J Gastrointest Surg (2009) 13:722–727
DOI 10.1007/s11605-008-0772-8

ORIGINAL ARTICLE

A Critical Analysis of the Surgical Management of Early-Stage Gallbladder Cancer in the United States

Eric H. Jensen · Anasooya Abraham · Elizabeth B. Habermann · Waddah B. Al-Refaie · Selwyn M. Vickers · Beth A. Virnig · Todd M. Tuttle

Received: 8 September 2008 / Accepted: 24 November 2008 / Published online: 13 December 2008

Abstract
Background Radical resection is recommended for selected patients with gallbladder (GB) cancer. We sought to determine whether radical resection improves survival for patients with early-stage cancer and to evaluate surgeon compliance with current treatment recommendations.
Patients and methods Patients with stage 0, I, or II GB cancer who underwent surgical resection were identified from the Surveillance, Epidemiology, and End Results (SEER) tumor registry from 1988 through 2004. Patients were classified by surgical procedure performed (simple vs. radical resection) and adjuvant treatment given (radiation therapy [RT] vs. no RT). Unadjusted and adjusted overall survival (OS) and cancer-specific survival (CSS) were compared.
Results Of the 4,631 patients who underwent surgery for early-stage GB cancer from 1988 through 2004, 4,188 (90.4%) underwent cholecystectomy alone and 443 (9.6%) underwent radical surgery including hepatic resection. The proportion of patients having radical surgery for T1b, T2, and T3 cancers was 4.5%, 5.6%, and 16.3%, respectively. For patients with T1b/T2 cancer, radical resection was associated with significant improvement in adjusted CSS ($p=0.01$) and OS ($p=0.03$). For patients with T3 cancers, we noted no improvement in CSS or OS. Survival for patients with node-positive disease (stage 2b) was universally poor and not improved by radical resection. For all patients who underwent radical resection, node negativity, female sex, age <70, low grade, and RT predicted improved CSS and OS.
Conclusions Despite a significant survival advantage for patients with T1b/T2 GB cancer who undergo radical resection, this treatment is significantly underutilized. Ensuring delivery of recommended surgical treatment is vital to improving outcomes for patients with this disease.

Keywords Gallbladder cancer · Radical cholecystectomy · Cholecystectomy · Practice guidelines

E. H. Jensen (✉) · W. B. Al-Refaie · S. M. Vickers · T. M. Tuttle
Division of Surgical Oncology,
University of Minnesota Medical Center,
420 Delaware Street SE, MMC 195,
Minneapolis, MN 55455, USA
e-mail: jense893@umn.edu

A. Abraham · E. B. Habermann · B. A. Virnig
Health Policy and Management,
University of Minnesota Medical Center,
Minneapolis, MN, USA

Background

Gallbladder (GB) cancer affects about 9,000 patients in the USA each year. Of these, it is estimated that only 15.1% will survive longer than 5 years after diagnosis.[1] Current National Comprehensive Cancer Network (NCCN) guidelines recommend radical resection of the GB fossa with dissection of the regional lymph nodes as optimal treatment for patients with early-stage GB cancer (i.e., stages 1 through 2b).[2] This group of patients includes those with T tumor invasion extending into the muscularis layer (T1b) or beyond and with no evidence of metastatic disease. These guidelines are based on retrospective data that show a survival benefit in patients who undergo radical resection.[3–7] Although radical resection is typically defined as resection of the GB and at least 2 cm of GB fossa in addition to

dissection of portal lymph nodes, many authors report improved survival with much more aggressive surgeries including bile duct resection, right hepatectomy, central hepatectomy, or extended right hepatectomy.[6] The choice of procedure is typically dictated by the extent of disease at the time of resection, with the ultimate goal of achieving negative margins.

Unfortunately, debate continues regarding appropriate patient selection for radical resection of GB cancer. Most authors agree that patients with early-stage GB cancer (stage 1 or 2) gain a survival benefit from radical resection. Even in this group, however, Wright et al. recently reported that only a very small percentage (4%) of patients with T2 cancers actually undergo the recommended surgery.[8] For patients with node-positive disease, the benefit of radical resection remains unclear. Moreover, most early GB cancers are found incidentally after laparoscopic cholecystectomy, without nodal sampling, so the decision to proceed with radical resection is typically made on the basis of T-stage alone.

Given the rarity of this disease and the inability to randomize patients to potentially less effective treatments (cholecystectomy alone), randomized prospective trials to directly compare cholecystectomy alone and radical resection are impossible. Similarly, most retrospective studies typically have few highly selected patients, spanning long periods of time with comparisons to historical controls. In our study, we used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to determine whether patients who underwent radical resection for early-stage GB cancer had any improvement in their overall survival (OS) and cancer-specific survival (CSS), as compared with those who underwent cholecystectomy alone. Our primary aims were (1) to determine the benefit of radical resection over cholecystectomy alone for patients with early-stage GB cancer and (2) to assess compliance with current NCCN recommendations for radical resection.

Methods

This study was given exempt status by the University of Minnesota Institutional Review Board Human Subjects Committee (Protocol #0707E13102). Data on the incidence of GB cancer, survival, treatment modalities, and staging were obtained from the SEER database. The SEER database collects population-based data on incident cancers from 17 registries composed of nine states (Connecticut, Hawaii, Iowa, New Mexico, Utah, Alaska, Kentucky, Louisiana, and New Jersey), six metropolitan areas (San Francisco, Detroit, Seattle, Atlanta, San Jose, Los Angeles), greater California, and rural Georgia. These areas represent about 26% of the US population; data span 1973 through 2004, all de-identified and publically available.

Case Definitions

We restricted our analyses to GB cancer diagnosed in or after 1988 and included patients 16 through 102 years old upon diagnosis. We selected codes to define radical resection as removal of the GB and hepatic resection with or without lymph node dissection. We defined cholecystectomy alone by codes corresponding to removal of the GB with or without dissection of lymph nodes. Excluded from our analysis were patients coded as not receiving surgery and patients who underwent debulking, excisional biopsy, exploratory surgery, cryosurgery, cautery, laser surgery, and nonspecified surgery. Also excluded were patient's classified as having sarcoma or lymphoma, metastatic disease, disease of unknown stage, and any T4 cancers. Thus, our analysis was limited to T1, T2, or T3 cancers. Our final cohort consisted of patients diagnosed with stage 1–2B GB adenocarcinoma (T1b–T3, node positive or negative) who underwent surgical resection (simple or radical cholecystectomy) between 1988 and 2004.

Analyses

For our univariate comparison of patient characteristics and tumor-related features by extent of resection (cholecystectomy alone vs. radical resection), we used the Student *t* test and chi-square test. To test for trends, we used the Cochran–Armitage test. When two or more subcategories of an independent variable were present, we used the most clinically relevant or the most frequent subgroup as a reference category. For each T stage, we calculated rates and trends by type of surgery and by presence or absence of RT. We measured CSS by censoring for noncancer-related deaths and for persons alive at follow-up. To measure 5 years OS and CSS, we used Kaplan–Meier methods and log-rank tests. To predict OS and CSS, we constructed multivariate Cox proportional hazard regression models, while controlling for patient age, race, sex, tumor grade, tumor stage, presence of absence of RT, and cancer registry. Nonsignificant predictors were dropped from the models if parameter estimates remained stable within 10%. p values ≤ 0.05 were considered statistically significant. All statistical analyses were performed using SAS 9.1 software (SAS Institute Inc., Cary, NC, USA).

Results

We identified 4,631 patients who underwent surgery for early-stage GB cancer from 1988 through 2004. Mean age at diagnosis was 71. Women comprised 72.5% of the total cohort. A total of 443 (9.6%) patients underwent radical

resection; 4,188 (90.4%) underwent cholecystectomy alone. The proportion of patients who underwent radical resection for T1b, T2, and T3 cancers was 4.5%, 5.6%, and 16.3%, respectively. Individuals with T3 primary tumors were significantly more likely to receive radical surgery than those with T1b or T2 tumors (both $p=0.0001$). Overall, only 11.3% of potentially operable patients underwent radical resection. Patients <70 years old, nonwhite patients, and individuals with high grade tumors were more likely to undergo radical resection. Sex was not significantly associated with radical resection. Our bivariate analysis showed that patients with unknown stage, unknown lymph node (LN) status, or unknown grade were significantly less likely to undergo radical resection than those with known pathologic diagnosis (all p values <0.05). Table 1 summarizes these findings.

Our initial analysis was performed without considering LN status, in order to replicate typical surgical decision making in which the decision to proceed with radical resection is made following laparoscopic cholecystectomy without nodal evaluation. We therefore initially classified patients by T stage only. Figure 1a–d shows unadjusted survival analysis comparing radical resection to cholecystectomy alone for patients with T1b/T2 cancers. For patients with tumor stage T1b/T2 cancer (node positive or negative), radical resection was associated with a significant improvement in CSS and OS (Fig. 1a). This benefit was also confirmed following multivariate analysis adjusting for patient age, race, sex, tumor grade, tumor stage, presence of absence of RT, and cancer registry (Table 2).

To evaluate the effect of LN metastases on survival, we further stratified patients into node-positive and node-negative groups. As expected, radical resection was associated with a significantly improved CSS and OS survival for T1b/T2 node-negative cancer (Fig. 1b). In unadjusted analysis, for patients with T1b/T2 node-positive cancer, the benefit of radical resection was also associated with a statistically significant improvement in CSS and OS (Fig. 1c); however, this benefit was not statistically significant following multivariate analysis. Patients whose LN's were not evaluated gained no benefit from radical resection (Fig. 1d). Table 2 shows the adjusted hazard ratios and 95% confidence intervals for patients with T1b/T2 cancer by type of surgery (radical resection vs. cholecystectomy alone).

For patients with T3 cancer, when we considered T stage only, CSS and OS did not differ by type of surgery. CSS and OS for stage 2B patients with node-positive cancer was

Table 1 Patient Characteristics

	Total	Cholecystectomy alone	Radical resection	p value[a]
n (%)	4,631	4,188 (90.4)	443 (9.6)	
Age				
Mean	71.0	71.3	68.5	<0.0001
SD	12.9	12.9	12.5	
Range	16–102	16–102	28–95	
Sex				
Male	1,275 (27.5)	1,144 (27.3)	131 (29.6)	
Female	3,356 (72.5)	3,044 (72.7)	312 (70.4)	0.3123
Race				
White	3,711 (80.1)	3,374 (80.6)	337 (76.1)	
Black	364 (7.9)	319 (7.6)	45 (10.2)	0.0404
Other	556 (12.0)	495 (11.8)	61(13.8)	0.1529
Stage				
0	61 (1.3)	58 (1.4)	3 (0.7)	
IA	217 (4.7)	192 (4.6)	25 (5.6)	0.1301
IB	201 (4.3)	177 (4.2)	24 (5.4)	0.1141
IIA	250 (5.4)	173 (4.1)	77(17.4)	<0.0001
IIB	715 (15.4)	596 (14.2)	119 (26.9)	0.0157
Unknown	3,187 (68.8)	2,992 (71.4)	195 (44.0)	<0.0001
Tumor grade				
Low	2,301 (49.7)	2,093 (50.0)	208 (47.0)	
High	1,504 (32.5)	1,322 (31.6)	182 (41.1)	0.0023
Unknown	826 (17.8)	773 (18.5)	53 (12.0)	0.0194
Radiation				
None	3,742 (80.8)	3,426 (81.8)	316 (71.3)	
Beam RT	791 (17.1)	671 (16.0)	120 (27.1)	<0.0001

[a] p values represent comparison of proportions of the variable of interest between radical and cholecystectomy group with respect to reference level

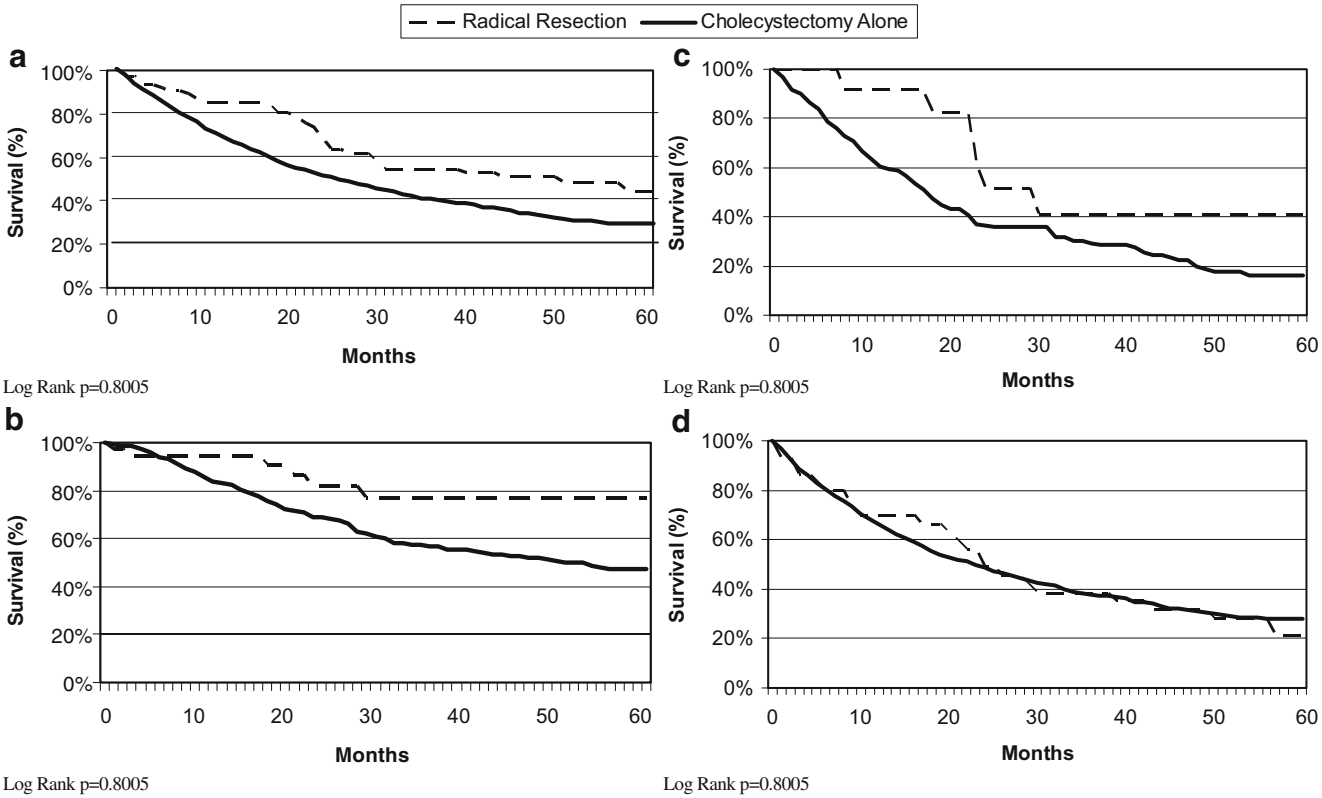


Figure 1 **a** Overall survival in patients with T1b and T2 tumors by type of surgery performed. *chole* cholecystectomy alone, *rad* radical resection. **b** Overall survival in patients with T1b and T2 node negative tumors by type of surgery performed. *chole* cholecystectomy alone, *rad* radical resection. **c** Overall survival in patients with T1b and T2 node positive tumors by type of surgery performed. *chole* cholecystectomy alone, *rad* radical resection. **d** Overall survival in patients with T1b and T2 node unexamined tumors by type of surgery performed. *chole* cholecystectomy alone, *rad* radical resection.

universally poor and was not improved by radical resection (Table 2).

Overall, 28.6% of patients who underwent cholecystectomy alone had at least one LN examined pathologically, compared with 56% of patients who underwent radical resection. LN involvement was most common with T3 cancer (63.7%); however, a significant proportion of patients with T1b/T2 cancer also had LN metastases (T1b, 24.4% and T2, 44.9%).

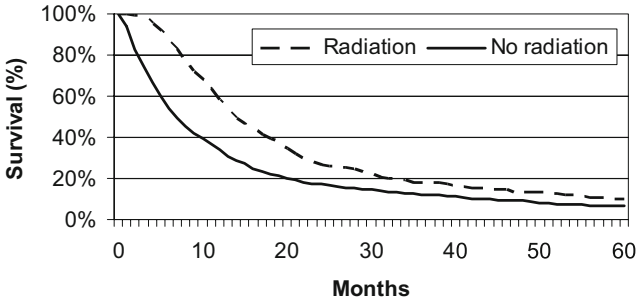
Table 2 Hazard Ratios Comparing Overall Survival Following Radical Resection Compared to Cholecystectomy Alone

Stage	Hazard ratio	95% Confidence interval	*p* value
All T1bT2	0.681	0.485–0.956	0.0265
Node-negative T1b–T2	0.432	0.189–0.986	0.0461
Node-positive T1b–T2	0.439	0.186–1.036	0.0602
All stage 2B	1.114	0.891–1.394	0.3437

[a] Reference group = cholecystectomy alone

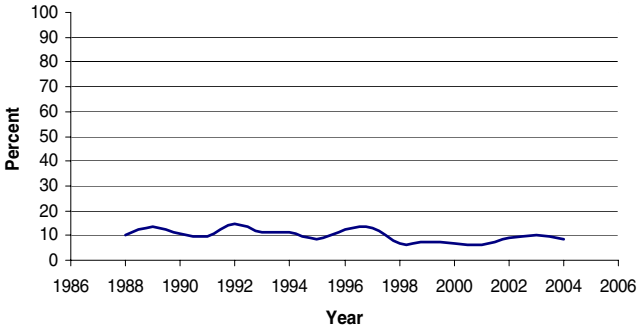
After surgery, 17.1% of patients received RT. RT was more likely for patients who underwent radical resection (27%) than for those who underwent cholecystectomy alone (16%; $p<0.0001$). Similarly, RT was more likely for patients with T3 cancer (23.1%) than for those with T1b/T2 cancer (17.6%; $p<0.0001$). For patients with T3 cancer, RT was associated with improved median OS and CSS independent of the type of surgery performed (both $p<0.0001$). Unadjusted overall survival curves are shown in Fig. 2. RT was less likely for patients with T3 cancer whose LNs were not evaluated (18.9%) than for those with known positive or negative LNs (30.7%; $p<0.0001$).

For all patients who underwent radical resection, node negativity, female sex, age <70, low grade, lower T stage, and RT were associated with improved CSS and OS (Table 3). Given the low rate of radical resection observed for early-stage GB cancer, we also evaluated the trend in radical resection rates since 1988. Figure 3 shows the rates of radical resection for early-stage cancers during our study time period. No significant change was identified.



Log rank p<0.0001

Figure 2 Overall survival in patients with T3 tumors by receipt of radiation.



GB=gallbladder

Figure 3 Trends in radical resection rates for GB cancer 1988–2004. *GB* gallbladder.

Discussion

This study provides population-based validation that radical resection improves survival for patients with early-stage GB cancer, as compared with cholecystectomy alone. Additionally, it highlights the wide gap between surgical guidelines and actual practice trends in this country: A very small proportion of patients actually received the nationally recommended treatment. We identified a subset of patients (those with T1b and T2 cancer) who seemed to derive the most benefit from radical resection (Fig. 1a–d). Unfortunately, only 5% of patients in that subset actually underwent the recommended treatment. In addition, only 56% of patients who underwent radical resection actually had LNs evaluated, even though LN evaluation is an integral part of recommended therapy. Thus, about 98% of patients received inadequate surgical care, a finding that raises concern regarding both surgical technique and pathologic evaluation for patients with GB cancer in the USA. Clearly, current practice is not in keeping with established NCCN guidelines.

We initially classified individuals by T stage alone, in an attempt to accurately reflect the typical clinical scenario of a patient being considered for radical resection after simple cholecystectomy. As expected, most patients with early-stage cancer who underwent cholecystectomy alone did not have LNs evaluated (71.4%). When evaluated solely on T stage, radical resection was associated with improved CSS and OS for patients with T1b/T2 cancer. This finding validates the current typical practice in which the decision to proceed with radical resection is made on T-stage information alone. It is also consistent with previous retrospective reports of improved survival after radical resection for early-stage tumors.[7,9]

In our study, patients with T3 cancer did not have an improvement in survival after radical resection. Even when considering only pathologically node-negative patients, radical resection did not seem to improve CSS or OS for those with T3 cancer. In retrospective review, others have reported that lymphadenectomy alone is an independent predictor of improved survival.[4] It is not clear whether this finding represents a benefit that is due to the surgical procedure alone, or if it is more reflective of patient selection and of improved delivery of care in general. In our study, we found a significant proportion of patients did not have LN evaluated at the time of radical surgery. We also noted that those who do not have LN evaluated are also less likely to receive adjuvant radiation, a therapy which has been shown to be beneficial in this group of patients.

Several other authors have reported a significant benefit to radical resection in patients with T3 cancer.[6,10,11] Those reports were all retrospective reviews and likely included a highly selected patient population. Particularly for those patients with stage 2B cancer (T3, node-positive), the benefit of radical resection is unclear.[5] In our study population, over 60% of patients with T3 cancer had positive LNs identified. For this group of patients, patient selection and a multidisciplinary approach (including RT and chemotherapy) likely play a significant role in improving outcomes.

Finally, we evaluated the role of RT for patients with GB cancer. For those with T1b/T2 cancer, RT did not appear to be associated with a significant improvement in survival

Table 3 Factors Associated with Improved Overall Survival After Radical Resection

	Hazard ratio[a]	Confidence interval	*p* value
Node negativity	0.665	0.483–0.915	0.0123
Female sex	0.686	0.541–0.870	0.0019
Age <70	0.666	0.529–0.839	0.0005
Low grade	0.618	0.487–0.784	<.0001
Receipt of radiation	0.737	0.570–0.951	0.0192

[a] Reference groups: node positive, male sex, age >70, high grade, no radiation

over radical resection alone. For those with T3 cancer, however, RT was associated with a significant improvement in both CSS and OS (Fig. 2): both for patients who underwent cholecystectomy alone and for those who underwent radical resection. These observations are consistent with previously reported data and suggest that RT may be important in the adjuvant treatment of localized GB cancer.[12,13] A total of 31.4% of our patients who underwent radical resection for T3 cancer received RT. As mentioned in our results, patients who did not have their LNs evaluated were less likely to receive RT than those who did, regardless of the type of surgery performed ($p<0.0001$).

Several limitations of the SEER database affect our results. Most notably, we are unable to determine margin status after resection. Particularly for patients with more advanced cancer (T3), this lack of information may lead to bias, making radical resection seem less beneficial than it truly is when negative margins are achieved. In addition, we have no record of adjuvant chemotherapy given. Our inability to identify a survival benefit for patients with T3 cancer who underwent radical resection may be related to our inability to determine which patients received appropriate adjuvant therapy. As noted previously, multiple authors have reported significantly improved survival rates for selected patients with T3 cancer,[6,10,11] a finding we were not able to validate in our study. Other limitations include the retrospective nature of the SEER database and the lack of information regarding patient performance status. Appropriate patient selection (which may be vital to optimizing outcomes) is also impossible to verify through the use of a database like this. Finally, despite large numbers of patients with early-stage GB cancer, so few of them received radical surgery that our power was somewhat limited for analysis.

Our aims in this study were to validate current NCCN guidelines recommending radical resection for early-stage GB cancer as well as to determine current practice trends in the USA. Clearly, radical resection for localized disease does provide a survival benefit over cholecystectomy alone. It is surprising and disappointing that such a small fraction of patients seem to receive appropriate therapy. In addition, this trend has not improved over time, despite widely recognized guidelines (Fig. 3). These findings suggest a significant lack of delivery of care, the reason for which remains unknown. Multiple retrospective reviews and now population-based studies have shown consistently improved CSS and OS for patients who underwent radical resection for GB cancer and the surgical mortality rate at most high-volume institutions is <2% for hepatic resection.

Our study validates the current NCCN guidelines recommending radical resection for early-stage GB cancer, including the necessity for appropriate LN evaluation. At the same time, we found that only a small fraction of patients actually received the recommended therapy. Only with a significant improvement in the quality and delivery of care in this country will we ever improve outcomes for patients with GB cancer.

References

1. Surveillance Epidemiology, End Results (SEER) Program. (http://www.seer.cancer.gov) Limited-Use Data (1973–2004), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission.
2. Benson AB, 3rd, Bekaii-Saab T, Ben-Josef E, et al. Hepatobiliary cancers. Clinical practice guidelines in oncology. J Natl Compr Netw 2006; 4(8):728-50.
3. Fong Y, Malhotra S. Gallbladder cancer: recent advances and current guidelines for surgical therapy. Adv Surg 2001;35:1–20.
4. Shih SP, Schulick RD, Cameron JL, et al. Gallbladder cancer: the role of laparoscopy and radical resection. Ann Surg 2007;245 (6):893–901. doi:10.1097/SLA.0b013e31806beec2.
5. Foster JM, Hoshi H, Gibbs JF, et al. Gallbladder cancer: defining the indications for primary radical resection and radical re-resection. Ann Surg Oncol 2007;14(2):833–840. doi:10.1245/s10434-006-9097-6.
6. Reddy SK, Marroquin CE, Kuo PC, et al. Extended hepatic resection for gallbladder cancer. Am J Surg 2007;194(3):355–361. doi:10.1016/j.amjsurg.2007.02.013.
7. Chan SY, Poon RT, Lo CM, et al. Management of carcinoma of the gallbladder: a single-institution experience in 16 years. J Surg Oncol 2008;97(2):156–164. doi:10.1002/jso.20885.
8. Wright BE, Lee CC, Iddings DM, et al. Management of T2 gallbladder cancer: are practice patterns consistent with national recommendations? Am J Surg 2007;194(6):820–825. discussion 825–6. doi:10.1016/j.amjsurg.2007.08.032.
9. Wise PE, Shi YY, Washington MK, et al. Radical resection improves survival for patients with pT2 gallbladder carcinoma. Am Surg. 2001;67(11):1041–1047.
10. Chijiiwa K, Kai M, Nagano M, et al. Outcome of radical surgery for stage IV gallbladder carcinoma. J Hepatobiliary Pancreat Surg 2007;14(4):345–350. doi:10.1007/s00534-006-1186-1.
11. Kai M, Chijiiwa K, Ohuchida J, et al. A curative resection improves the postoperative survival rate even in patients with advanced gallbladder carcinoma. J Gastrointest Surg 2007;11 (8):1025–1032. doi:10.1007/s11605-007-0181-4.
12. Mojica P, Smith D, Ellenhorn J. Adjuvant radiation therapy is associated with improved survival for gallbladder carcinoma with regional metastatic disease. J Surg Oncol 2007;96(1):8–13. doi:10.1002/jso.20831.
13. Kresl JJ, Schild SE, Henning GT, et al. Adjuvant external beam radiation therapy with concurrent chemotherapy in the management of gallbladder carcinoma. Int J Radiat Oncol Biol Phys 2002;52 (1):167–175. doi:10.1016/S0360-3016(01)01764-3.