Received: 12 January 2017 | Revised: 30 January 2017 | Accepted: 1 February 2017

DOI 10.1002/jso.24591

RESEARCH ARTICLE

WILEY Journal of SURGICAL ONCOLOGY

Routine port-site excision in incidentally discovered gallbladder cancer is not associated with improved survival: A multi-institution analysis from the US Extrahepatic Biliary Malignancy Consortium

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Funding information
National Center for Advancing Translational Sciences of the National Institutes of Health, Grant number: UL1TR000454

BACKGROUND: Current data on the utility of port-site excision (PSE) during re-resection for incidentally discovered gallbladder cancer (IGBC) in the US are conflicting and limited to single-institution series.

METHODS: All patients with IGBC who underwent curative re-resection at 10 institutions from 2000 to 2015 were included. Patients with and without PSE were compared. Primary outcome was overall survival (OS).

RESULTS: Of 449 pts with GBC, 266 were incidentally discovered, of which 193(73%) underwent curative re-resection and had port-site data; 47 pts(24%) underwent PSE, 146(76%) did not. The PSE rate remained similar over time (2000-2004: 33%; 2005-2009: 22%; 2010-2015:22%; $P = 0.36$). Both groups had similar demographics, operative procedures, and post-operative complications. There was no difference in T-stage (T1: 9 vs. 11%; T2: 52 vs. 52%; T3: 39 vs. 38%; $P = 0.96$) or LN involvement (36

This paper was presented as an Oral Presentation at the International Hepato-Pancreato-Biliary Association 12th World Congress, held April 20-23, 2016 in Sao Paulo, Brazil.

vs. 41%; $P = 0.7$) between groups. A 3-year OS was similar between PSE and no PSE groups (65 vs. 43%; $P = 0.07$). On univariable analysis, residual disease at re-resection (HR = 2.1, 95% CI 1.4-3.3; $P = 0.001$), high tumor grade, and advanced T-stage were associated with decreased OS. Only grade and T-stage, but not PSE, persisted on multivariable analysis. Distant disease recurrence-rate was identical between PSE and no PSE groups (80 vs. 81%; $P = 1.0$).

CONCLUSION: Port-site excision during re-resection for IGBC is not associated with improved overall survival and has the same distant disease recurrence compared to no port-site excision. Routine port-site excision is not recommended.

KEYWORDS

abdominal wall, disease recurrence, peritoneal carcinomatosis

1 | INTRODUCTION

Gallbladder cancer is a rare and aggressive disease, with a 5-year survival of 50-13%.[1–3] Although surgery is the only potentially curative treatment option, long-term survival following surgery is variable, ranging from 10 to 100% at 5 years, and depends on the stage of disease and extent of resection.[1,4,5] Approximately 50-70% of gallbladder cancers are found incidentally on pathologic examination after elective cholecystectomy performed for presumed benign disease.[6–9]

Current guidelines for the management of incidental gallbladder cancer (IGBC) state that re-resection should be performed for T1b, T2, and T3 lesions, unless contraindicated by advanced disease or poor performance status.[10] This recommendation is based on the findings that up to 60% of patients have residual disease, much of which is microscopic, in and around the gallbladder fossa at the time of re-resection.[7–9,11,12] Furthermore, re-resection with partial hepatectomy of liver segments IVb/V and portal lymph node dissection is associated with improved survival compared with no re-resection.[7,8,13] 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 rate of port-site recurrence due to potential contamination from occult tumor seeding during the initial laparoscopic cholecystectomy.[14,15] Other investigators have questioned this claim, citing a low incidence of disease in port site specimens, increased morbidity, and no difference in survival following the procedure.[16,17] Due to the rarity of this disease, however, data on IGBC have been largely limited to small cohorts of patients, and in the United States, primarily derive from single-institution analyses. The purpose of this study was to utilize a large, US-based, multi-institutional database to investigate the practice patterns of port site management over time, as well as to assess the association of port site resection with overall survival (OS).

2 | METHODS

The US Extrahepatic Biliary Malignancy Consortium (USEBMC) is a collaboration of 10 academic institutions: Emory University, Johns Hopkins University, New York University, Ohio State University, Stanford University, University of Louisville, University of Wisconsin, Vanderbilt University, Wake Forest University, and Washington University in St. Louis. 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.

Pertinent baseline demographic, perioperative, and pathologic data were recorded. Pathology review was performed by experienced GI pathologists at each institution. Staging was based on American Joint Committee on Cancer (AJCC) 7th edition guidelines.[18] Data regarding adjuvant therapy, disease recurrence, and survival were additionally recorded. Survival information was verified with the Social Security Death Index, when necessary.

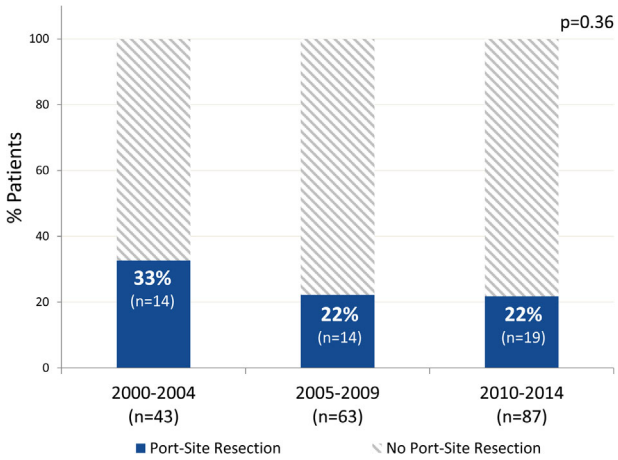

FIGURE 1 Incidence of port site resection over time. There was no change in the incidence of port site resection over three time periods: 2000-2004 (33%), 2005-2009 (22%), and 2010-2014 (22%); $P = 0.36$

TABLE 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* (%)			0.17
White	107 (80)	32 (76)	
African-American	16 (12)	4 (10)	
Other	11 (8)	6 (14)	
ASA class, *n* (%)			0.90
1	2 (2)	0 (0)	
2	35 (34)	10 (36)	
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* (%)			0.42
Bile duct	8 (13)	3 (19)	
Liver	18 (30)	4 (25)	
Lymph node	20 (33)	5 (31)	
Multiple	14 (24)	4 (25)	
Type of resection, *n* (%)			0.51
Bile duct only	7 (5)	1 (2)	
Cholecystectomy only	4 (3)	0 (0)	
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* (%)			0.31
R0	132 (92)	46 (98)	
R1	11 (8)	1 (2)	
AJCC T-stage			0.48
T1	14 (11)	4 (9)	
T2	68 (52)	23 (52)	
T3/T4	48 (37)	17 (39)	
Grade, *n* (%)			0.43
Well	16 (14)	3 (9)	
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

(Continues)

TABLE 1 (Continued)

Baseline variables	No port-site (*n* = 146, 76%)	Port-site (*n* = 47, 24%)	*P*-value
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)	

BMI, body mass index; ASA, American Society of Anesthesiologists; INR, international normalized ratio; LN, lymph node; AJCC, American Joint Committee on Cancer.
[a]≥Clavien-Dindo grade IIIa.

Institutional Review Board approval was obtained at each institution prior to data collection.

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.

All statistical analysis was conducted using SPSS 22.0 software (IBM Inc., Armonk, NY). Patients with and without port site resection were compared. Chi-squared 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. Kaplan-Meier survival plots for OS were calculated for the entire cohort and to compare port site and no port site excision groups. Statistical significance for each endpoint was predefined as two-tailed $P < 0.05$.

3 | 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 to 2009, and 22% from 2010 to 2015 ($P = 0.36$; Fig. 1).

Comparative analyses of baseline demographics and clinico-pathologic factors between port site and no port site groups are shown in Table 1. There was no difference in baseline demographics or underlying comorbidities between the two groups. There was also

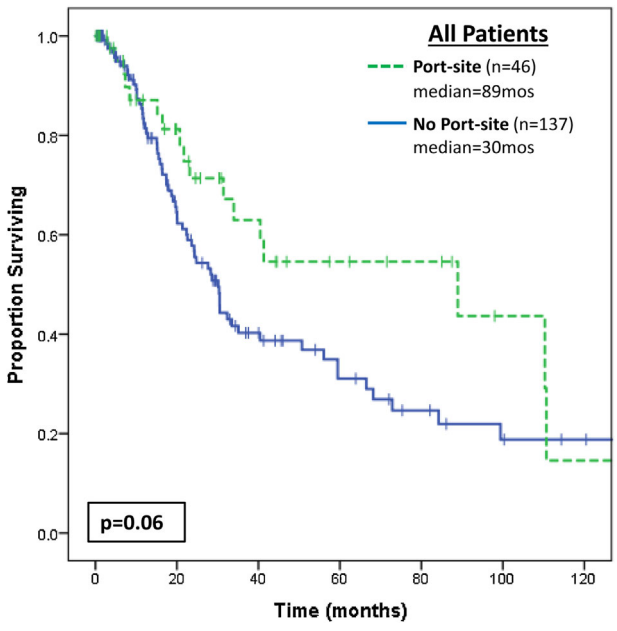

FIGURE 2 Kaplan-Meier curve for overall survival among all patients, comparing port site and no port site resection. Port site resection was not associated with improved survival compared to no port site resection (log rank $P = 0.06$)

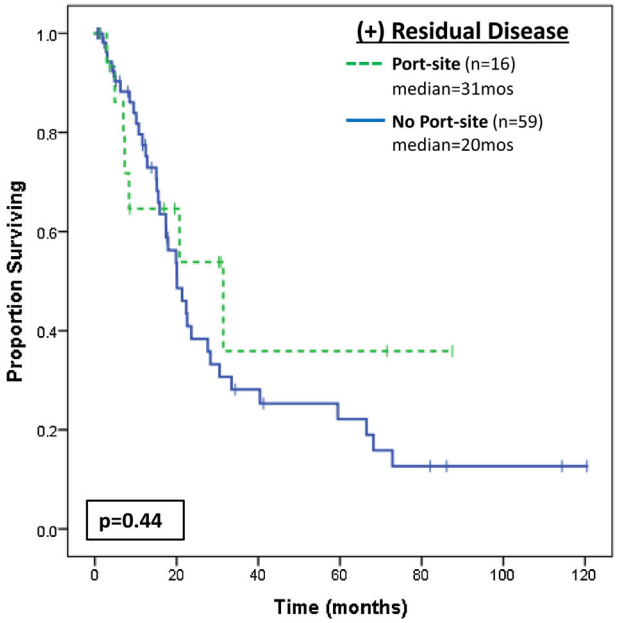

FIGURE 3 Kaplan-Meier curve for overall survival among patients with residual disease, comparing port site and no port site resection. Port site resection was not associated with improved survival compared to no port site resection among only patients with residual disease at the time of reoperation (log rank $P = 0.44$)

TABLE 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	Ref		Ref	
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	Ref		Ref	
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.

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 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; $P = 0.06$; Fig. 2). When examining only patients who had residual disease at the time of reoperation, still port site resection was 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; $P = 0.44$; Fig. 3).

Univariable and multivariable Cox regression analyses for OS are shown in Table 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; $P = 0.18$).

4 | 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.[8,9,19] 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.[10] However, the role of additional resection, such as port site resection, is controversial. In this study, we utilized a large, US-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.

Citing high rates of disease recurrence at laparoscopic port sites, some surgeons advocate for routine port site resection.[14] Lundberg et al [20] found port site recurrences in 16% of patients, and in their review of 409 IGBC cases, Paolucci et al [15] 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.[16,17] In a single-institution review of 69 patients with IGBC who underwent port site resection at Memorial Sloan Kettering Cancer Center, Maker et al [17] 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.[17] Fuks et al [16] 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.[16]

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 [17] and Fuks et al [16], 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. Thus, 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 additionally associated with distant disease recurrence and generalized peritoneal carcinomatosis, surgical resection of the port sites likely carries very little benefit.

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, there may have been a selection bias for who underwent port site resection. 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 United States. Furthermore, despite any potential selection bias, groups were well-matched on all clinicopathologic variables examined. Second, 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 associated with improved survival, regardless of port site pathology. Finally, pathologic analysis was not standardized across institutions; however, all involved academic centers have experienced GI pathologist who performed all pathologic review.

5 | 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.

DISCLOSURES OF INTEREST

This research was supported in part by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR000454. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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How to cite this article: Ethun CG, Postlewait LM, Le N, et al. Routine port-site excision in incidentally discovered gallbladder cancer is not associated with improved survival: A multi-institution analysis from the US Extrahepatic Biliary Malignancy Consortium. *J Surg Oncol*. 2017;115:805–811. https://doi.org/10.1002/jso.24570