World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i28.3567

World J Gastroenterol 2010 July 28; 16(28): 3567-3572
ISSN 1007-9327 (print)

BRIEF ARTICLE

Rational therapeutic strategy for T2 gallbladder carcinoma based on tumor spread

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Received: January 13, 2010 Revised: February 22, 2010
Accepted: February 29, 2010
Published online: July 28, 2010

Abstract

AIM: To evaluate the adequacy of surgical treatment of T2 gallbladder carcinoma (GBCa) according to tumor spread in the subserosal layer.

METHODS: A series of 84 patients with GBCa were treated at Saga University Hospital, Japan between April 1989 and October 2008. The tumor stage was graded according to the TNM staging for GBCa from the American Joint Committee on Cancer Manual 6th edition. Tumor staging revealed 30 patients with T2 tumors. T2 GBCa was divided into three groups histologically by the extent of tumor spread in the subserosal layer, using a score of ss minimum (ss min), ss medium (ss med) or ss massive (ss mas).

RESULTS: For ss min GBCa, there was no positive pathological factor and patient survival was satisfactory with simple cholecystectomy, with or without extra-hepatic bile duct resection. For ss med GBCa, some pathological factors, h-inf (hepatic infiltration), ly (lymphatic invasion) and n (lymph node metastasis), were positive. For ss mas GBCa, there was a high incidence of positive pathological factors. The patient group with extra-hepatic bile duct resection with D2 lymph node dissection (BDR with D2) and those with S4a5 hepatectomy had significantly better survival rates.

CONCLUSION: We suggest that radical surgery is not necessary for ss min GBCa, and partial hepatectomy and BDR are necessary for both ss med and ss mas GBCa.

Key words: Hepatectomy; Bile duct resection; Gallbladder carcinoma; Tumor spread

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Kohya N, Kitahara K, Miyazaki K. Rational therapeutic strategy for T2 gallbladder carcinoma based on tumor spread. *World J Gastroenterol* 2010; 16(28): 3567-3572 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i28/3567.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i28.3567

INTRODUCTION

Gallbladder carcinoma (GBCa) is a relatively rare tumor[1-3], however, its mortality has increased worldwide over the past few decades[4], and the prognosis still remains poor[1,2]. There is no effective therapy for GBCa, except for surgical resection. However, the overall 5-year survival rate is 5%-42.3%, even after radical resection of the tumor[1,2,5,6]. The prognosis for patients with early GBCa, defined as pT1a/b lesions, shows a 5-year survival rate of 82%-100%[6-9]. Due to the anatomical proximity to important organs, surgery for advanced gallbladder cancer requires an aggressive approach. For pT2 or more advanced tumors, many authors advocate radical resection with lymph node dissection[10-14]. Previous reports have shown a second radical resection to be associated with significantly better survival than cholecystectomy alone in pT2 GBCa

patients whose cancers were incidentally found after cholecystectomy[15-18], whereas, Wakai *et al*[19] have reported that 40.5% of patients with unapparent pT2 tumors survived > 5 years after cholecystectomy alone. S4a5 hepatectomy combined with extra-hepatic bile duct resection (BDR) and D2 lymph node dissection is a highly recommended operation for the treatment of T2 and T3 GBCa[6], although, in T2 GBCa, the surgical procedure remains controversial, and there is no standard operation.

Recent reports have shown improved survival in patients with bile duct cancer who were treated with newly developed chemotherapy agents, gemcitabine and S-1. Several studies of single-agent gemcitabine have reported response rates of 8%-60%, and a median survival time ranging from 6.5 to 11.5 mo[20-25]. S-1 is an oral anticancer drug that contains two biochemical modulators, 5-chloro-2,4-dihydroxypridine and potassium oxonate, which improve the tumor-selective toxicity of 5-fluorouracil (5-FU)[26]. A phase Ⅱ study of S-1 has shown promising results with response rates ranging from 21% to 35% in biliary tract cancer[27,28].

The present retrospective study evaluated the limits of extended resection, such as hepatectomy, extra-hepatic BDR, and pancreatoduodenectomy (PD), especially for T2 GBCa, according to the extent of tumor spread in the subserosal layer, and to the characteristics of the clinicopathological or the prognostic factors. The good candidates were therefore recommended to receive adjuvant chemotherapy in T2 GBCa to obtain better survival.

MATERIALS AND METHODS

Between April 1989 and October 2008, 84 consecutive patients, 27 men and 57 women, with GBCa underwent surgical resection at Saga University Hospital, Japan. The mean age was 67.6 years, with a range of 45-87 years. The clinical and histopathological staging was based on the 6th edition of the American Joint Committee on Cancer Manual[29]. Nine (10.7%) patients were classified as T1a, eight (9.5%) as T1b, 30 (35.7%) as T2, 31 (36.9%) as T3, and six (7.1%) as T4. We evaluated the 30 patients with T2 GBCa who were treated with resection. These patients were divided into three groups histologically, according to the extent of tumor spread in the subserosal layer, using resected specimens. The pathological sections were examined and diagnosed using the most invaded slice.

In Table 1, the subserosal cancer invasion score (ss score) was histologically determined by dividing the vertical and horizontal tumor spread in the subserosal layer into three groups according to the ss score. Finally the extent of the subserosal invasion was divided subjectively into three categories: namely, ss minimum (ss min), ss medium (ss med), and ss massive (ss mas). As a result, the tumors were classified as ss min in four specimens, ss med in 10, and ss mas in 16.

Our fundamental strategy of S4a5 hepatectomy for T2 GBCa was indicated for highly suspected subserosal or serosal invasion preoperatively, and BDR for highly suspected lymph node metastases along the hepatoduodenal ligament. PD or pylorus-preserving PD (PPPD) was added for highly suspected retro-pancreatic lymph node metastases or direct invasion to the duodenum.

Table 1 Extent of tumor spread by ss score

Vertical invasion	< 1/3 in depth	α: score 1
	⩾ 1/3 and < 2/3	β: score 2
	⩾ 2/3	γ: score 3
Horizontal invasion	< 5 mm	A: score 1
	⩾ 5 mm and < 10 mm	B: score 2
	⩾ 10 mm	C: score 3

The sum total of ss score was calculated. ss minimum (ss min): 2; ss medium (ss med): 3-4; ss massive (ss mas): 5-6.

Table 2 ss score and clinicopathological factors *n* (%)

	ss min (*n* = 4)	ss med (*n* = 10)	ss mas (*n* = 16)
h-inf (+)	0	5 (50.0)	2 (12.5)
b-inf (+)	0	0	1 (6.3)
ly (+)	0	6 (60.0)	15 (93.8)
v (+)	0	0	5 (35.7)
pn (+)	0	1 (10.0)	6 (37.5)
n (+)	0	3 (30.0)	4 (25.0)

h-inf: Hepatic invasion; b-inf: Bile duct invasion; ly: Lymphatic invasion; v: Venous invasion; pn: Peri-neural invasion; n: Lymph node metastasis.

Statistical analysis

The clinicopathological factors and patient survival were statistically analyzed. The χ^2 and Fisher's exact tests were used to compare the two groups, and the Mann-Whitney *U* test was used for differences between the means. The survival was calculated according to the Kaplan-Meier method and compared between the groups by the log-rank test. Cox proportional hazards models were applied for the multivariate analysis. A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

Relationship between ss score and pathological factors

Table 2 describes the relationship between ss classification and clinicopathological factors. The ss min group had no positive pathological factors. In the ss med group, pathological factors of h-inf (hepatic infiltration), ly (lymphatic invasion), pn (perineural invasion) and n (lymph node metastasis) were positive in 50%, 60%, 10%, and 30% of the patients, respectively. All pathological factors were positive at a high rate in the ss mas group. The positive rate of pathological factors increased along with the degree of the ss score.

Survival according to ss score

Figure 1A shows the disease-specific survival curve of the patients with T2 GBCa by ss classification. All the patients with ss min and ss med survived until the end of the follow-up period and the 5-year survival rate was 100% in

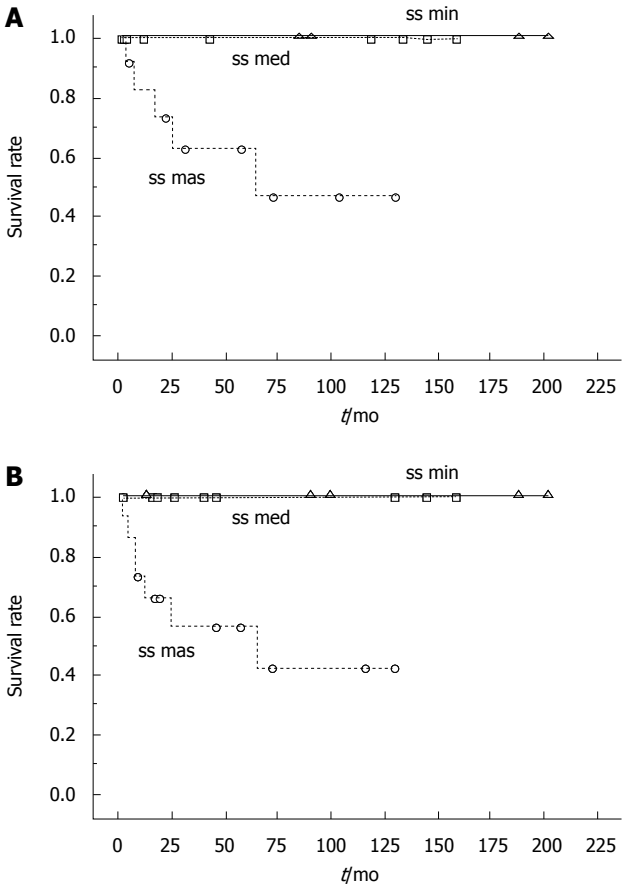

Figure 1 Kaplan-Meier survival analysis of patients with T2 gallbladder carcinoma by ss score. A: Disease-specific survival; the 5-year survival rate for ss min and ss med was 100%. In ss mas gallbladder carcinoma (GBCa), the 5-year survival rate was 59.7%; B: Disease-free survival; the 5-year survival rate for ss min and ss med was 100%. In ss mas GBCa, the 5-year survival rate was 56.6%.

the ss min and ss med groups. In ss mas GBCa, the survival was significantly worse than for ss min and ss med GBCa, and the 5-year survival rate was 59.7%. Figure 1B shows the disease-free survival curve. The 5-year survival rate in the ss min and ss med groups was 100%. In ss mas GBCa, the disease-free 5-year survival rate was 56.6%. There were seven patients with cancer recurrence in the ss mas group. The pattern of recurrence was three patients with lymph node recurrence, two with local recurrence, one with liver metastasis, and one with peritoneal dissemination.

Evaluation of surgical procedures in T2 GBCa

Table 3 summarizes the surgical procedures in each ss group. The procedure in ss min GBCa was based on simple cholecystectomy, and there was no hepatectomy, PD or PPPD. Six of 10 (60.0%) patients with ss med GBCa underwent S4a5 hepatectomy. In ss mas GBCa, the surgical procedures varied from simple cholecystectomy to extended right hepatectomy or PD, according to the mode of cancer spread.

Surgical procedures and survival in ss mas GBCa

To evaluate the appropriate surgical procedure for ss mas

Table 3 Surgical procedures in T2 gallbladder carcinoma

Surgical procedure	ss min (n = 4)	ss med (n = 10)	ss mas (n = 16)
Cx	3	2	3
Cx + Liver bed resection + D2ex			1
Cx + BDR + D2ex	1	2	1
S4a5 hepatectomy + D2ex		2	3
S4a5 hepatectomy + BDR+ D2ex		2	5
S4a5 hepatectomy + PD or PPPD		2	1
Extended right hepatectomy			1
PD alone			1

BDR: Bile duct resection; PD: Pancreatoduodenectomy; PPPD: Pylorus-preserving PD.

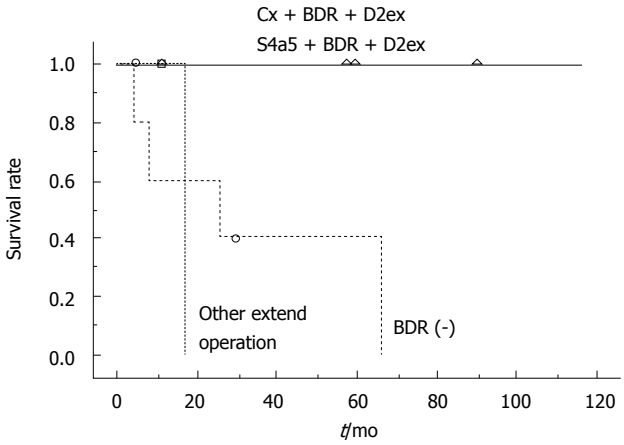

Figure 2 Kaplan-Meier survival analysis by surgical procedure for T2 gallbladder carcinoma. BDR: With extra-hepatic BDR; BDR (-): Without extra-hepatic BDR; S4a5: S4a5 hepatectomy; Cx: Simple cholecystectomy; D2ex: D2 lymph node dissection with para-aortic lymph node sampling. BDR: Bile duct resection.

GBCa, survival was analyzed according to the surgical procedures: simple cholecystectomy + extra-hepatic BDR + D2 lymph node dissection (Cx + BDR + D2ex); S4a5 hepatectomy + BDR + D2ex; S4a5 hepatectomy + PD (HPD); and cholecystectomy without BDR [Cx BDR (-)]. In ss mas GBCa, the Cx + BDR + D2ex and S4a5 + BDR + D2ex groups showed significantly better survival than the other groups (Figure 2). The 5-year survival of the Cx BDR(-) group was 33.3%, which was worse than for the Cx + BDR + D2ex group. Other extended operations, including HPD, PD, and extended hepatectomy, showed a dismal outcome. Surgery in these patients revealed massive lymph node metastasis during the operation.

DISCUSSION

In spite of the recent progress in diagnostic modalities, GBCa still tends to be found at an advanced stage[30], and only 15%-40% of patients who present with GBCa are candidates for surgical intervention[31]. Surgical management of T1 GBCa reveals almost no lymph node involvement and shows a relatively sufficient 5-year survival rate of 82%-100% with simple cholecystectomy[8,9,19].

The surgical management of T2 GBCa remains controversial. In these patients, the appropriateness of simple cholecystectomy versus radical resection remains the subject of debate. Some groups believe that most T2 lesions require only simple cholecystectomy, thus contending that radical resection is unnecessary and should be reserved for only a small subset of patients who meet certain pathological criteria[32-34]. On the other hand, proponents of radical resection believe that all T2 lesions should be treated with radical resection, because 40% of these patients will have residual lymphatic disease after resection. Radical cholecystectomy is associated with a significant survival benefit when liver surgery can be performed with minimal mortality and acceptable morbidity[35-37]. Radical surgery consisting of partial hepatectomy around the gallbladder fossa, and regional lymphadenectomy with or without resection of the extra-hepatic bile duct, yields 50%-86% 5-year survival rates[38-41]. Wakai *et al*[33] have reported the significance of the depth of subserosal invasion in patients with pT2 GBCa. The incidence of lymph node metastasis is significantly higher in patients with subserosal invasion > 2 mm (63%) than in patients with invasion < 2 mm (27%). Sasaki *et al*[42] have reported that lymph node involvement is seen in 33.3% of ss1, the upper third of subserosal invasion, 37.5% of ss2, middle third of subserosal invasion, and 85.7% of ss3, lower third of subserosal invasion. In the current study, the 5-year survival rate for T2 GBCa was 78.3%, including patients who underwent whole surgical procedures (data not shown). No positive pathological factors were observed in the ss min patient group, and simple cholecystectomy with or without extrahepatic BDR was associated with good survival (Table 3 and Figure 1). These data indicate that radical surgery, such as a hepatectomy or PD, is not necessary for ss min GBCa. For ss med GBCa, there were some positive pathological factors, h-inf, ly, pn, and n (Table 1). Partial hepatectomy, such as S4a5 hepatectomy or liver bed resection, and complete lymphadenectomy including BDR might therefore be necessary for ss med GBCa. For ss mas GBCa, a high incidence of multiple pathological factors was observed. Figure 2 shows that patients without BDR had a dismal outcome. To achieve better survival for ss mas GBCa, partial hepatectomy, such as S4a5 hepatectomy or liver bed resection, and complete lymphadenectomy including BDR, are the minimum requirement. However, radical surgery, such as major hepatectomy or hepatectomy with PD, had no survival benefit. In addition, the importance of S4a5 hepatectomy and BDR for T2 and T3 GBCa has also been previously reported[6].

To avoid unnecessary surgery, such as extended resection for ss min GBCa, the actual depth of GBCa in the subserosal layer should be determined pre- or intraoperatively. No report has previously described an effective pre- or intraoperative method to determine the actual extent of subserosal invasion. In addition, previous studies have employed intraoperative ultrasonography and frozen section histology to detect the actual depth of subserosal invasion, but it is still not sufficiently accurate, as well as being very difficult to determine the actual depth of invasion intraoperatively. A new method for the pre- or intraoperative determination of the actual extent of subserosal invasion is necessary to avoid unnecessary operation.

There is no current standard chemotherapy in advanced gallbladder cancer. In previous studies that have used chemotherapeutic agents, 5-FU, mitomycin C, methotrexate, etoposide, doxorubicin, or cisplatin, against biliary tract tumors, only 10%-20% revealed a partial response[43-46]. However, gemcitabine has shown remarkable biological activity against biliary tract cancers in some clinical studies. Several reports have described the efficacy of single-agent gemcitabine, with a response rate of approximately 30% and a median survival time of approximately 15 mo, and phase Ⅱ investigations into a gemcitabine-based combination have increased[47,48]. Gemcitabine is a novel nucleoside analog that demonstrates biological activities in a broad spectrum of solid tumors[49]. The ribonucleotide reductase subunit M1 (RRM1) plays an important role in gemcitabine resistance for biliary tract carcinomas. The expression of RRM1 has been investigated as a drug sensitivity marker for gemcitabine therapy of biliary tract carcinoma, through *in vitro* study and clinical analysis[50]. These results indicate that ss mas cancer with low RRM1 expression is therefore a good candidate for gemcitabine adjuvant chemotherapy to achieve better survival after surgical resection. S-1 has greater inhibition of thymidylate synthase (TS) and pemetrexed is classified as a multi-targeted antifolate. Orotate phosphoribosyl transferase (OPRT), dihydropyrimidine dehydrogenase (DPD) and TS play a critical role in the efficacy of antifolates. A low level of DPD and TS activity, and a high level of OPRT activity enhance the antitumor effect of S-1[51]. A phase Ⅱ study of S-1 in biliary tract cancer has shown promising results with a response rate of 21%-35%[27,28], and S-1 can be expected to have a good effect on gallbladder cancer. In T2 GBCa, ss mas cancers showed a high rate of recurrence, regardless of the radical surgical approach. Therefore, patients with ss mas cancer are thus considered to be good candidates for gemcitabine or S-1 adjuvant chemotherapy. Further studies of adjuvant chemotherapy against gallbladder cancer are necessary. The current algorithm of therapeutic strategy for T2 GBCa is shown in Figure 3.

In conclusion, the surgical management of T2 GBCa remains controversial. Radical surgery is not necessary for ss min GBCa. Furthermore, BDR may be necessary to complete lymphadenectomy for the hepato-duodenal ligament to achieve better survival for ss med and ss mas GBCa. S4a5 hepatectomy also contributed to better survival for ss med and ss mas GBCa. S4a5 hepatectomy with extra-hepatic BDR and lymphadenectomy should therefore be a standard operation for the treatment of ss med and ss mas GBCa. However, new methods for the pre- or intraoperative detection of the actual extent of subserosal invasion are still necessary to avoid unnecessary operations. In ss mas GBCa, survival remains unsatisfactory. Patients with ss mas GBCa are therefore

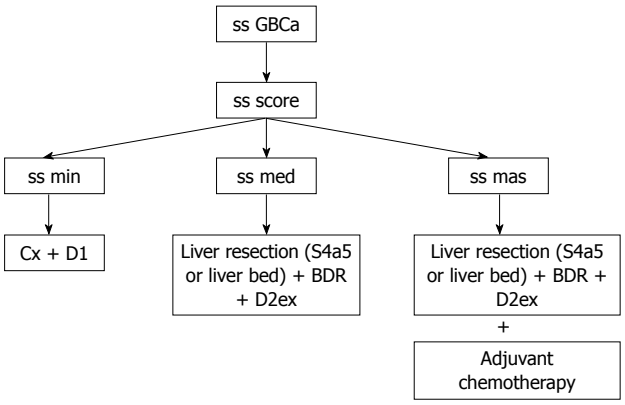

Figure 3 Algorithm of therapeutic strategy for T2 gallbladder carcinoma. Cx: Simple cholecystectomy; BDR: With extra-hepatic BDR; S4a5: S4a5 hepatectomy; D2ex: D2 lymph node dissection with para-aortic lymph node sampling.

considered to be good candidates for gemcitabine or S-1 adjuvant chemotherapy to achieve better survival.

COMMENTS

Background

Gallbladder carcinoma (GBCa) is a relatively rare tumor, however, the mortality of this tumor has increased worldwide over the past few decades, and the prognosis still remains poor. There is no effective therapy for GBCa, except for surgical resection. The prognosis for patients with early GBCa is good even with only cholecystectomy, but that for patients with advanced GBCa is poor even after radical surgery. The surgical management of T2 GBCa remains controversial.

Research frontiers

T2 GBCa was divided into three groups histologically by the extent of tumor spread in subserosal layer using the ss score. The ss score was histologically determined by dividing the vertical and horizontal tumor spread in the subserosal layer. Finally the extent of the subserosal invasion was divided subjectively into three categories: ss minimum (ss min), ss medium (ss med) and ss massive (ss mas).

Innovations and breakthroughs

For ss min GBCa, there was no positive pathological factor and survival was satisfactory after simple cholecystectomy. For ss med GBCa, some pathological factors were positive. For ss mas GBCa, there was a high incidence of positive pathological factors.

Applications

After surgical procedure analysis of T2 GBCa, the patient group with extra-hepatic bile duct resection with D2 lymph node dissection, and the group with S4a5 hepatectomy had significantly better survival rates. In ss mas GBCa, the survival of the patients remains unsatisfactory. Patients with ss mas GBCa are therefore considered to be good candidates for chemotherapy to achieve better survival.

Terminology

S4a5 hepatectomy is a type of hepatectomy for advanced GBCa. S4 is the lower half of the left medial segment of the liver, and S5 is the anterior medial segment of the liver, according to the Couinaud classification of liver segments. D2 lymph node dissection is based on the method described in the General Rules for Surgical and Pathological Studies on Cancer of the Biliary Tract from the Japanese Society of Biliary Surgery, 5th edition, 2003.

Peer review

This study investigated an important subject, namely, the best therapeutic approach for GBCa.

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