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Carcinoma of the gallbladder: Patterns of presentation, prognostic factors and survival rate. An 11-year single centre experience

M. D'Hondt [a], R. Lapointe [b], Z. Benamira [a], H. Pottel [c], M. Plasse [b], R. Letourneau [b], A. Roy [b], M. Dagenais [b], F. Vandenbroucke-Menu [b,*]

[a] Hopital Saint Luc – CHUM, Service de chirurgie hépatobiliaire et pancréatique, Université de Montréal, Canada
[b] Hopital Saint Luc – CRCHUM, Service de chirurgie hépatobiliaire et pancréatique, Université de Montréal, 1058 rue Saint Denis, Montreal, QC H2X3J4, Canada
[c] Interdisciplinary Research Center, Katholieke Universiteit Leuven, Kortrijk, Belgium

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Abstract

Background: This report examines the patterns of presentation, prognostic factors and survival rate of all patients with gallbladder cancer (GBC) evaluated at our tertiary academic hospital over an 11-year period.
Methods: A retrospective review of a prospectively collected database of all patients with GBC presenting between January 1998 and December 2008 was performed.
Results: 102 GBC-patients were included: 69 women and 33 men (median age: 65,5 years). Forty-five patients presented with incidental gallbladder cancer (IGC) and 57 with nonincidental cancer (NIGC). Curative surgery rate was 84.4% for IGC and 29.8% for NIGC ($p < 0.001$). Five-year actuarial survival rate was 63.2% for patients with curative intent surgery and 0% for patients with palliative approach. Patients with IGC had a longer survival rate compared to patients with NIGC (median: 25.8 vs. 4.4 months, $p < 0.0001$). For patients with radical resection (42 patients), there was no difference between IGC and NIGC. The incidence of liver involvement was respectively 0%, 20.8%, 58.3%, 100% for pT1, pT2, pT3 and pT4 tumors. Univariate analysis showed that survival rate was significantly affected by perineural invasion, T, N and M-stage, R0 resection, liver involvement, CA-19.9. In multivariate analysis, liver involvement was the only independent factor.
Conclusions: Majority of patients with a potentially curable disease had IGC. Almost 80% of patients with NIGC presented with unresectable disease. For patients who underwent resection with curative intent, actuarial 5-year survival was 63.2%. Liver involvement was the only independent prognostic factor. All patients with IGC and a pT2 or more advanced T stage should undergo a second radical resection.

Keywords: Gallbladder cancer; Incidental; Nonincidental; Prognostic factors; Liver involvement

Introduction

Gallbladder cancer (GBC) is a relatively rare disease accounting for 4% of all gastrointestinal cancers.[1] The prognosis is poor with only about a 32% 5-year survival rate for lesions confined to the gallbladder mucosa and a 10% 1-year survival rate for more advanced stages.[2,3] In a more recent published series 5-year survival of 38% has been reported for radically resected patients.[4]

Laparoscopic cholecystectomy (LC) is now the gold standard for symptomatic cholelithiasis with more than 80% of all cholecystectomies being performed by this approach.[5,6] Therefore, the likelihood of incidentally discovering GBC during or after laparoscopic cholecystectomy (LC) has increased. GBC after LC is reported with an incidence between 0.3 and 1%.[7] Because gallbladder carcinomas lack specific clinical presentations they usually present in two different ways. Either they are diagnosed at advanced stages or incidentally during or after cholecystectomy. The latter represents more patients with carcinomas that are confined to the mucosa or muscularis layers without growth beyond the serosa. In these patients surgical treatment of so-called early gallbladder carcinoma could result in a better prognosis and longer survival.

The aim of our study was to evaluate patterns of presentation (incidental vs nonincidental GBC), prognostic factors

* Corresponding author. Tel.: +1 514 890 8444; fax: +1 514 412 7380.
E-mail address: fvdbm.UdeM@me.com (F. Vandenbroucke-Menu).

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and survival rate of patients with GBC evaluated at our tertiary academic hospital over an 11-year period.

Patients and methods

After Institutional Review Board approval (10.082), a review of a prospectively collected database of all patients with GBC treated at our tertiary academic hospital between January 1998 and December 2008 was done. Data collected included patient demographics, presence of medical comorbidities, symptoms at presentation, preoperative CA19-9 level, serum bilirubin levels, extents of resection, complications, pathology and survivals.

Liver resection and hilar lymph nodes dissection were performed either as a primary surgery or as second stage surgery according to the time of discovery of GBC.

The follow-up end point was June 2011. The 6th edition of the American Joint Committee on cancer (AJCC) staging system was used for pathological and/or clinical staging. In the incidental group, pTNM was based on the first pathological report.

Statistical analysis were performed using univariate tests (Chi-square test, *t*-test) to evaluate differences in categorical or continuous variables with regard to survival. Factors that appeared to be significantly associated with survival were entered into a Cox proportional hazards model to test for significant effects while adjusting for multiple factors simultaneously. Actuarial survival was calculated using the Kaplan–Meier method. Differences in survival were examined using the log-rank test. A p value less than 0.05 was considered significant. Statistical significance used to enter patients from univariate to multivariate analysis was 0.05. SAS version 9.1.3 (Cary, NC) was used for all statistical analysis.

Results

Clinical characteristics (Table 1)

A total of 102 patients with gallbladder carcinoma were treated between January 1998 and December 2008. Clinical features of these patients are presented in Table 1. There were 69 women and 33 men. The median patient was 65.5 years (range: 39.8–85.2 years). Forty-five out of 102 patients (44.1%) presented with incidental gallbladder cancer (IGC) found after cholecystectomy (1 open/44 laparoscopic). One patient in the incidental group had bile spillage during the laparoscopic cholecystectomy.

A higher incidence of jaundice (43.9%) and weight loss (43.9%) was noted in the nonincidental group compared to the incidental group (24.4% and 26.7% respectively) but only jaundice was statistically more common in the nonincidental group ($p = 0.04$).

Forty patients (70.2%) in the nonincidental group were found to have unresectable disease on preoperative imaging compared to only 7 (15.6%) patients in the incidental group, which was highly statistically significant ($p < 0.001$). At surgical exploration, the number of patients found to have unresectable disease was no significantly different between both groups respectively: 5 in the incidental group vs 8 patients in the nonincidental group ($p = 0.1$). For patients with radical resection, the level of CA 19.9 was statistically higher in the nonincidental group (63.1 ± 81.2 kU/l vs 15.1 ± 12.5 kU/l, $p = 0.004$).

Table 1
Clinical features of all patients with gallbladder carcinoma and comparism between the incidental GBC -and Nonincidental GBC group.

	Incidental GBC ($N = 45$)	Nonincidental GBC ($N = 57$)	Total ($N = 102$)	P
Male	14	19	43	0.8
Age (median)	63.5 ± 10	66.3 ± 12	65.5	0.17
Symptoms				
Pain	31	38	71	0.8
Weight loss	12	25	37	0.07
Jaundice	11	25	36	0.04
Gallstones	30	25	55	0.02
Non resectable				
On imaging	7	40	47	<0.001
On exploration	8	5	13	0.1

Surgery

Of the 60 patients who were deemed unresectable, 47 were clearly unresectable based on preoperative imaging. Thirteen patients were found to have unresectable disease at laparotomy. Patients with unresectable disease at laparotomy always had small lesions (carcinomatosis or positive lymph nodes), undetectable on preoperative imaging. The reason for unresectability was peritoneal metastases in 7, vascular (with our without biliary) involvement in 3 and positive distant lymph nodes in 3 (para-aortic lymph nodes). The reasons for unresectability in the incidental group were small peritoneal metastases in 4 patients and a positive para-aortic lymph node in one patient.

Forty-two patients underwent a radical resection: 30 in incidental group and 12 in nonincidental group. After the specimen was resected out, intraoperative frozen biopsy was performed in all patients to evaluate involvement of the cystic duct margin. In the current series all frozen sections were negative.

There was no significant difference in time interval between patients who presented with unresectable disease compared to patients with resectable disease after prior cholecystectomy (mean time: 3.16 months vs 1.82 months respectively, $p = 0.06$).

All but two had a bi-segmentectomy (segments IVB and V). A right hepatectomy extended to the caudate lobe with bile duct resection was performed in two patients of the nonincidental group.

Data regarding radical resection is shown in Table 2.

Perioperative complications

Postoperative one-month mortality and in-hospital mortality was 0% in both groups. Sixteen postoperative complications were reported (38.1%). Postoperative ileus was noted in 4 patients, 2 improved with conservative treatment and 2 had a reintervention for adhesions. There was one grade B bile leak. One patient (2.4%) suffered from postoperative cholangitis which was treated with antibiotics. Pulmonary complications were noted in six patients: in 2 patients chest tube placement was necessary for major pleural effusion, 2 patients had pulmonary oedema treated with diuretics and 2 patients had a pneumonia treated with antibiotics. Other complications included wound infection ($n = 1$), urinary tract infection ($n = 2$) and myocardial infarct ($n = 1$).

Tumor characteristics

Tumor charactertistics for the 42 patients who underwent radical resection are shown in Table 3. Ten patients had positive lymph nodes. Average lymph node yield was 11.1 (range 7–16). Liver involvement was identified in 13 patients. Five patients of the incidental group, initially classified pT2, had microscopic liver involvement on the final pathological report, Two patients were found to have the mucinous variant and 5 were found to have the papillary variant. Tumors were identified as well differentiated in 12 patients, moderately differentiated in 18 patients and poorly differentiated in 10 patients. Microscopically positive surgical margins were found in 2 patients. No further surgery was performed in both cases. One patient had micronodular cirrhosis of alcoholic etiology (Child A) precluding a right hemihepatectomy extended to segment IV. The other patient with an R1 resection on final pathology refused further surgery. This was the patient with the prolonged hospital stay due to a grade B bile leak.

Survival

Median survival of the entire group (102 patients) was 7.2 months. Patients with incidental GBC ($n = 45$) had longer survival when compared to nonincidental GBC ($n = 57$) patients (median survival 25.8 months vs 4.4 months respectively, $p < 0.0001$) (Fig. 1). Median survival for the 60 palliated patients was 4.0 months and 5-year survival was 0% and for the 42 patients who underwent resection, actuarial 5-year survival was 63.2% (median not reached) ($p < 0.001$).

For resected patients, the survival rate was not significantly different between the incidental and nonincidental groups (Fig. 2).

Table 2
Operative data of incidental vs Nonincidental gallbladder cancer (GBC). Data regarding radical resection.

	Incidental GBC ($n = 30$)	Nonincidental GBC ($n = 12$)	p	Total ($n = 42$)
R1 resection	2	0	1.000	2
Blood loss (ml)	323.3 ± 263.2	213.3 ± 280.7	0.237	291.9 ± 190.1
Hepatectomy				
Minor (IVb+V)	30	10	0.0767	40
Extended right	0	2	0.0767	2
Operating time (hours)	4.40 ± 1.32	3.60 ± 0.110	0.110	4.17 ± 0.72

Table 3
TNM tumor characteristics. Data regarding radical resection.

T	Number of patients	N1 disease	Liver involvement
T1b	5 (11.9%)	0 (0.0%)	0 (0.0%)
T2	24 (38.1%)	6 (20.0%)	5 (20.8%)
T3	12 (14.3%)	4 (33.3%)	7 (58.3%)
T4	1 (2.4%)	0 (100.0%)	1(100%)

Stage	Number of patients
Ia	5 (11.9%)
Ib	16 (38.1%)
IIa	6 (14.3%)
IIb	9 (21.4%)
III	1 (2.4%)
IV	5 (11.9%)

	Incidental GBC ($n = 30$)	Non-incidental GBC ($n = 12$)	p	Total ($n = 42$)
T (%)				
T1b	3 (10%)	2 (16.7%)	0.6134	5 (11.9%)
T2	19 (63.3%)	5 (41.7%)	0.3024	24 (57.1%)
T3	8(26.7%)	4 (33.3%)	0.7154	12 (28.6%)
T4	0 (0%)	1 (8.3%)	0.2857	1 (2.4%)
N+	8 (26.7%)	2 (16.7%)	0.6956	10 (23.8%)
Liver involvement	9 (30%)	4 (33.3%)	1.000	13 (30.9%)

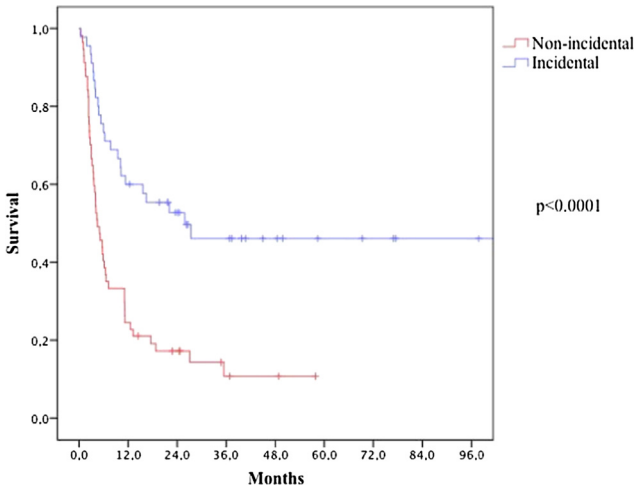

Figure 1. Overall survival of incidental gallbladder cancer found after cholecystectomy ($n = 45$) vs non-incidental gallbladder cancer ($n = 57$).

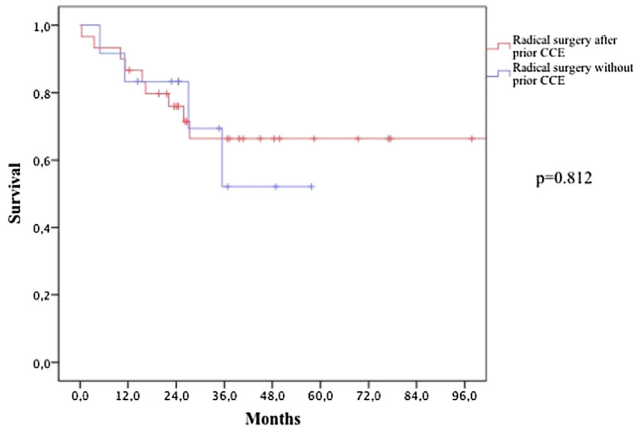

Figure 2. The effect of prior cholecystectomy on survival after radical resection for gallbladder cancer.

Tumor recurrence occurred in 15 patients. Two patients had stage Ib disease, 1 patient had stage IIa disease, 9 patients had stage IIb disease, 1 stage III and two stage IV disease. Three patients had a local recurrence only, 2 patients had metastatic disease and local recurrence, 6 patients had metastatic disease only and 4 patients had peritoneal dissemination. Interestingly, no tumor recurrence occurred in the patient in the incidental group with bile spillage during prior laparoscopic cholecystectomy. Final pathology of this patient was pT1bN0. Regarding both patients with stage Ib disease, one patient had several metastases in the right liver lobe and mediastinum and the other patient has multiple peritoneal metastases. According to univariate analysis in resected patients, significant survival factors were: perineural invasion ($p = 0.013$), T ($p = 0.009$), N ($p = 0.0026$), M ($p < 0.0001$), R0 resection ($p < 0.0001$), liver involvement ($p < 0.0001$) and CA-19.9 ($p = 0.0017$) while other factors including gender, age, weight loss, jaundice, pain, incidental finding, histological grade and histological type did not affect survival. In the multivariate analysis, liver involvement was the only independent factor for survival.

Discussion

An aggressive surgical approach is the mainstay of treatment in patients with localized GBC. However, symptomatic patients often present with a recent history of vague abdominal symptoms, jaundice, a palpable mass or ascites.[8] Most of these patients have advanced disease not amendable to curative resection.[9,10] Historically only 15–40% of all patients with gallbladder cancer were candidates for surgery.[11] In the present series 41.1% of patients underwent surgery with curative intent.

Incidental gallbladder cancer

Unsuspected GBC can be diagnosed incidentally following 0.3–1% of routine cholecystectomies.[7,12] The majority of patients with a potentially curable disease belong to this group as confirmed by our current series (85%). However, most patients with nonincidental GBC will be presenting with unresectable disease.

Although Gall et al. found a decreased survival in patients subjected to two operations, prior cholecystectomy had no negative impact on overall survival after radical surgery in the current study.[13] This was also reported in several other series.[4,14] There is no consensus regarding the ideal interval between cholecystectomy and radical surgery for patients with incidentally discovered GBC and the impact on survival of this interval is unknown.[15] The German recommendations are to perform the second intervention within six weeks after previous cholecystectomy.[16] In the current series there was no significant difference in time interval between patients who were deemed unresectable after prior cholecystectomy compared those with resectable disease within the incidental group. In other words, delay in referral to our tertiary center after prior cholecystectomy was not a risk factor for finding inoperable disease. Although non-significant, the interval was even somewhat longer for the resectable patients when compared to the unresectable patients within the incidental group. Since gallbladder carcinoma is known to be rapidly growing tumor with a tendency for early dissemination, the interval time could allow to identify patients with unfavorable tumor biology and precluded from major resection.

Impact of T-stage on surgical strategy

Although there is controversy regarding the optimal management for T1b lesion, our policy is to treat all patients with a radical resection when incidentally a T1b is diagnosed after cholecystectomy. Although no nodal or liver involvement in patients with T1b disease was noted in this study, previous published series reported a 15.6–20% incidence of nodal metastasis and 13% liver involvement.[10,17] Furthermore Ouchi et al. reported a 60% recurrence rate in patients with T1b disease treated by simple cholecystectomy.[10]

For pT2 disease, majority of reports have shown a benefit of radical resection.[18,19] Almost 20 years ago, Shirai et al. reported 5-year survival rate of 40% after simple cholecystectomy which increased to 90% in patients undergoing radical resection.[18] Furthermore, positive lymph nodes can be found in 20–62% of patients with pT2 disease.[18,19] In the current series 20% of patients with pT2 disease had positive lymph nodes and 20.8% had liver involvement. Hepatic invasion has been reported to occur in 51% of patients with advanced stage (stage III and IV) and was an independent prognostic factor in those series.[20] However, a recent study from the Memorial Sloan-Kettering Cancer Center (MSKCC) reported a 31% incidence of liver involvement in patients with pT2 disease.[21] The current study confirms the importance of liver involvement as an independent prognostic factor even in early stage disease. Liver involvement was so dominant that no other covariates remained in the model when cox proportional hazard regression was

performed. Previous reports suggested not all cases of T2 tumors should be treated with an aggressive resection and a curative resection for pT2 disease can be achieved without hepatectomy.[22,23] However, the plane of dissection for a simple cholecystectomy is the subserosal plane, therefore a simple cholecystectomy in patients with T2 disease could result in an involved margin if the tumor invades through the muscular layer of the gallbladder wall. On the basis of the current data, liver resection combined to hilar lymph node radical dissection must be performed in all resectable patients. Moreover we reported liver involvement in 20.8% of T2 tumors. These recommendations are supported by historical data demonstrating that a radical resection for pT2 GBC is associated with a two to fourfold increase in 5-year survival when compared to simple cholecystectomy alone (80% vs 20–40% respectively).[24,25]

In advanced gallbladder patients, the proportion of patients eligible for curative resection is known to be very limited. These results were confirmed in the current series, 28.6% (12/42) of T3 tumors and only one out of 24 patients (4.2%) with a T4 tumor were eligible for a curative resection. However, 5-year survival rates of 15–67% for T3 and 7–25% T4 have been reported.[4,8,26,27] Regarding the extent of resection, routine major hepatectomies (right hepatectomies or extended right hepatectomies) are recommended by several groups although these major resections are associated with increased morbidity and mortality.[28,29] However, survival benefit has been questioned recently by others.[30] No difference in long-term outcome between patients who underwent major hepatectomy and those submitted to a limited hepatic resection (segmentectomy IVB/V) was noted in a recent published series by D'Angelica et al.[30] In the current series, hepatic resection consisted of a bisegmentectomy (IVB + V) in most patients. In two 2 cases, a right extended hepatectomy to segment IV was necessary to have a curative (R0) resection.

Prognostic factors

Several published series have identified a number of prognostic factors that stratified patients with regard to prognosis following resection for GBC. Potentially significant factors included stage, nodal involvement, jaundice, incidental finding, choledochal invasion, differentiation, perineural invasion, R0 resection.[4,14,20,23,31–34] In the current series, univariate analysis also revealed that survival was significantly affected by perineural invasion, TNM stage, R0 resection, liver involvement and CA-19.9. Multivariate analysis revealed that liver involvement was so dominant that no other covariates remained. Therefore, once a carcinoma is incidentally found after prior cholecystectomy, depth of cancer invasion should be precisely determined by pathological examinations. Since a standard cholecystectomy is performed in the subserosal plane and since some patients with T2 (20.8% in the current series) have a risk of liver involvement, tumor cells will be left behind in the plane of dissection in those cases. Thus, all patients with pT2 disease should undergo a radical resection.

Conclusion

An aggressive surgical approach remains the mainstay of treatment in patients with localized GBC. The majority of patients with a potentially curable disease were patients with incidental GBC. Almost 80% of patients with nonincidental GBC presented with unresectable disease. For patients who underwent resection with curative intent, actuarial 5-year survival was 63.2% in the current series. The current study underlines the importance of liver involvement as an independent prognostic factor even in early stage disease. A radical resection in patients with pT2 or more is highly recommended.

Conflict of interest statement

The authors declare that they have nothing to disclose.

References

1. de Groen PC, Gores GJ, LaRusso NF, et al. Biliary tract cancers. *N Engl J Med* 1999;**341**:1368–78.
2. Carriaga M, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. *Cancer* 1995;**75**:171–90.
3. Henson D, Albores-Saavedra J, Corle D. Carcinoma of the gallbladder: histologic types, stage of disease, grade, and survival rates. *Cancer* 1992;**70**:1493–7.
4. Fong Y, Jarnagin W, Blumgart LH. Gallbladder cancer: comparism of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. *Ann Surg* 2000;**232**:557–69.
5. Rosenmuller M, Haapamaki MM, Nordin P, et al. Cholecystectomy in Sweden 2000–2003: a nationwide study on procedures, patient characteristics, and mortality. *BMC Gastroenterol* 2007;**7**:35.
6. Kozak LJ, DeFrances CJ, Hall MJ. National hospital discharge survey: 2004 annual summary with detailed diagnosis and procedure data. *Vital Health Stat 13* 2006;**162**:1–209.
7. Chan CP, Chang HC, Chen YL, et al. A 10-year experience of unsuspected gallbladder cancer after laparoscopic cholecystectomy. *Int Surg* 2003;**88**:175–9.
8. Misra S, Chatuverdi A, Misra NC, et al. Carcinoma of the gallbladder. *Lancet Oncol* 2003;**4**(3):167–76.
9. Smith GCS, Parks RW, Madhavan KK, et al. A 10-year experience in the management of gallbladder cancer. *HPB* 2003;**5**:159–66.
10. Ouchi K, Owada Y, Matsuno S, et al. Prognostic factors in the surgical treatment of gallbladder carcinoma. *Surgery* 1987;**101**:731–7.
11. Piehler JM, Crichlow RW. Primary carcinoma of the gallbladder. *Surg Gynecol Obstet* 1978;**147**:929–42.
12. Akyurek N, Irkorucu O, Salman B, et al. Unexpected gallbladder cancer during laparoscopic cholecystectomy. *J Hepatobiliary Pancreat Surg* 2004;**11**:357–61.
13. Gall FP, Kockerling F, Scheele J, et al. Radical operations for carcinoma of the gallbladder: present status in Germany. *World J Surg* 1991;**15**:328–36.
14. Shih S, Schulick R, Cameron J, et al. Gallbladder cancer: the role of laparoscopy and radical resection. *Ann Surg* 2007;**6**:893–901.
15. Regimbeau JM, Fuks D, Pruvot FR, et al. Cancer de la vésicule biliaire: principes du traitement chirurgical à visée curative. In: Monographies de l' AFC, editor. *Cholangiocarcinomes*. Paris: Arnette Blackwell; 2009, p. 102–51.

16. Goetze TO, Paolucci V. Benefits of reoperation of T2 and more advanced incidental gallbladdercarcinoma: analysis of the German registry. *Ann Surg* 2008;**247**:104–8.
17. Ogura Y, Mizumoto R, Isaji S, et al. Radical operations for carcinoma of the gallbladder. *World J Surg* 1991;**15**:337–43.
18. Shirai Y, Yoshida K, Tsukuda K, et al. Inapparent carcinoma gallbladder. *Ann Surg* 1992;**215**:326–31.
19. Chijiiwa K, Nakano K, Ueda J, et al. Surgical treatment of patients with T2 gallbladder carcinoma invading the subserosal layer. *J Am Coll Surg* 2001;**192**:600–7.
20. Murakami Y, Uemura K, Sudo T, et al. Prognostic factors of patients with advanced gallbladder carcinoma following aggressive surgical resection. *J Gastrointest Surg* 2011;**15**:1007–16.
21. Ito H, Ito K, D'Angelica M, et al. Accurate staging for gallbladder cancer: implications for surgical therapy and pathological assessment. *Ann Surg* 2011;**254**:320–5.
22. Wakai T, Shirai Y, Yokoyama N, et al. Depth of subserosal invasion predicts long-term survival after resection in patients with T2 gallbladder carcinoma. *Ann Surg Oncol* 2003;**10**:447–54.
23. Yokomizo H, Yamane T, Hirata T, et al. Surgical treatment of pT2 gallbladder carcinoma: a reevaluation of the therapeutic effect of hepatectomy and extrahepatic bile duct resection based on the long-term outcome. *Ann Surg Oncol* 2007;**14**:1366–73.
24. Shirai Y, Yoshida K, Tsukada K, et al. Radical surgery for gallbladder carcinoma. *Ann Surg* 1992;**216**:565–8.
25. de Aretxabala X, Roa IS, Burgos LA, et al. Curative resection in potentially resectable tumors of the gallbladder. *Eur J Surg* 1997;**163**:419–26.
26. Behari A, Sikora SS, Wagholikar GD, et al. Long-term survival after extended resections in patients with gallbladder cancer. *J Am Coll Surg* 2003;**196**:82–8.
27. Bartlett DL, Fong Y, Fortner JG, et al. Long-term results after resection for gallbladder cancer. Implications for staging and management. *Ann Surg* 1996;**224**:639–46.
28. Kondo S, Nimura Y, Hayakawa N, et al. Regional and para-aortic lymphadenectomy in radical surgery for advanced gallbladder carcinoma. *Br J Surg* 2000;**87**:418–22.
29. Todoroki T, Kawamoto T, Takahashi H, et al. Treatment of gallbladder cancer by radical resection. *Br J Surg* 1999;**86**:622–7.
30. D'Angelica M, Dalal KM, DeMatteo RP, et al. Analysis of the extent of resection for adenocarcinoma of the gallbladder. *Ann Surg Oncol* 2009;**16**(4):806–16.
31. Puhalla H, Wild T, Bareck E, et al. Long-term follow-up of surgically treated gallbladder cancer patients. *Eur J Surg Oncol* 2002;**28**:857–63.
32. Shimizu H, Kimura F, Yoshidome H, et al. Aggressive surgical approach for stage IV gallbladder carcinoma based on Japanese society of biliary surgery classification. *J Hepatobiliary Pancreat Surg* 2007; **14**:358–65.
33. Choi SB, Han HJ, Kim CY, et al. Surgical outcomes and prognostic outcomes for T2 gallbladder cancer following surgical resection. *J Gastrointest Surg* 2010;**14**:668–78.
34. Kim WS, Choi DW, You DD, et al. Risk factors influencing recurrence, patterns of recurrence, and the efficacy of adjuvant therapy after radical resection for gallbladder carcinoma. *J Gastrointest Surg* 2010; **14**:679–87.