A (0-4 wks) | 1.94 (1.06 – 3.56) | 0.03 | 2.63 (1.25 – 5.54) | **0.01** |
| Group B (4.1-8wks) | Reference | | Reference | |
| Group C (>8wks) | 1.68 (1.08 – 2.59) | 0.02 | 2.07 (1.17 – 3.66) | **0.01** |
| Clinical Jaundice | 1.69 (0.85 – 3.38) | 0.14 | | |
| Extent of resection | | | | |
| Partial hepatectomy + Portal LN | Reference | | – | – |
| Major hepatectomy | 1.35 (0.67 – 2.73) | 0.40 | | |
| Residual disease at reoperation | 3.10 (2.01 – 4.76) | <0.001 | 1.51 (0.90 – 2.54) | 0.12 |
| **Final margin status** | | | | |
| R0 | Reference | | Reference | |
| R1 | 2.73 (0.98 – 7.59) | 0.05 | 1.19 (0.34 – 4.18) | 0.79 |
| R2 | 4.33 (2.77 – 6.77) | <0.001 | 2.69 (1.27 – 5.69) | **0.009** |
| **AJCC T-stage** | | | | |
| T1a/b | 0.16 (0.02 – 1.18) | 0.07 | 0.28 (0.04 – 2.08) | 0.21 |
| T2 | Reference | | Reference | |
| T3/4 | 2.16 (1.39 – 3.36) | 0.001 | 1.85 (1.11 – 3.08) | **0.02** |
| Grade | | | | |
| Well/Moderate | Reference | | – | – |
| Poor/Undifferentiated | 1.40 (0.87 – 2.26) | 0.16 | | |
| Lymph node positive | 1.72 (1.07 – 2.76) | 0.03 | 1.56 (0.94 – 2.60) | 0.09 |
| Adjuvant chemotherapy | 0.99 (0.62 – 1.59) | 0.98 | – | – |

Table 3.1

Comparison of Clinicopathologic Variables between Patients with Incidental Gallbladder Cancer who Underwent Port Site Resection and Those who Did Not

| **Baseline Variables** | **No Port-site (n=146, 76%)** | **Port-site (n=47, 24%)** | **p-value** |
|---|---|---|---|
| Age (yrs), mean ± SD | 65 ± 12 | 65 ± 10 | 0.88 |
| Male, n (%) | 54 (38) | 15 (32) | 0.58 |
| BMI (kg/m2), mean ± SD | 30 ± 8 | 29 ± 5 | 0.20 |
| Race, n (%) | | | |
| White | 107 (80) | 32 (76) | 0.17 |
| African-American | 16 (12) | 4 (10) | |
| Other | 11 (8) | 6 (14) | |
| ASA class, n (%) | | | |
| 1 | 2 (2) | 0 (0) | |
| 2 | 35 (34) | 10 (36) | 0.90 |
| 3 | 62 (61) | 17 (61) | |
| 4 | 3 (3) | 1 (4) | |
| Bilirubin (mg/dL), mean ± SD | 0.6 ± 0.4 | 0.6 ± 0.2 | 0.44 |
| Creatinine (mg/dL), mean ± SD | 0.9 ± 0.4 | 0.8 ± 0.2 | 0.24 |
| INR, mean ± SD | 1.1 ± 0.2 | 1.1 ± 0.2 | 0.63 |
| Time to re-resection (wks), mean ± SD | 11.4 ± 18.4 | 7.2 ± 3.9 | 0.16 |
| Staging laparoscopy at reoperation, n (%) | 39 (27) | 15 (32) | 0.61 |
| Residual disease at reoperation, n (%) | 62 (43) | 17 (36) | 0.51 |
| Location of residual disease, n (%) | | | |
| Bile duct | 8 (13) | 3 (19) | 0.42 |
| Liver | 18 (30) | 4 (25) | |
| Lymph node | 20 (33) | 5 (31) | |
| Multiple | 14 (24) | 4 (25) | |
| Type of Resection, n (%) | | | |
| Bile duct only | 7 (5) | 1 (2) | |
| Cholecystectomy only | 4 (3) | 0 (0) | 0.51 |
| Partial hepatectomy + Portal LN | 127 (87) | 45 (96) | |
| Major hepatectomy | 6 (5) | 1 (2) | |
| EBL (mL), mean ± SD | 424 ± 370 | 378 ± 332 | 0.48 |
| Major Complication[a], n (%) | 9 (17) | 2 (17) | 1.00 |
| Length of Stay (days), mean ± SD | 6.9 ± 5.7 | 6.5 ± 3.0 | 0.64 |
| Tumor size (mm), mean ± SD | 33 ± 23 | 24 ± 20 | 0.10 |
| Final margin status, n (%) | | | |
| R0 | 132 (92) | 46 (98) | 0.31 |
| R1 | 11 (8) | 1 (2) | |
| AJCC T-Stage | | | |
| T1 | 14 (11) | 4 (9) | 0.48 |
| T2 | 68 (52) | 23 (52) | |
| T3/T4 | 48 (37) | 17 (39) | |
| Grade, n (%) | | | |
| Well | 16 (14) | 3 (9) | 0.43 |
| Moderate | 69 (60) | 19 (54) | |
| Poor/Undifferentiated | 31 (27) | 13 (37) | |
| Lymphovascular invasion, n (%) | 28 (41) | 9 (45) | 0.92 |
| Perineural invasion, n (%) | 34 (51) | 10 (46) | 0.85 |

| | | | |
|---|---|---|---|
| Lymph node positive, n (%) | 54 (42) | 16 (36) | 0.67 |
| Adjuvant therapy, n (%) | 53 (46) | 21 (57) | 0.35 |
| Recurrence, n (%) | 42 (37) | 11 (28) | 0.38 |
| Locoregional | 8 (20) | 2 (20) | 1.00 |
| Distant | 33 (81) | 8 (80) | |

[a] ≥ Clavien-Dindo grade IIIa

BMI, body mass index; ASA, American Society of Anesthesiologists; INR, international normalized ratio; LN, lymph node; AJCC, American Joint Committee on Cancer

Table 3.2

Univariable and Multivariable Cox Regression Analysis for Overall Survival

| | **Univariable Cox Regression** | | **Multivariable Cox Regression** | |
|---|---|---|---|---|
| Variable | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Port-site resection | 0.60 (0.35 – 1.03) | 0.07 | 0.64 (0.33 – 1.22) | 0.18 |
| **AJCC T-Stage** | | | | |
| T1 | Reference | | Reference | |
| T2 | 2.56 (0.79 – 8.32) | 0.12 | 2.65 (0.62 – 11.3) | 0.19 |
| T3/T4 | 4.80 (1.47 – 15.7) | 0.01 | 4.52 (1.04 – 19.6) | **0.04** |
| **Grade** | | | | |
| Well/Moderate | Reference | | Reference | |
| Poor | 1.92 (1.16 – 3.17) | 0.01 | 1.84 (1.09 – 3.12) | **0.02** |
| **Margin positive** | 3.20 (1.58 – 6.46) | 0.001 | 2.54 (1.03 – 6.22) | **0.04** |
| Lymph node positive | 1.51 (0.96 – 239) | 0.08 | – | – |
| Residual Disease | 2.16 (1.40 – 3.34) | 0.001 | 1.67 (0.97 – 2.89) | 0.07 |

HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer

## FIGURES

Figure 1.1

Gallbladder Cancer Risk Score (GBRS). The values for each pathologic factor are added to obtain a total risk score, ranging from 3 to 10. Patients are categorized into either the low, intermediate, or high GBRS group based on their total risk score. Each progressive GBRS group is associated with an increased prevalence of locoregional residual disease (p=0.01) and distant disease (p=0.006) at the time of reoperation.

**Gallbladder Cancer Predictive Risk Score**

| | |
|---|---|
| T-Stage | |
| Tis/T1a | 0 |
| T1b | 1 |
| T2 | 2 |
| T3/T4 | 3 |
| Grade | |
| G1 (Well-diff) | 1 |
| G2 (Mod-diff) | 2 |
| G3 (Poor-diff) | 3 |
| LVI | |
| Negative | 1 |
| Positive | 2 |
| PNI | |
| Negative | 1 |
| Positive | 2 |

| TOTAL RISK | Locoregional Residual | Distant Disease |
|---|---|---|
| Low (3-4) | 0% | 0% |
| Intermediate(5-7) | 24% | 3% |
| High (8-10) | 61% | 32% |

Figure 1.2a-c

a, Increasing T-stage was associated with worse OS. T1b (n=13), T2 (n=111), and T3/T4 (n=88). Log-rank p-value = <0.001. b, Increasing histologic grade was associated with worse OS. Well-differentiated (n=23), moderately-differentiated (n=111), and poorly-differentiated (n=59). Log-rank p-value = 0.012. c, Positive LVI was associated with worse OS. LVI negative (n=59), and LVI positive (n=51). Log-rank p-value = 0.007. d, Positive PNI was associated with worse OS. PNI negative (n=53), and PNI positive (n=61). Log-rank p-value = 0.008.

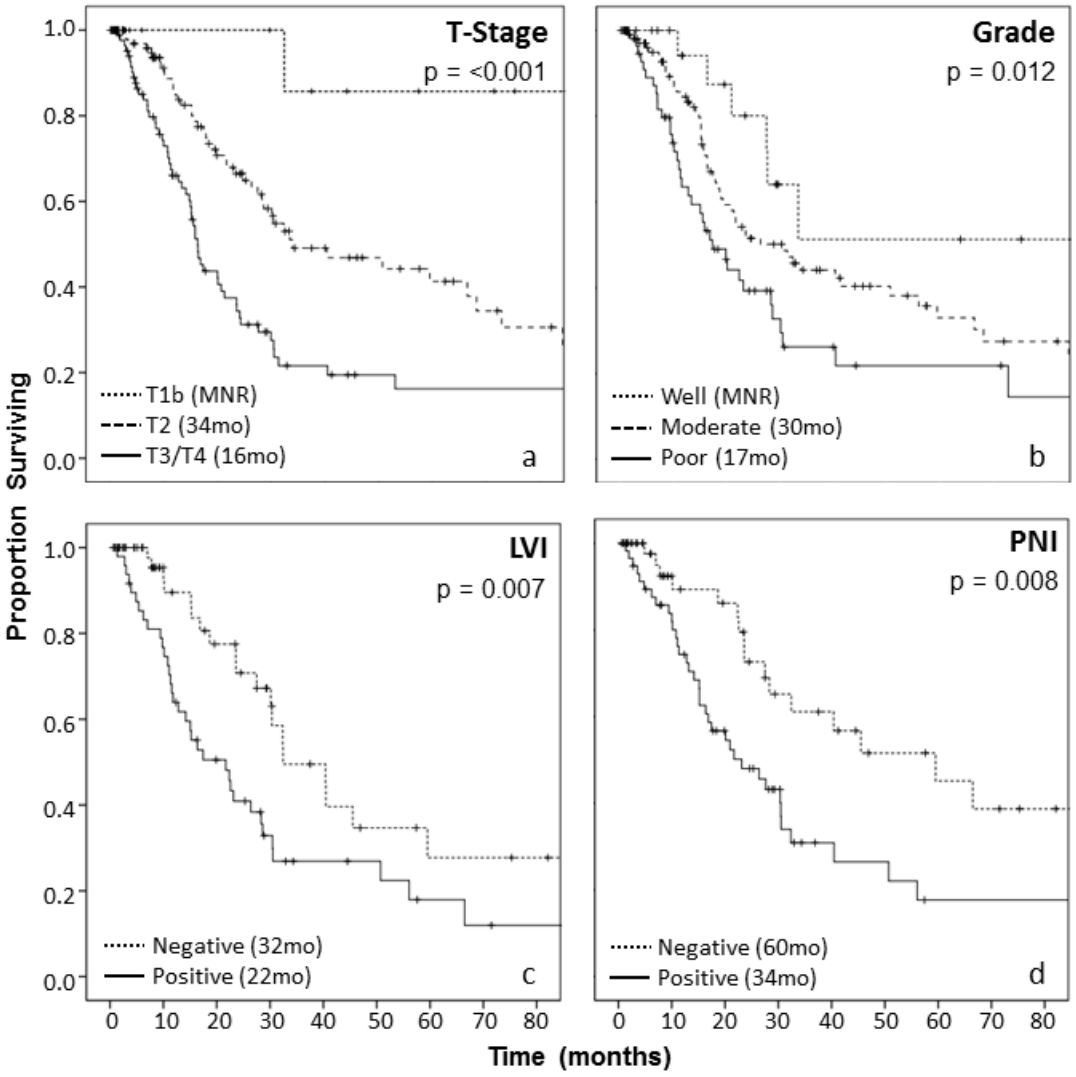

Figure 1.3a-b

a, Each progressive GBRS group was associated with a significant decrease in OS. Low-risk group (n=4), intermediate-risk group (n=42), and high-risk group (n=42). Log-rank p-value = <0.001. b, Overall survival was better for T2 patients in the intermediate GBRS group (n=28) than T2 patients in the high-risk group (n=13). Log-rank p-value = 0.03.

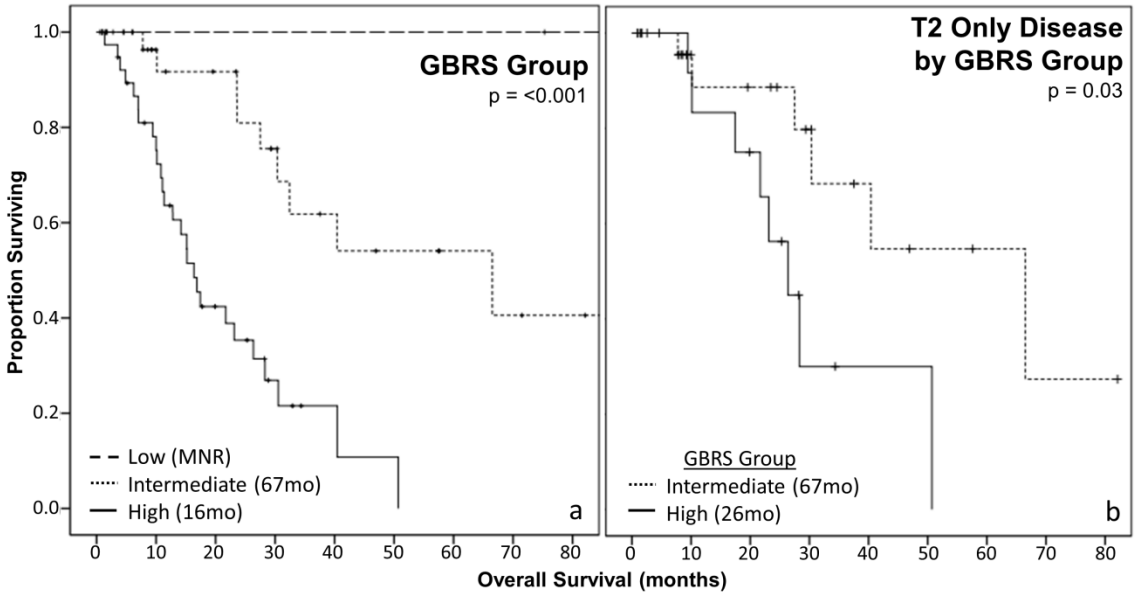

Figure 2.1a-c

a, OS from date of reoperation for all patients. Group B was associated with improved OS (40.4 months, n=89) compared to Groups A (17.4 months, n=25) and C (22.4 months, n=89); b, OS from date of reoperation, excluding aborted procedures and R2 resections. Group B was associated with improved OS (110.3 months, n=72) compared to Groups A (33.5 months, n=22) and C (24.3 months, n=71); c, OS from date of initial cholecystectomy for all patients. Group B was associated with improved OS (40.4 months, n=89) compared to Groups A (17.4 months, n=25) and C (23.6 months, n=91).

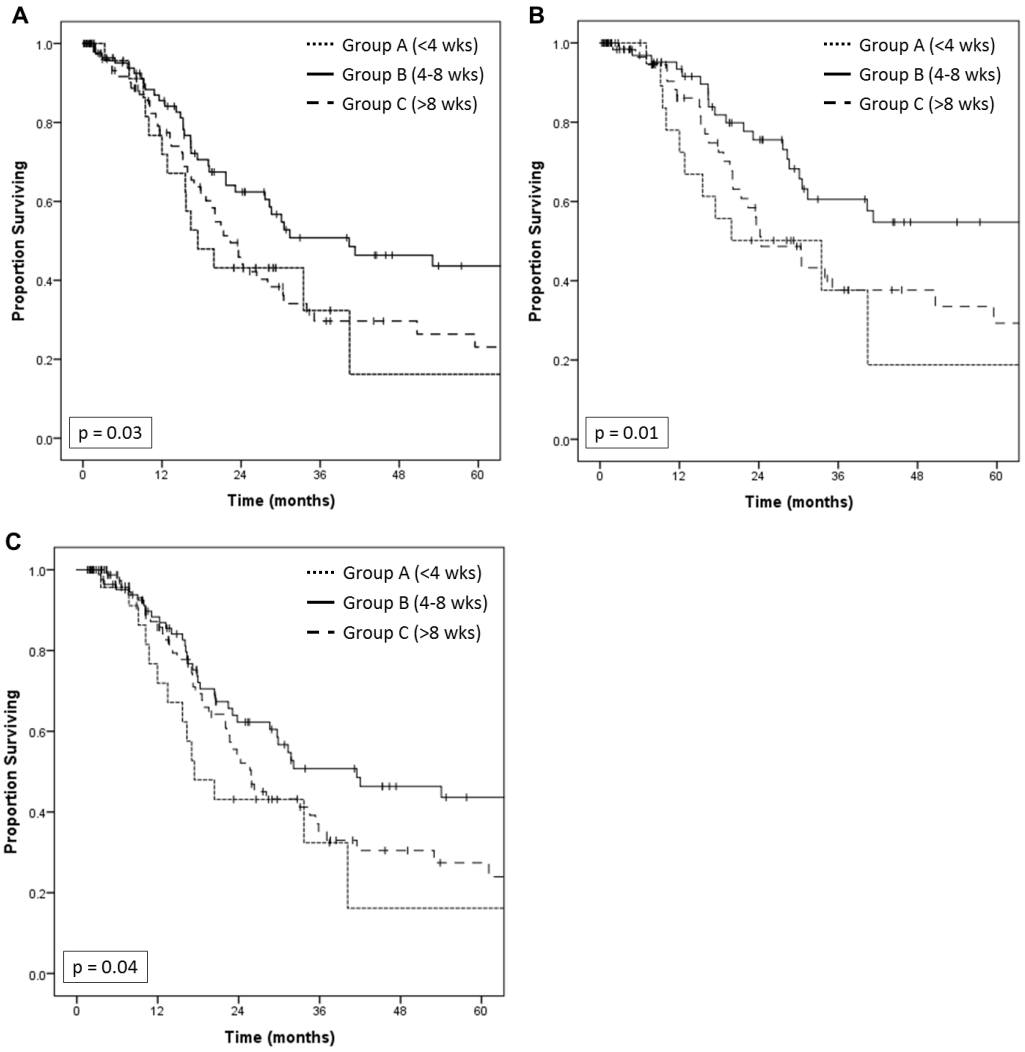

Figure 3.1

Incidence of port site resection over time. There was no change in the incidence of port site resection over three time periods: 2000-2004 (33%), 2005-2009 (22%), and 2010-2014 (22%); p=0.36.

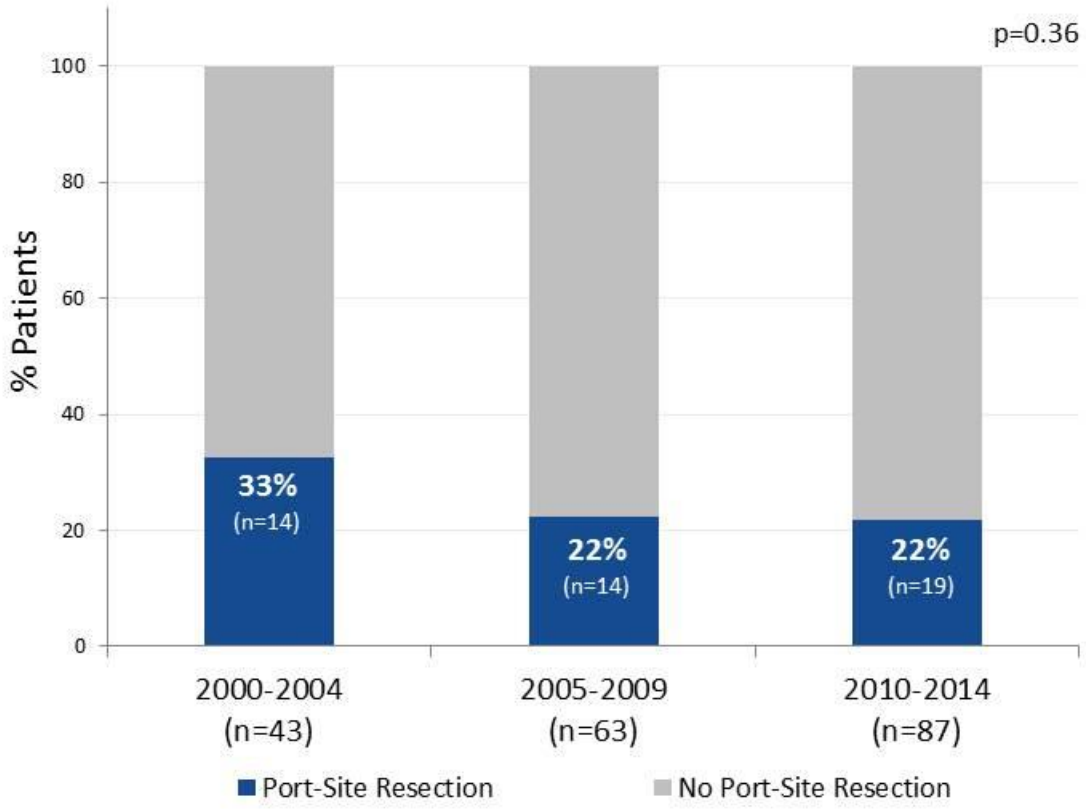

Figure 3.2

Kaplan-Meier curve for overall survival among all patients, comparing port site and no port site resection. Port site resection was not associated with improved survival compared to no port site resection (log rank p=0.06).

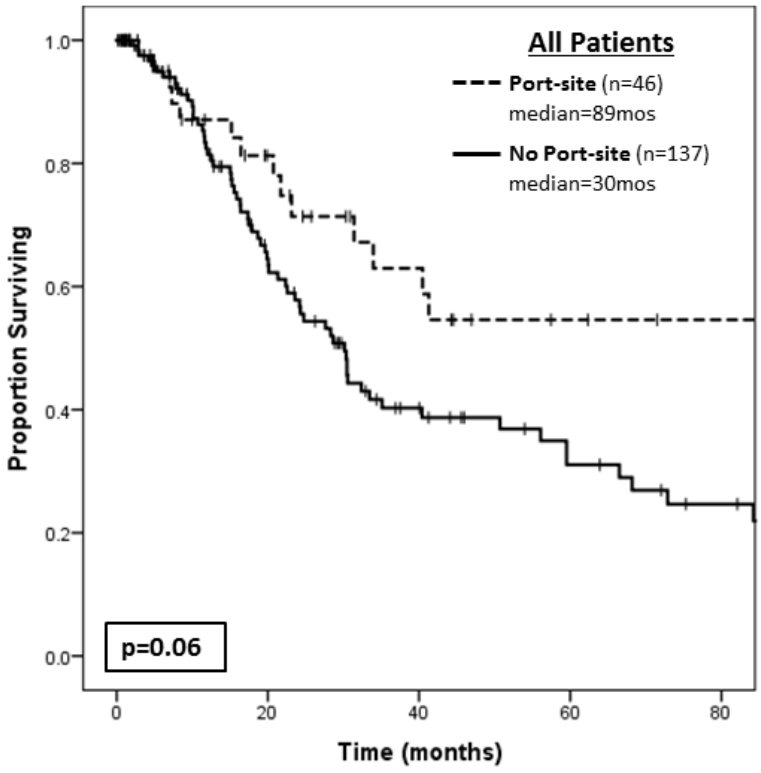

Figure 3.3

Kaplan-Meier curve for overall survival among patients with residual disease, comparing port site and no port site resection. Port site resection was not associated with improved survival compared to no port site resection among only patients with residual disease at the time of reoperation (log rank p=0.44).