Practical Guidelines for the Surgical Treatment of Gallbladder Cancer

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Received: 10 June 2014  Accepted: 24 July 2014

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At present, surgical treatment is the only curative option for gallbladder (GB) cancer. Many efforts therefore have been made to improve resectability and the survival rate. However, GB cancer has a low incidence, and no randomized, controlled trials have been conducted to establish the optimal treatment modalities. The present guidelines include recent recommendations based on current understanding and highlight controversial issues that require further research. For T1a GB cancer, the optimal treatment modality is simple cholecystectomy, which can be carried out as either a laparotomy or a laparoscopic surgery. For T1b GB cancer, either simple or an extended cholecystectomy is appropriate. An extended cholecystectomy is generally recommended for patients with GB cancer at stage T2 or above. In extended cholecystectomy, a wedge resection of the GB bed or a segmentectomy IVb/V can be performed and the optimal extent of lymph node dissection should include the cystic duct lymph node, the common bile duct lymph node, the lymph nodes around the hepatoduodenal ligament (the hepatic artery and portal vein lymph nodes), and the posterior superior pancreaticoduodenal lymph node. Depending on patient status and disease severity, surgeons may decide to perform palliative surgeries.

Keywords: Gallbladder; Neoplasm; General Surgery; Guideline

INTRODUCTION

According to the Korea Central Cancer Registry’s annual report of 2011, as published by the Korean Ministry of Health and Welfare, gallbladder (GB) cancer accounts for 1.1% of all cancers in Korea, making it the 11th most prevalent cancer in the country (1). In patients aged 65 yr or older, it is the fifth most prevalent cancer. Its incidence continually increased between 1999 and 2002 and given that Korea is an aging society, this trend is expected to continue. It is therefore imperative to establish practical guidelines for the diagnosis and appropriate treatment of GB cancer.

GB cancer can be cured with radical surgery, and many efforts have been made in the attempt to improve resectability and the survival rate. However, GB cancer has a low incidence, and no randomized, controlled trials have been conducted to establish the optimal treatment modalities. Although a few retrospective studies have been conducted in large series of patients with GB cancer, these have been limited in scope. Treatment guidelines for GB cancer have been published in peer-reviewed journals in countries outside of Korea, but these have been limited in their provision of established, evidence-based rationales for the most optimum surgical treatment of GB cancer (2-4). The Korean Association of Hepato-Biliary and Pancreas Surgery conducted a systematic review of the Korean and English literature to establish standard treatment guidelines for GB cancer and to improve treatment outcomes. The treatment guidelines described herein present evidence-based rationales to assist our colleagues in establishing optimal treatment strategies for GB cancer patients in clinical settings. Recommendations for treatment are noted (the grades of these recommendations are defined in Table 1) and the levels of evidence are also given (in parentheses) in the reference citations (see the definitions of levels in Table 2).
SURGICAL APPROACHES FOR PATIENTS WITH SUSPECTED GB CANCER

According to published treatment guidelines, it is recommended that patients undergo laparotomy if they are suspected of having GB cancer based on the preoperative work-up (2, 3). This is based on the rationale that GB cancer should be treated by surgical modalities, such as laparotomic cholecystectomy, hepatectomy for GB fossa, and lymph node dissection. However, several recent studies have recommended that a simple cholecystectomy should be the standard treatment modality for T1 GB cancer (5-11). Laparoscopic cholecystectomy has shown equivalent or better treatment outcomes compared to those for laparotomy (5-7). This has led to the suggestion that patients should undergo laparoscopic cholecystectomy unless there is evidence of invasion to the GB fossa (Level of evidence 4, Level of recommendation B). Otherwise, a laparotomy would be advised (Level of evidence 3, Level of recommendation B). Table 3 summarizes the recommendation for suspected GB cancer.

Table 1. Definitions of evidence by level

| Levels | Definition of evidence |
|--------|-----------------------|
| 1      | Evidence obtained from systematic review (SR) of all the randomized controlled trials (RCTs) |
| 2      | Evidence obtained from more than one well-controlled RCT |
| 3      | Evidence obtained from well-controlled trials (CT), multi-center cohorts, or case-control studies or that were obtained from longitudinal studies without intervention |
| 4      | Evidence obtained from the clinical experiences of key opinion leaders or those obtained from study |

Table 2. Recommendation levels

| Level of recommendation | Conditions |
|-------------------------|------------|
| A                       | There is a sufficient amount of clinical evidence to make convincing recommendations and agreement has been reached among the board members as to the appropriateness of recommendations. |
| B                       | There is an insufficient amount of clinical evidence. However, based on low-level clinical evidence, agreement has still been reached among the board members as to the appropriateness of these recommendations. |
| C                       | Recommendations have been made based on low-level clinical evidence. No agreement has been reached on whether such recommendations are appropriate, although there is no great disagreement among the board members. |
| D                       | There is great disagreement among the board members on the recommendations. |

Table 3. Summary of recommendations for patients with suspicious GB cancer

| Surgical intervention | Level of evidence | Level of recommendation |
|-----------------------|-------------------|-------------------------|
| Patients may undergo laparoscopic cholecystectomy unless there is preoperative evidence of GB fossa invasion. | 4 | B |
| Laparotomy is recommended for definite preoperative evidence of GB fossa invasion. | 3 | B |

Table 4. Summary of recommendations for patients with T1a GB cancer

| Surgical intervention | Level of evidence | Level of recommendation |
|-----------------------|-------------------|-------------------------|
| The optimal treatment modality for T1a GB cancer is simple cholecystectomy, which can be carried out as either a laparotomy or a laparoscopic surgery. | 3 | A |
| A histopathologic examination should be performed to evaluate whether there is invasion in the resection margin of the cystic duct. | 3 | A |
| Intraoperative perforation of the GB should be avoided, and the resected GB should be removed using a vinyl bag during laparoscopic surgery. | 3 | A |

SURGICAL TREATMENT FOR EARLY GB CANCER

T1a GB cancer

Based on a literature review, simple cholecystectomy is the optimal treatment for patients with T1a GB cancer confined to mucosa. Laparoscopic cholecystectomy is also an appropriate modality (5-8, 12, 13). The five-year survival rate for simple cholecystectomy is as high as 95%-100%. An extended cholecystectomy is not effective in prolonging long-term survival unless there are tumor invasions into the resection margin of the cystic duct (9). According to a systematic review of the T1a GB cancer literature, the recurrence rate is 1.1% in such cases. The most frequent site of recurrence was the common bile duct (6) (more than 50% of the total cases). Therefore, histopathologic examination should be performed to determine whether there are tumor invasions into the resection margin of the cystic duct. If this is the case, extrahepatic bile duct (EHBD) resection should be considered (6, 7) (Level of evidence 3, level of recommendation A). Lymph node metastasis has been reported in less than 2.5% of total cases; therefore, lymph node dissection is not recommended for patients with T1a GB cancer (6, 10). The five-year survival rate is estimated at 100% for T1a GB patients who undergo laparoscopic cholecystectomy (6, 7), but there are some reports that bile juice leakage during laparoscopic cholecystectomy associated with peritoneal metastasis and tumor recurrence at trocar sites. As such the surgical procedure should be carefully performed so as to prevent intraoperative GB perforation, and the resected GB should be removed using a vinyl bag (6, 12) (Level of evidence 3, level of recommendation A). Table
Table 5. Summary of recommendations for patients with T1b GB cancer

| Surgical intervention                                                                 | Level of evidence | Level of recommendation |
|-------------------------------------------------------------------------------------|------------------|------------------------|
| There is an insufficient amount of clinical evidence demonstrating that extended cholecystectomy increases T1b GB cancer patient survival. It can therefore be inferred that either simple or an extended cholecystectomy is appropriate. | 3                | B                      |
| There is no evidence demonstrating that a laparoscopic cholecystectomy is likely to lead to a poor prognosis. It can therefore be inferred that laparoscopic cholecystectomy may be performed. | 3                | B                      |
| Extended cholecystectomy can be carried out in patients who are not at increased risk for developing postoperative complications. | 3                | B                      |
| Histopathologic examination should be performed to evaluate whether there is invasion in the resection margin of the cystic duct. | 3                | A                      |
| To avoid intraoperative perforation of the GB, special attention should be paid to surgical procedures. During the laparoscopic surgery, the resected GB should be removed using a vinyl bag. | 3                | A                      |

Table 6. Summary of recommendations for extent of hepatic resection or lymph node dissection in extended cholecystectomy

| Surgical intervention                                                                 | Level of evidence | Level of recommendation |
|-------------------------------------------------------------------------------------|------------------|------------------------|
| A wedge resection of the GB bed or a segmentectomy IVb/V can be performed.           | 3                | B                      |
| Regional lymph node dissection is routinely performed within an extended cholecystectomy. The optimal extent of lymph node dissection should include the cystic duct lymph node, the common bile duct lymph node, the lymph nodes around the hepatoduodenal ligament (the hepatic artery and portal vein lymph nodes), and the posterior superior pancreaticoduodenal lymph node. | 3                | C                      |
| For accurate determination of the TNM stage, more than three lymph nodes should be collected for histopathologic examinations. | 4                | C                      |

4 summarizes the recommendations for T1a GB cancer.

T1b GB cancer
There is no clear evidence that extended cholecystectomy increases survival compared to the results for simple cholecystectomy in patients with T1b GB cancer (5, 6, 12). Moreover, several studies have shown that there is no significant difference in five-year survival between patients who undergo laparoscopic cholecystectomy and those who undergo laparotomy. It can therefore be inferred that laparoscopic cholecystectomy is not associated with poor prognosis (8, 11, 12). According to a systematic review of the T1 GB cancer literature, lymph node metastasis is present in approximately 11% of all cases, and the recurrence rate is 9.3% (6). However, this rate is higher in patients with T1b GB cancer who have undergone simple cholecystectomy (5, 6). Although there is a lack of clear evidence demonstrating that extended cholecystectomy increases patient’s survival as compared with a simple cholecystectomy, the former may nevertheless be recommended for patients who are not at increased risk of developing postoperative complications in that simple cholecystectomy has a relatively higher recurrence rate (6, 7, 9, 14) (Level of evidence 3, level of recommendation B). Table 5 summarizes the recommendations for T1b GB cancer.

SURGICAL TREATMENTS FOR OTHER GB CANCER STAGES
An extended cholecystectomy is generally recommended for patients with GB cancer at stage T2 or above (15-20) (Level of evidence 3, Level of recommendation B). In patients who are indicated for radical cholecystectomy, a combined approach can also be considered.

Extent of hepatic resection in extended cholecystectomy
A wedge resection of the GB bed or segmentectomy IVb/V can be performed (Level of evidence 3, Level of recommendation B). In a wedge resection, it is recommended that the hepatic resection margin width should be proposed to be approximately 2-3 cm; however, there is by no means universal consensus on this point. Table 6 summarizes the recommendations for the ideal extent of hepatic resection in extended cholecystectomy.

Extent of lymph node dissection in extended cholecystectomy
Lymph node metastasis is a well-known prognostic indicator, and its incidence varies depending on the depth of mural invasion as follows: pT1a, 0%-2.5%; pT1b, 5%-16%; pT2, 9%-30%; T3, 39%-72%; and T4, 67%-80% (6, 9, 21, 22). There is no consensus on the optimal extent of lymph node dissection in extended cholecystectomy for GB cancer patients. The seventh edition of the AJCC Cancer Staging Manual (23), defines, regional lymph node group 1 (N1) as comprising the cystic duct lymph node, common bile duct lymph node, and the lymph nodes around the hepatoduodenal ligament (i.e., the hepatic artery and portal vein lymph nodes). The posterior pancreaticoduodenal lymph node, celiac artery lymph node, superior mesenteric artery lymph node, para-aortic lymph node, and pericaval lymph node are classified as belonging to regional lymph node group 2 (N2). N2 metastasis would be interpreted as remote metastasis, and such patients would be classified as TNM IVB. In most cases, the long-term survival cannot be predicted for patients with N2 metastasis, and radical lymph node dissection is not routinely performed (17, 24-26). Regional lymph node dissection is recommended for the cystic duct lymph node, common bile duct lymph node, the lymph nodes...
around the hepatoduodenal ligament (hepatic artery and portal vein lymph nodes), and the posterior superior pancreaticoduodenal lymph node (Level of evidence 3, Level of recommendation C). There is no consensus on the minimum or optimal number of resected lymph nodes required to accurately determine the TNM stage. The sixth edition of the AJCC Staging Manual stated that more than three lymph nodes are required to accurately determine the N-stage. However, this point was deleted in the manual’s seventh edition. Some surgeons are of the opinion that only 3-4 lymph nodes can be collected despite N1 regional lymph node dissection although 1-2 lymph nodes can be collected using a simple cholecystectomy. Based on this, we propose that more than three lymph nodes should be collected for histopathologic examinations (Level of evidence 4, Level of recommendation C). Table 7 summarizes the recommendations for extent of the optimal lymph node dissection in extended cholecystectomy.

### Clinical significance of extrahepatic bile duct resection in radical surgery

Since the early 1990s, it has been maintained that EHBD resection should be performed for GC cancer irrespective of the TNM stage (27). This is based on the rationale that this procedure achieves complete lymph nodes resection around the hepatoduodenal ligament in early GC cancer and also helps achieve radical tumor mass resection with perineural invasion in advanced GC cancer. However, it has been subsequently found that EHBD resection is not associated with increased survival (28-32). There are also contradictory reports that the incidence of early and late-stage complications is increased by this procedure (28, 33). Therefore, EHBD resection should not be seen as mandatory in the radical resection of GC cancer but rather as an option to be selectively performed in specific types of cases, such as GC cancer with extrahepatic bile duct invasion (Level of evidence 3, Level of recommendation C). Table 7 summarizes the recommendations for EHBD resection in radical surgery.

### Clinical significance of surgery in GC cancer patients with para-aortic lymph node metastasis

It is generally known that patients with advanced GC cancer with para-aortic lymph node metastasis are contraindicated in surgery. However, it has been reported that survival is significantly prolonged following radical resection that includes para-aortic lymph node dissection in patients with GC cancer with para-aortic lymph node metastasis, compared to results for patients with distant metastasis or advanced, unresectable GC cancer (34). Conversely, another study reported that patients with TNM stage III or IV GC cancer should undergo extended lymph node dissection involving the para-aortic lymph node (35). Currently, surgical treatment efficacy cannot be predicted in GC cancer patients with para-aortic lymph node metastasis. The decision to perform radical surgery should thus be based on the surgeon’s judgment (Level of evidence 3, Level of recommendation C). Table 7 summarizes the recommendations for surgery in GC cancer patients with para-aortic lymph node metastasis.

### Clinical significance of surgical treatments in patients with invasion of the hepatic artery, portal vein, and adjacent organs

Very poor prognoses are expected in advanced GB cancer cases, and most patients refuse to undergo surgery when invasion of the hepatic artery and portal vein are suspected. Kobayashi et al. (36) performed analysis in 71 patients with GB cancer and found that the prognosis was poorer if surgeons performed a combined resection of the hepatic artery and portal vein for patients with invasion of both vessels as compared with results for those patients who had no invasion. Moreover, the authors reported that invasion of the hepatic artery and portal vein is a key prognostic indicator (36, 37). There are no effective treatment modalities other than surgery for patients with GC cancer. Surgical treatments are recommended for GC cancer patients if complete tumor removal (R0 resection) can be achieved through a combined resection of the hepatic artery and portal vein (Level of evidence 3, Level of recommendation C).

Combined resection is routinely recommended for advanced GB cancer cases in which there is invasion of adjacent organs (colon and duodenum). As this requires both a combined resection and R0 resection, favorable prognoses are not guaranteed. The selection of appropriate patients is essential (38) (Level of evidence 3, Level of recommendation C). Table 7 summarizes the recommendations for surgical treatment in patients with invasion of the hepatic artery, portal vein, and adjacent organs.

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**Table 7. Summary of recommendations for extrahepatic bile duct (EHBD) resection in radical surgery, surgery in GC cancer patients with para-aortic lymph node metastasis, surgical treatments in patients with invasion of the hepatic artery, portal vein, and adjacent organs, and palliative surgery in patients who are not indicated for radical surgery**

| Surgical resection | Level of evidence | Level of recommendation |
|--------------------|-------------------|-------------------------|
| EHBD resection is not mandatory for radical resection of GC cancer, but can be performed in certain cases. | 3 | C |
| In patients with GC cancer with para-aortic lymph node metastasis, radical surgery can also be performed based on the surgeon’s judgment. | 3 | C |
| Both combined resection and R0 one are essential for achieving a good prognosis. A combined resection of the adjacent organs cannot guarantee a good prognosis for all the patients. Selection of appropriate patients is therefore essential. | 3 | C |
| Depending on patient status and disease severity, surgeons may decide to perform palliative surgeries, such as non-radical cholecystectomy, biliary bypass surgery, or gastric bypass surgery. | 3 | C |
Clinical significance of palliative surgery in patients who are not indicated for radical surgery

The median and one-year survival rates in patients with unresectable GB cancer are reported to be approximately 2–4 months and less than 5%, respectively. It is also known that cytoreductive surgery is not useful in patients with GB cancer (39–42). However, palliative surgery will most likely be able to prolong the short-term survival period and improve the quality of life of patients with unresectable GB cancer. Palliative surgery options here include non-radical, simple cholecystectomy. If biliary atresia or gastric outlet obstruction are concurrently present, bypass surgery would also improve patient quality of life. Surgeons should therefore decide the optimal treatment modality in view of the patient status involved (43, 44) (Level of evidence 3, Level of recommendation C). Table 7 summarizes the recommendations for palliative surgery in patients who are not indicated for radical surgery.

**TREATMENT OF INCIDENTALLY FOUND GB CANCER AFTER CHOLECYSTECTOMY**

GB cancer incidentally found on postoperative histopathology

The core principles for the surgical treatment of GB cancer incidentally found on postoperative histopathology are identical to those described earlier. That is, no additional surgeries should be considered for histologically-proven T1a GB cancer if the GB was completely resected during surgery (5–8, 12, 13) (Level of evidence 3, Level of recommendation A). However, in cases of histologically-proven T1b GB cancer, there is still controversy regarding whether extended cholecystectomy or follow-up without additional surgeries should be performed (5, 6, 8, 11, 12) (Level of evidence 3, Level of recommendation B). In cases of GB cancer at T2 or above, the additional use of extended cholecystectomy is recommended (Level of evidence 3, Level of recommendation B). There are no established reports regarding the timing of additional surgeries; however, some studies have been performed immediately after GB cancer diagnosis (45, 46) (Level of evidence 3, Level of recommendation C). Table 8 summarizes the recommendations for GB cancer incidentally found on postoperative histopathology.

**GB cancer incidentally found during surgery**

The surgical treatment principles for histologically-proven GB cancer found during surgery are identical to those for GB cancer incidentally found on postoperative histopathology. However, in patients who are suspected of having T1 GB cancer during surgery, it is difficult to differentiate between T1a and T1b cancers. Therefore, extended cholecystectomy should be the first-choice treatment. It is recommended that additional surgeries should be determined based on the postoperative histopathology (Level of evidence 4, Level of recommendation C). In GB cancer at T2 or above, extended cholecystectomy should be performed based on a tentative or revised diagnosis (Level of evidence 4, Level of recommendation C). Table 9 summarizes the recommendations for GB cancer incidentally found during surgery.

**SURGICAL TREATMENT OF GB CANCER ACCOMPANIED BY ACUTE CHOLECYSTITIS**

GB cancer is often accompanied by bile stones, leading to acute cholecystitis symptoms in many cases. There are no accurate reports on the incidence of acute cholecystitis, although it has been reported to range from 8.8% to 20% (47–49). A preoperative differential diagnosis of acute cholecystitis accompanied by GB cancer is essential for determining surgical plans, but there are some situations in which such a differential diagnosis is difficult. Indeed, surgery should possibly be delayed in patients with GB cancer who have concurrent acute cholecystitis. In addition, the appropriate extent of surgery cannot be intraoperatively determined, leading to poor prognoses (50). Surgeons are recommended to consider the possibility of GB can-
cer in patients who are suspected of having acute cholecystitis if they are older and exhibit focal GB wall thickening, a mass within the internal GB lumen, overall GB wall thickening with decreased GB size, or lymphadenopathy around the GB (51) (Level of evidence 4, Level of recommendation C).

POSTOPERATIVE ADJUVANT THERAPY

Complete surgical excision of GB cancer is the only radical treatment modality at present, but the rate of resection is at most 25%-30%. Nearly half of patients are at increased risk for recurrent GB cancer despite having undergone complete resection (52, 53). Recurrent GB cancer may be the result of distant metastasis, but it may also be characterized by local recurrence (54-56). Patients with recurrent GB cancer are therefore required to undergo local treatment modalities, such as postoperative adjuvant chemotherapy or concurrent chemoradiation therapy (CCRT). For postoperative adjuvant chemotherapy, fluoropyrimidine drugs such as 5-fluorouracil or capecitabine are the preferred choice. CCRT is also recommended to be carried out in conjunction with these drugs. Depending on patient status or surgeon preference, monotherapy or combination treatment regimens using gemcitabine or fluoropyrimidine may also be considered (6). However, postoperative adjuvant chemotherapy or CCRT are not recommended in patients with T1 GB cancer who have undergone radical resection (58-60) (Level of evidence 3, Level of recommendation C). Table 10 summarizes the recommendations for the optimum postoperative adjuvant therapy for GB cancer.

CONCLUSIONS

There are no randomized, prospective studies assessing the surgical treatments for GB cancer. Moreover, there are only a few systematic reviews of the GB cancer surgical literature. There are many retrospective studies in this series, but when taken as a whole, these have the following limitations: 1) small numbers of enrolled patients; 2) heterogeneity of patient populations across studies, and 3) inconsistent surgical procedures across studies. Therefore, we experienced considerable difficulty in drawing conclusions and developing recommendations based on the existing clinical evidence. Nevertheless, the current report is based on a systematic review of the literature and in-depth discussion among board members. We believe that these treatment guidelines are of value for selecting the optimal surgical modalities in GB cancer patients.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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REFERENCES

1. Ministry of Health and Welfare, Korea Central Cancer Registry, National Cancer Center. Annual report of cancer statistics in Korea in 2009. Available at http://ncc.re.kr/manage/manage03_033_views.jsp?bbsnum=229 &htmlSearch=&hTxtKeyword=&current_page=1&cd=null [accessed on 1 September 2014].
2. Ettinger DS, Agulnik M, Cates JM, Cristea M, Denlinger CS, Eaton KD, Fidias PM, Gierada D, Gockerman JP, Handorf CR, et al. Occult primary. J Natl Compr Canc Netw 2011; 9: 1358-95.
3. Kondo S, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Nagino M, Furuse J, Saito H, Tsuyuguchi T, Yamamoto M, et al. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. J Hepatobiliary Pancreat Surg 2008; 15: 41-54.
4. Eckel F, Brummer T, Jelic S, ESMO Guidelines Working Group. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011; 22: v40-4.
5. Lee SE, Jang JY, Kim SW. The surgical strategy for treating T1 gallbladder cancer. Korean J Hepatobiliary Pancreat Surg 2009; 13: 69-75.
6. Lee SE, Jang JY, Lim CS, Kang MJ, Kim SW. Systematic review on the surgical treatment for T1 gallbladder cancer. World J Gastroenterol 2011; 17: 174-80.
7. Hardiman KM, Sheppard BC. What to do when the pathology from last

Table 10. Summary of recommendations for postoperative adjuvant therapy for GB cancer

| Adjuvant therapy | Level of evidence | Level of recommendation |
|------------------|-------------------|-------------------------|
| Anti-cancer chemotherapy regimens involving fluoropyrimidine or gemcitabine or their combinations with local radiotherapy i.e., CCRT, can be used. | 3 | C |
| Postoperative adjuvant chemotherapy and CCRT are not recommended for T1 GB cancer patients who have undergone radical resection. | 3 | C |
week's laparoscopic cholecystectomy is malignant and T1 or T2. J Gastrointest Surg 2009; 13: 2037-9.
8. Lee HS, Kim KS, Choi JS, Lee SH, Lee WJ, Kim BR. Gallbladder carcinoma diagnosed after laparoscopic cholecystectomy. Korean J Hepatobiliary Pancreat Surg 2002; 6: 73-9.
9. Isambert M, Leux C, Météairie S, Puineau J. Incidentally-discovered gallbladder cancer: When, why and which resection? J Visc Surg 2011; 148:e77-84.
10. Pilgrim C, Usatoff V, Evans PM. A review of the surgical strategies for the management of gallbladder carcinoma based on T stage and growth type of the tumour. Eur J Surg Oncol 2009; 35: 903-7.
11. Choi ST, Hwang S, Lee SJ, Park KM, Kim KH, Ahn CS, Moon DB. Prognosis of patients with the gallbladder carcinoma undergone laparoscopic cholecystectomy as an initial operation. J Korean Surg Soc 2003; 65: 140-4.
12. Ouchi K, Mukuni J, Kakugawa Y. Laparoscopic cholecystectomy for gallbladder carcinoma: results of a Japanese survey of 498 patients. J Hepatobiliary Pancreat Surg 2002; 9: 256-60.
13. Choi SB, Han HJ, Kim CV, Kim WB, Song TJ, Suh SO, Kim YC, Choi SY. Incidental gallbladder cancer diagnosed following laparoscopic cholecystectomy. World J Surg 2009; 33: 2657-63.
14. Varshney S, Butturini G, Gupta R. Incidental carcinoma of the gallbladder. Eur J Surg Oncol 2002; 28: 4-10.
15. Chijiwa K, Nakano K, Ueda I, Noshiro H, Nagai E, Yamaguchi K, Tanaka M. Surgical treatment of patients with T2 gallbladder carcinoma invading the subserosal layer. J Am Coll Surg 2001; 192: 600-7.
16. Wise PE, Shi YY, Washington MK, Chapman WC, Wright JK, Sharp KW, Pinson CW. Radical resection improves survival for patients with pT2 gallbladder carcinoma. Am Surg 2001; 67: 1041-7.
17. Kai M, Chijiwa K, Ohuchida J, Nagano M, Hiyoshi M, Kondo K. A curative resection improves the postoperative survival rate even in patients with advanced gallbladder carcinoma. J Gastrointest Surg 2007; 11: 1025-32.
18. Shah SP, Schlicker RD, Cameron JL, Lillemoe KD, Pitt HA, Choti MA, Campbell KA, Yeo CJ, Talalini MA. Gallbladder cancer: the role of laparoscopy and radical surgery. Ann Surg 2007; 245: 893-901.
19. Kohya N, Miyazaki K. Hepatomectomy of segment 4a and 5 combined with extra-hepatic bile duct resection for T2 and T3 gallbladder carcinoma. J Surg Oncol 2008; 97: 498-502.
20. Dai M, Fong Y, Lowy A. Treatment of T3 gallbladder cancer. J Gastrointest Surg 2009; 13: 2040-2.
21. Miyakawa S, Ishihara S, Horiguchi A, Takada T, Miyazaki M, Nagakawa T. Biliary tract cancer statistics in Japan from 1998 to 2004 in Japan. J Hepatobiliary Pancreat Surg 2009; 16: 1-7.
22. Kiran RP, Pokala N, Dudrick SJ. Incidence pattern and survival for gallbladder cancer over three decades—an analysis of 10301 patients. Ann Surg Oncol 2007; 14: 827-32.
23. Edge SB, American Joint Committee on Cancer, American Cancer Society. AJCC cancer staging manual. 7th ed. New York: Springer, 2010.
24. Shimada H, Endo I, Fujii Y, Kamiya N, Masunari H, Kunihoro O, Tanaka K, Misura K, Togo S. Appraisal of surgical resection of gallbladder cancer with special reference to lymph node dissection. Langenbecks Arch Surg 2000; 385: 599-14.
25. Kondo S, Nimura Y, Hayakawa N, Kamiya J, Nagino M, Uesaka K. Regional and para-aortic lymphadenectomy in radical surgery for advanced gallbladder carcinoma. Br J Surg 2000; 87: 418-22.
26. Sasaki R, Ihabashi H, Fujita T, Takeda Y, Hoshikawa K, Takahashi M, Funato O, Nitta H, Kannoo S, Saito K. Significance of extensive surgery including resection of the pancreas head for the treatment of gallbladder cancer—from the perspective of mode of lymph node involvement and surgical outcome. World J Surg 2006; 30: 36-42.
27. Nakamura S, Sakaeguchi S, Suzuki M, Muro H. Aggressive surgery for carcinoma of the gallbladder. Surgery 1989; 106: 467-73.
28. Shimada H, Endo I, Togo S, Nakano A, Izumi T, Nakagawara G. The role of lymph node dissection in the treatment of gallbladder cancer. Cancer 1997; 79: 892-9.
29. Wakah T, Shirai Y, Yokoyama N, Nagakura S, Watanabe H, Hatakeyama K. Early gallbladder carcinoma does not warrant radical resection. Br J Surg 2001; 88: 675-8.
30. Reid KM, Ramos-De la Medina A, Donohue JH. Diagnosis and surgical management of gallbladder cancer: a review. J Gastrointest Surg 2007; 11: 671-81.
31. Suzuki S, Yokoi Y, Kurachi K, Inaba K, Ota S, Azuma M, Konno H, Baba S, Nakamura S. Appraisal of surgical treatment for pT2 gallbladder carcinomas. World J Surg 2004; 28: 160-5.
32. Shuakl PJ, Barreto SG. Systematic review: should routine resection of the extra-hepatic bile duct be performed in gallbladder cancer? Saudi J Gastroenterol 2010; 16: 161-7.
33. Kosuge T, Sano K, Shimada K, Yamamoto J, Yamazaki S, Makuuchi M. Should the bile duct be preserved or removed in radical surgery for gallbladder cancer? Hepatogastroenterology 1999; 46: 2133-7.
34. Nishio H, Nagino M, Ebata T, Yokoyama Y, Igami T, Nimura Y. Aggressive surgery for stage IV gallbladder carcinoma; what are the contraindications? J Hepatobiliary Pancreat Surg 2007; 14: 351-7.
35. Coburn NG, Cleary SP, Tan JC, Law CH. Surgery for gallbladder cancer: a population-based analysis. J Am Coll Surg 2008; 207: 371-82.
36. Kobayashi A, Oda T, Fukunaga K, Sasaki R, Ohkohchi N. Invasion of the hepatic artery is a crucial predictor of poor outcomes in gallbladder carcinoma. World J Surg 2012; 36: 645-50.
37. Murakami Y, Uemura K, Sudo T, Hashimoto Y, Nakamura N, Konno H, Hatakeyama K. Surgical outcome. World J Surg 2006; 30: 36-42.
38. Nishio H, Nagino M, Ebata T, Yokoyama Y, Igami T, Nimura Y. Aggressive surgery for stage IV gallbladder carcinoma; what are the contraindications? J Hepatobiliary Pancreat Surg 2007; 14: 351-7.
39. Coburn NG, Cleary SP, Tan JC, Law CH. Surgery for gallbladder cancer: a population-based analysis. J Am Coll Surg 2008; 207: 371-82.
44. Xiao WD, Peng CH, Zhou GW, Wu WD, Shen BY, Yan JQ, Yang WP, Li HW. Surgical treatment for Nevin stage IV and V gallbladder carcinoma: report of 70 cases. Hepatobiliary Pancreat Dis Int 2005; 4: 589-92.
45. Goetze TO, Paolucci V. Immediate re-resection of T1 incidental gallbladder carcinomas: a survival analysis of the German Registry. Surg Endosc 2008; 22: 2462-5.
46. Goetze TO, Paolucci V. Adequate extent in radical re-resection of incidental gallbladder carcinoma: analysis of the German Registry. Surg Endosc 2010; 24: 2156-64.
47. Chao TC, Jeng LB, Jan YY, Hwang TL, Wang CS, Chen MF. Concurrent primary carcinoma of the gallbladder and acute cholecystitis. Hepatogastroenterology 1998; 45: 921-6.
48. Lam CM, Yuen AW, Wai AC, Leung RM, Lee AY, Ng KK, Fan SF. Gallbladder cancer presenting with acute cholecystitis: a population-based study. Surg Endosc 2005; 19: 697-701.
49. Liu KJ, Richter HM, Cho MJ, Jarad J, Nadimpalli V, Donahue PE. Carcinoma involving the gallbladder in elderly patients presenting with acute cholecystitis. Surgery 1997; 122: 748-54; discussion 54-6.
50. Han HS, Cho JY, Yoon YS, Ahn KS, Kim H. Preoperative inflammation is a prognostic factor for gallbladder carcinoma. Br J Surg 2011; 98: 111-6.
51. Liang JL, Chen MC, Huang HY, Ng SH, Sheen-Chen SM, Liu PP, Kung CT, Ko SE. Gallbladder carcinoma manifesting as acute cholecystitis: clinical and computed tomographic features. Surgery 2009; 146: 861-8.
52. Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002; 11: 941-54.
53. Kim WS, Choi DW, You DD, Ho CY, Heo JS, Choi SH. 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.
54. Kopelson G, Galdabini J, Warshaw AL, Gunderson LL. Patterns of failure after curative surgery for extra-hepatic biliary tract carcinoma: implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 1981; 7: 413-7.
55. Jarnagin WR, Ruo L, Little SA, Klimstra D, D’Angelica M, DeMatteo RP, Wagman R, Blumgart LH, Fong Y. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. Cancer 2003; 98: 1689-700.
56. Jung SJ, Woo SM, Park HK, Lee WJ, Han MA, Han SS, Kim SH, Park SJ, Kim TH, Koh YH, et al. Patterns of initial disease recurrence after resection of biliary tract cancer. Oncology 2012; 83: 83-90.
57. Hezel AF, Zhu AX. Systemic therapy for biliary tract cancers. Oncologist 2008; 13: 415-23.
58. Park HS, Lim JY, Yoon DS, Park JS, Lee DK, Lee SJ, Choi HJ, Song SY, Lee WJ, Cho JY. Outcome of adjuvant therapy for gallbladder cancer. Oncology 2010; 79: 168-73.
59. Cho SY, Kim SH, Park SJ, Han SS, Kim YK, Lee KW, Lee WJ, Woo SM, Kim TH. Adjuvant chemoradiation therapy in gallbladder cancer. J Surg Oncol 2010; 102: 87-93.
60. Gold DG, Miller RC, Haddock MG, Gunderson LL, Quevedo F, Donohue JH, Bhatia S, Naugarsky DM. Adjuvant therapy for gallbladder carcinoma: the Mayo Clinic Experience. Int J Radiat Oncol Biol Phys 2009; 75: 150-5.