World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i43.12211

World J Gastroenterol 2015 November 21; 21(43): 12211-12217
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Gallbladder carcinoma: Prognostic factors and therapeutic options

Thorsten Oliver Goetze

Thorsten Oliver Goetze, Institut of Clinical Cancer Research, UCT-University Cancer Center Frankfurt, Krankenhaus Nordwest, 60488 Frankfurt, Germany

Author contributions: Goetze TO solely contributed to this paper, who analyzed the data, wrote, revised the manuscript and approved the final manuscript.

Conflict-of-interest statement: No conflict of interest.

Correspondence to: Dr. Thorsten Oliver Goetze, PD, Institut of Clinical Cancer Research, UCT-University Cancer Center Frankfurt, Krankenhaus Nordwest, Steinbacher Hohl 2-26, 60488 Frankfurt, Germany. thgoetze@aol.com
Telephone: +01577-2527799
Fax: +49-6074-4846206

Received: July 1, 2015
Peer-review started: July 4, 2015
First decision: August 26, 2015
Revised: September 20, 2015
Accepted: October 17, 2015
Article in press: October 20, 2015
Published online: November 21, 2015

Abstract

The outcome of gallbladder carcinoma is poor, and the overall 5-year survival rate is less than 5%. In early-stage disease, a 5-year survival rate up to 75% can be achieved if stage-adjusted therapy is performed. There is wide geographic variability in the frequency of gallbladder carcinoma, which can only be explained by an interaction between genetic factors and their alteration. Gallstones and chronic cholecystitis are important risk factors in the formation of gallbladder malignancies. Factors such as chronic bacterial infection, primary sclerosing cholangitis, an anomalous junction of the pancreaticobiliary duct, and several types of gallbladder polyps are associated with a higher risk of gallbladder cancer. There is also an interesting correlation between risk factors and the histological type of cancer. However, despite theoretical risk factors, only a third of gallbladder carcinomas are recognized preoperatively. In most patients, the tumor is diagnosed by the pathologist after a routine cholecystectomy for a benign disease and is termed "incidental or occult gallbladder carcinoma" (IGBC). A cholecystectomy is performed frequently due to the minimal invasiveness of the laparoscopic technique. Therefore, the postoperative diagnosis of potentially curable early-stage disease is more frequent. A second radical re-resection to complete a radical cholecystectomy is required for several IGBCs. However, the literature and guidelines used in different countries differ regarding the radicality or T-stage criteria for performing a radical cholecystectomy. The NCCN guidelines and data from the German registry (GR), which records the largest number of incidental gallbladder carcinomas in Europe, indicate that carcinomas infiltrating the muscularis propria or beyond require radical surgery. According to GR data and current literature, a wedge resection with a combined dissection of the lymph nodes of the hepatoduodenal ligament is adequate for T1b and T2 carcinomas. The reason for a radical cholecystectomy after simple CE in a formally R0 situation is either occult invasion or hepatic spread with unknown lymphogenic dissemination. Unfortunately, there are diverse interpretations and practices regarding stage-adjusted therapy for gallbladder carcinoma. The current data suggest that more radical therapy is warranted.

Key words: Gallbladder carcinoma; Stage-adjusted therapy; Radical cholecystectomy; Gallbladder polyps;

Cholecystitis; Gallstones; Laparoscopic cholecystectomy

Core tip: The outcome of gallbladder carcinoma is poor. In patients with early-stage disease, a 5-year survival rate of 75% is possible. Stage-adjusted therapy is key for improving survival. Despite the theoretical risk factors of gallbladder malignancies, only a third of gallbladder carcinomas are recognized preoperatively, and radical re-resection in cases of incidental discoveries of incidental or occult gallbladder carcinomas is often crucial to complete a so called radical cholecystectomy. Unfortunately, there are diverse interpretations and practices regarding stage-adjusted therapy for gallbladder carcinoma patients. The current data suggest that more radical therapy is warranted.

Goetze TO. Gallbladder carcinoma: Prognostic factors and therapeutic options. *World J Gastroenterol* 2015; 21(43): 12211-12217 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i43/12211.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i43.12211

GENERAL DATA

Gallbladder carcinoma is the fifth most common neoplasm of the digestive tract and has an overall incidence of 3 per 100000 people. Gallbladder carcinoma is the most common cancer of the biliary tract[1]. A gallbladder carcinoma is found in 0.2%-3% of all cholecystectomies and 0.09%-2% of all laparoscopic cholecystectomies[2,3]. A gallbladder carcinoma is suspected preoperatively in only 30% of all patients[1]. The other 70% of cases are diagnosed using postoperative incidental findings by a pathologist. These cancers are termed incidental or occult gallbladder carcinomas. Only 15%-47% of the preoperatively known gallbladder carcinomas are suitable for resection[4]. The majority of symptomatic patients with malignant gallbladder disease have an incurable tumor. The outcome of gallbladder carcinoma is poor, and the overall 5-year survival rate is less than 5%. In early-stage disease, a 5-year survival rate of 75% can be achieved if stage-adjusted therapy is performed[5].

Gallbladder carcinoma is described in up to 3.4% of autopsies conducted on cholelithiasis patients over 60 years of age[6]. The risk of gallbladder carcinoma increases with age. There are 2 peaks observed in gallbladder tumor incidence. The first peak occurs at 50-60 years of age. The second peak occurs at 70-80 years of age and has a higher prevalence among women[7-9].

There is a wide geographic variance in the frequency of gallbladder carcinoma. The incidence rates are extraordinarily high in Mapuche Indians in Chile, South America. This population exhibits the highest rate of gallbladder cancer: 12.3/100000 for males and 27.3/100000 for females[10]. The women of north India have an incidence of 22/100000. In North American Indians (New Mexico) and Pakistan, the incidence is 11/100000. Europe has a low overall incidence of 0-4/100000. There are also relatively high rates observed in several Eastern European countries such as Poland, which has an incidence of 14/100000. The literature reports Japan as having a high incidence rate at 7/100000, though this value is low compared with that of Poland[11]. Epidemiological studies suggest that the mortality rates are related to the incidence. Countries with the highest incidence have the highest mortality rates. There is an inverse relationship regarding the cholecystectomy rate and incidence of gallbladder carcinoma. Thus, countries with a higher rate of cholecystectomy have a lower rate of gallbladder carcinomas because the patients with risk factors have their gallbladders removed before carcinoma develops. Therefore, a survey of disease risk factors is important.

RISK FACTORS

Gallstones represent an important risk factor in the formation of gallbladder malignancies. Concrements are present in up to 85% of patients with gallbladder carcinomas[12]. Furthermore, gallbladder cancer rates are correlated with the prevalence of gallstone disease[12]. Increasing stone size elevates the risk of developing gallbladder cancer. Gallstones larger than 3 cm are associated with a greater than tenfold increased risk of cancer compared with that of small gallstones[13,14]. The type of concrement also matters. Cholesterol gallstones resulting from a distinct local mucosal irritation and chronic inflammation are associated with a higher risk of cancer.

Chronic inflammation is strongly associated with the malignant transformation of cells. Chronic inflammation causes DNA damage, which provokes repeated tissue proliferation and restoration attempts. This response involves the release of cytokines and growth factors and, thus, predisposes cells to oncogenic transformation[15].

Chronic cholecystitis is typically caused by chronic irritation due to a cholelithiasis, which may provoke cancer development after many years. Chronic inflammation can also result in calcium enclosure in the gallbladder wall. Only those with punctual calcium enclosures are considered premalignant, cases with transmural enclosures are associated with a decreased risk of carcinoma[16]. Porcelain gallbladder is a rare type of chronic inflammation that occurs in approximately 0.8% of all cholecystectomies and is associated with an increased carcinogenic risk. Porcelain gallbladder

is a form of diffuse transmural calcification. Several authors have reported a 62% carcinogenic risk, which appears to be an overestimation[16]. Additionally, xanthogranulomatous cholecystitis is associated with the development of gallbladder cancer but is not considered a precancerous lesion[17]. A prophylactic cholecystectomy is recommended for patients showing these particular disease patterns. The diagnosis is often based on postoperative findings. Chronic bacterial infection of the biliary tract is also a risk factor for biliary malignancy (*e.g.*, Salmonella typhi, Paratyphi and Helicobacter bilis). The bacterial colonization causes the degradation of bile, chronic irritation, and inflammation of the biliary wall. These changes may affect malignant transformation by altering tumor suppressor genes or proto-oncogenes[18,19].

Primary sclerosing cholangitis (PSC) is a chronic inflammatory syndrome with a neoplastic "field effect" that further supports the role of chronic inflammation of the gallbladder and consecutive carcinogenesis as there is an increased rate of gallbladder tumors that occur *via* a metaplasia-dysplasia-carcinoma sequence[20]. The AASLD recommends an annual ultrasound to detect mass lesions in the gallbladder. A cholecystectomy is advised in patients found to have gallbladder mass lesions regardless of the lesion size[21]. According to the EASL, gallbladder mass lesions in PSC frequently (> 50%) represent adenocarcinomas regardless of their size. Therefore, a cholecystectomy is recommended in PSC patients with a gallbladder mass of even < 1 cm in diameter[22].

The association between environmental exposures and gallbladder cancer are unclear. The risk factors for gallstones and gallbladder carcinoma include obesity, metabolic syndrome, and diabetes. There is a risk of malignancy in diabetes mellitus patients in the absence of concrements in the organ[23-27].

An anomalous junction of the pancreaticobiliary duct is a congenital malformation that is rare in Western countries; however, the malformation occurs frequently in Asian populations and especially Japan[28]. The histological subtype is usually a papillary carcinoma. A prophylactic cholecystectomy is recommended for these patients.

When considering the risk factors for gallbladder cancer, it is important to assess the management of gallbladder polyps that are present in up to 5% of adults and are more frequently diagnosed due to better imaging modalities[24,29]. Approximately 60% of gallbladder polyps are cholesterol polyps and 25% have an adenomyosis with hyperplastic mucosa. An additional 10% of polyps are inflammatory polyps, and 4% of all gallbladder polyps harbor benign adenomas and have neoplastic potential[30]. It is not clear if benign adenomas progress to gallbladder carcinoma because the absence of adenomatous polyp residuum in gallbladder adenocarcinoma histology challenges an adenoma-carcinoma sequence. The following factors are signs of potential malignant growth: polyps greater than 10 mm, rapidly increasing polyps, solitary or sessile polyps, association with gallstones, patients over 50 years of age, and K-ras positivity. The S3 Guidelines[31] in Germany recommend a conventional cholecystectomy by laparotomy for polyps larger than 18 mm. Polyps > 5 mm warrant an endoscopic ultrasound. Observation *via* transabdominal ultrasound is recommended for polyps < 1 cm without additional risk factors. A laparoscopic cholecystectomy is recommended for polyps < 1 cm with risk factors or polyps > 1 cm independent of the presence of risk factors.

The worldwide variation in the prevalence of gallbladder cancer can only be explained by genetic factors and their alteration. One method of assessing possible environmental influences on the risk of developing gallbladder cancer is to examine changes in the cancer incidence after immigration events. First-generation immigrants in Sweden were studied by Hemminki *et al*[32] using the nationwide Swedish Family Cancer Database. Only women from India and Chile had an increased risk and Northern European immigrants showed decreased risks of developing gallbladder malignancies. The increased rate of gallbladder carcinomas in Chilean and Indian immigrants suggests that carcinogenesis susceptibility was present before emigration and was responsible for the cancer[9]. A study by Kim *et al*[33] identified potential markers of GBC. The close genetic similarity between early and advanced gallbladder carcinoma cases highlights the aggressive biology of early-stage gallbladder carcinomas[33].

Gallstones are one of the most important risk factors for developing cancer. The genetic alterations that occur in the gallbladder wall are important for understanding cancer development. The gallbladder wall is altered by gallstones. The molecular pathogenesis results in an accumulation of mutations that may lead to malignancy. The common genetic mutations responsible for carcinogenesis include the activation of oncogenes, deactivation of tumor suppressor genes, microsatellite instability, and methylation of gene promoter regions[34].

Several of these genetic changes are associated with particular risk factors. For example, cases with papillary carcinomas are 100% K-ras positive and K-ras is increased in cases of an anomalous pancreatobiliary ductal junction. Squamous-cell carcinomas and adenocarcinomas are K-ras positive in 33% and 66% of cases, respectively. There was no detectable K-ras mutation in undifferentiated adenocarcinomas[35].

The genetic mutation profile is interesting in the context of chemotherapy for different histological types of gallbladder carcinomas. Papillary tumors are more responsive to EGFR tyrosine kinase inhibitors. Thus, EGFR targeted therapy could be an option. Adenocarcinoma histology carcinomas should be treated with gemcitabine and cisplatin. However, squamous-cell and adenosquamous-cell carcinoma are

not sensitive to chemotherapeutics[35-39].

There is also an interesting correlation between risk factors and the histological cancer type. Approximately 80%-97% of gallbladder carcinomas are adenocarcinomas. The remaining 3%-20% of tumor types include squamous-cell, adenosquamous-cell carcinomas, or papillary carcinomas. Additionally, gallstones and sludge are coexistent in 96% of cases. There are gallstones present in nearly 100% of squamous-cell and adenosquamous-cell carcinomas. In particular, large (> 1.5 cm) cholesterol, composite, or combination gallstones were found more frequently in gallbladders with squamous-cell and adenosquamous-cell carcinomas. In nearly 88% of gallbladder adenocarcinoma cases, there are also gallstones present. In particular, large, cholesterol, composite, or combination gallstones (> 1.5 cm) have been found in 68.2% of adenocarcinomas. Furthermore, small cholesterol, mixed, or pigmented gallstones and biliary sludge are found in 31.8% of adenocarcinomas[35].

The association between gallstones and carcinoma in cases of SCC requires longer periods of time. Thus, the patients with SCC are often older. SCC is more locally aggressive and is less sensitive to chemotherapeutics. In locally advanced stages, the prognosis of SCC is worse than adenocarcinomas. However, it has also been shown that R0 resection of an intramucosal pure squamous-cell carcinoma has a comparable prognosis to adenocarcinomas[35].

Papillary adenocarcinoma normally has K-ras mutations that are associated with pancreatobiliary reflux, but not with gallstones. Papillary adenocarcinoma patients are younger and have an abnormal pancreatico-choledochoductal junction, cystic duct dilatation, long common pancreatobiliary channel and adenomatous polyps. The patients are common in Eastern countries and Japan.

Approximately one-third of gallbladder carcinomas are known preoperatively despite understanding the theoretic risk factors. In the majority of cases, the tumor is diagnosed by the pathologist after a routine cholecystectomy for a benign disease[40,41], and these tumors are termed "incidental or occult gallbladder carcinomas".

SURGICAL APPROACH AND STAGE ADJUSTED THERAPY

The gallbladder is currently removed laparoscopically in more than 75% of cases[5,40]. In western countries such as Germany more than 90% of gallbladders are removed by the laparoscopic technique. However, the laparoscopic approach for treating gallbladder carcinoma remains controversial. In cases of preoperative suspicion, the laparoscopic approach is contraindicated for gallbladder carcinoma because of an increased risk of organ perforation due to grasping instruments, bile spillage, and port-site recurrences[7,42-44]. Consequently, when GBC is suspected preoperatively, an open technique is recommended for performing a radical cholecystectomy. However, due to the minimally invasive nature of the laparoscopic technique, a cholecystectomy is performed more frequently. As a result, the postoperative diagnosis of early gallbladder carcinoma is more frequent[45]. A second surgery for radical re-resection is required for IGBCs, depending on tumor stage[31]. Several studies have suggested that laparoscopy for IGBC is associated with a greater risk of tumor dissemination than is the open approach[46-48]. However, these conclusions are based on small sample sizes, inhomogeneous patient groups, and older data. Multiple studies including the GR, which has the largest number of IGBCs in Europe with more than 900 IGBC cases[40,41,45,49], indicated the primary access technique (laparoscopy *vs* the primary open technique) did not affect prognosis. A study by Cho *et al*[50] showed that the laparoscopic approach is feasible for suspected early-stage gallbladder carcinoma. However, stage-adjusted therapy should be performed regardless of the primary access technique[49].

Although there are guidelines in different countries, the literature, guidelines, and the compliance with those guidelines can vary for stage-adjusted therapy[49]. Stage-adjusted therapy includes radical surgery of the liver and a lymphadenectomy. According to the S3 Guidelines in Germany[31], the recommended treatment for gallbladder carcinoma is liver resection in the form of wedge resection of the gallbladder bed or a resection of liver segments 4b and 5. This surgery is always combined with a lymphadenectomy of the hepatoduodenal ligament in cases of T2 and more advanced T-stages. A similar procedure is recommended even for T1b and more advanced carcinomas by the Guidelines of the National Comprehensive Cancer Network, which is an alliance of 25 of the world's leading cancer centers[51].

The reason for a so called radical cholecystectomy after simple CE in a formally R0 situation is an occult invasion or hepatic spread, respectively a not known lymphogenic dissemination. A radical resection following R1 or R2 surgery should always be an individual decision based on the opinion of several surgical and oncologic specialists.

The types of liver invasion were described by Nagai *et al*[52] and include liver-bed and hepatic-hilar type. Ogura *et al*[53] further defined a gallbladder confined type, a liver bed type, and a hepatic-hilar type with an expansive and infiltrating pattern with continuous or discontinuous spread.

Endo *et al*[54] described a venous and lymphogenic pathway of microscopic tumor cell seeding in the liver in T2 GBCs, which is a T-stage without direct infiltration in the liver. The use of venous drainage in the liver is well described by Boerma *et al*[55], in form of a drainage in portal system of both lobes of the liver and direct drainage in segments Ⅳ and Ⅴ through so called vesicohepatic vessels.

Different modes of lymphatic spread were described by Fahim *et al*[56] based on the anatomical work in fetuses of Clermont in 1909 and the 3 pathways described by Ito *et al*[57] in adult cadavers. Shirai *et al*[58] identified the regional lymphatic system of the gallbladder by intraoperative vital staining. Uesaka *et al*[59] visualized the routes of lymphatic drainage in the gallbladder with a carbon particle suspension and found 3 different pathways. The final destination of all of the lymphatic routes is the confluence in the abdominal aortic nodes near the left vena renal location and the paraaortic nodes. Thus, preoperative knowledge regarding the paraaortic nodes is crucial if planning an ultraradical resection termed HPD (hepato-pancreatic-duodenectomy) as shown by Sasaki *et al*[60] or Kondo *et al*[61]. Kondo *et al*[62] shows a combined (lymphatic and liver) mode of spread in GBC that could be subdivided into the following categories: a hepatic bed type, hepatic hilum type, bed and hilum type, lymph node type, cystic duct type and a localized type.

The T-stage that requires radical liver resection is still a matter of debate. The NCCN clinical practice guidelines in oncology recommend a liver resection and lymph node dissection in T1b and more advanced T-stages[51]. The literature[63-73] supports radical GBC surgical therapy for the T1b stage and above. The German registry contains more than 900 IGBC cases and supports radical resection for the T1b stage. The GR data highlight the importance of IRR in cases of T2 and T3 carcinomas[72,73]. The radical liver resection techniques are supported by evidence from the GR and the literature[74]. The data support a wedge-resection technique with respect to prognosis and preoperative morbidity in T1b and even T2 cases. The prognostic impact of positive lymph nodes in stage T1b to T3 incidental gallbladder[75] and node dissection is important. The rate of positive nodes is 15.7% in T1b carcinomas, 46% in T2, and 75% in T3 GBCs.

Despite the many known risk factors, only 1/3 of all carcinomas are detected preoperatively. Less than half of these carcinomas are suitable for resection. Thus, it is important that the early-stage gallbladder carcinomas found in the 2/3 of patients who are diagnosed postoperatively as an incidental finding are treated with stage-adjusted therapy that includes liver resection and lymph node dissection.

REFERENCES

1 **Varshney S**, Butturini G, Gupta R. Incidental carcinoma of the gallbladder. *Eur J Surg Oncol* 2002; **28**: 4-10 [PMID: 11869005 DOI: 10.1053/ejso.2001.1175]

2 **Romano F**, Franciosi C, Caprotti R, De Fina S, Porta G, Visintini G, Uggeri F. Laparoscopic cholecystectomy and unsuspected gallbladder cancer. *Eur J Surg Oncol* 2001; **27**: 225-228 [PMID: 11373097]

3 **Toyonaga T**, Chijiiwa K, Nakano K, Noshiro H, Yamaguchi K, Sada M, Terasaka R, Konomi K, Nishikata F, Tanaka M. Completion radical surgery after cholecystectomy for accidentally undiagnosed gallbladder carcinoma. *World J Surg* 2003; **27**: 266-271 [PMID: 12607049]

4 **Mekeel KL**, Hemming AW. Surgical management of gallbladder carcinoma: a review. *J Gastrointest Surg* 2007; **11**: 1188-1193 [PMID: 17712596 DOI: 10.1007/s11605-007-0115-1]

5 **Goetze TO**, Paolucci V. Adequate extent in radical re-resection of incidental gallbladder carcinoma: analysis of the German Registry. *Surg Endosc* 2010; **24**: 2156-2164 [PMID: 20177938 DOI: 10.1007/s00464-010-0914-4]

6 **Mlinarić-Vrbica S**, Vrbica Z. Correlation between cholelithiasis and gallbladder carcinoma in surgical and autopsy specimens. *Coll Antropol* 2009; **33**: 533-537 [PMID: 19662775]

7 **Fong Y**, Jarnagin W, Blumgart LH. Gallbladder cancer: comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. *Ann Surg* 2000; **232**: 557-569 [PMID: 10998654]

8 **Roa JC**, Tapia O, Cakir A, Basturk O, Dursun N, Akdemir D, Saka B, Losada H, Bagci P, Adsay NV. Squamous cell and adenosquamous carcinomas of the gallbladder: clinicopathological analysis of 34 cases identified in 606 carcinomas. *Mod Pathol* 2011; **24**: 1069-1078 [PMID: 21532545 DOI: 10.1038/modpathol.2011.68]

9 **Lazcano-Ponce EC**, Miquel JF, Muñoz N, Herrero R, Ferrecio C, Wistuba II, Alonso de Ruiz P, Aristi Urista G, Nervi F. Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J Clin* 2001; **51**: 349-364 [PMID: 11760569]

10 **Hundal R**, Shaffer EA. Gallbladder cancer: epidemiology and outcome. *Clin Epidemiol* 2014; **6**: 99-109 [PMID: 24634588 DOI: 10.2147/CLEP.S37357]

11 **Stinton LM**, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. *Gut Liver* 2012; **6**: 172-187 [PMID: 22570746 DOI: 10.5009/gnl.2012.6.2.172]

12 **Zatonski WA**, Lowenfels AB, Boyle P, Maisonneuve P, Bueno de Mesquita HB, Ghadirian P, Jain M, Przewozniak K, Baghurst P, Moerman CJ, Simard A, Howe GR, McMichael AJ, Hsieh CC, Walker AM. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. *J Natl Cancer Inst* 1997; **89**: 1132-1138 [PMID: 9262251]

13 **Lowenfels AB**, Walker AM, Althaus DP, Townsend G, Domellöf L. Gallstone growth, size, and risk of gallbladder cancer: an interracial study. *Int J Epidemiol* 1989; **18**: 50-54 [PMID: 2722383]

14 **Diehl AK**. Gallstone size and the risk of gallbladder cancer. *JAMA* 1983; **250**: 2323-2326 [PMID: 6632129]

15 **Rashid A**, Ueki T, Gao YT, Houlihan PS, Wallace C, Wang BS, Shen MC, Deng J, Hsing AW. K-ras mutation, p53 overexpression, and microsatellite instability in biliary tract cancers: a population-based study in China. *Clin Cancer Res* 2002; **8**: 3156-3163 [PMID: 12374683]

16 **Stephen AE**, Berger DL. Carcinoma in the porcelain gallbladder: a relationship revisited. *Surgery* 2001; **129**: 699-703 [PMID: 11391368]

17 **Houston JP**, Collins MC, Cameron I, Reed MW, Parsons MA, Roberts KM. Xanthogranulomatous cholecystitis. *Br J Surg* 1994; **81**: 1030-1032 [PMID: 7922056]

18 **Kumar S**, Kumar S, Kumar S. Infection as a risk factor for gallbladder cancer. *J Surg Oncol* 2006; **93**: 633-639 [PMID: 16724347]

19 **Gonzalez-Escobedo G**, Marshall JM, Gunn JS. Chronic and acute infection of the gall bladder by Salmonella Typhi: understanding the carrier state. *Nat Rev Microbiol* 2011; **9**: 9-14 [PMID: 21113180 DOI: 10.1038/nrmicro2490]

20 **Lewis JT**, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC. Prevalence and risk factors for gallbladder neoplasia in patients with primary sclerosing cholangitis: evidence for a metaplasia-dysplasia-carcinoma sequence. *Am J Surg Pathol* 2007; **31**: 907-913 [PMID: 17527079]

21 **Chapman R**, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ. Diagnosis and management of primary sclerosing cholangitis. *Hepatology* 2010; **51**: 660-678 [PMID: 20101749 DOI: 10.1002/hep.23294]

22 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol* 2009; **51**: 237-267 [PMID: 19501929 DOI: 10.1016/j.jhep.2009.04.009]

23 **Calle EE**, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003; **348**: 1625-1638 [PMID: 12711737]

24 **Hariharan D**, Saied A, Kocher HM. Analysis of mortality rates for gallbladder cancer across the world. *HPB* (Oxford) 2008; **10**: 327-331 [PMID: 18982147 DOI: 10.1080/13651820802007464]

25 **Wolin KY**, Carson K, Colditz GA. Obesity and cancer. *Oncologist* 2010; **15**: 556-565 [PMID: 20507889 DOI: 10.1634/theoncologist.2009-0285]

26 **Larsson SC**, Wolk A. Obesity and the risk of gallbladder cancer: a meta-analysis. *Br J Cancer* 2007; **96**: 1457-1461 [PMID: 17375043]

27 **Lai HC**, Chang SN, Lin CC, Chen CC, Chou JW, Peng CY, Lai SW, Sung FC, Li YF. Does diabetes mellitus with or without gallstones increase the risk of gallbladder cancer? Results from a population-based cohort study. *J Gastroenterol* 2013; **48**: 856-865 [PMID: 23065035]

28 **Roa I**, de Aretxabala X, Morgan R, Molina R, Araya JC, Roa J, Ibacahe G. [Clinicopathological features of gallbladder polyps and adenomas]. *Rev Med Chil* 2004; **132**: 673-679 [PMID: 15332368]

29 **Sarkut P**, Kilicturgay S, Ozer A, Ozturk E, Yilmazlar T. Gallbladder polyps: factors affecting surgical decision. *World J Gastroenterol* 2013; **19**: 4526-4530 [PMID: 23901228 DOI: 10.3748/wjg.v19.i28.4526]

30 **Gallahan WC**, Conway JD. Diagnosis and management of gallbladder polyps. *Gastroenterol Clin North Am* 2010; **39**: 359-367, x [PMID: 20478491 DOI: 10.1016/j.gtc.2010.02.001]

31 **Lammert F**, Neubrand MW, Bittner R, Feussner H, Greiner L, Hagenmüller F, Kiehne KH, Ludwig K, Neuhaus H, Paumgartner G, Riemann JF, Sauerbruch T. [S3-guidelines for diagnosis and treatment of gallstones. German Society for Digestive and Metabolic Diseases and German Society for Surgery of the Alimentary Tract]. *Z Gastroenterol* 2007; **45**: 971-1001 [PMID: 17874360 DOI: 10.1055/s-2007-963437]

32 **Hemminki K**, Mousavi SM, Brandt A, Ji J, Sundquist J. Liver and gallbladder cancer in immigrants to Sweden. *Eur J Cancer* 2010; **46**: 926-931 [PMID: 20064704 DOI: 10.1016/j.ejca.2009.12.031]

33 **Kim JH**, Kim HN, Lee KT, Lee JK, Choi SH, Paik SW, Rhee JC, Lowe AW. Gene expression profiles in gallbladder cancer: the close genetic similarity seen for early and advanced gallbladder cancers may explain the poor prognosis. *Tumour Biol* 2008; **29**: 41-49 [PMID: 18497548 DOI: 10.1159/000132570]

34 **Dutta U**. Gallbladder cancer: can newer insights improve the outcome? *J Gastroenterol Hepatol* 2012; **27**: 642-653 [PMID: 22168580 DOI: 10.1111/j.1440-1746.2011.07048.x]

35 **Cariati A**, Piromalli E, Cetta F. Gallbladder cancers: associated conditions, histological types, prognosis, and prevention. *Eur J Gastroenterol Hepatol* 2014; **26**: 562-569 [PMID: 24614695 DOI: 10.1097/MEG.0000000000000074]

36 **Thomas MB**. Biological characteristics of cancers in the gallbladder and biliary tract and targeted therapy. *Crit Rev Oncol Hematol* 2007; **61**: 44-51 [PMID: 17164111]

37 **Valle J**, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010; **362**: 1273-1281 [PMID: 20375404 DOI: 10.1056/NEJMoa0908721]

38 **Cariati A**, Piromalli E. Chemotherapy and histological stratification of biliary tract cancers. *Oncology* 2012; **82**: 352-353 [PMID: 22677952 DOI: 10.1159/000338660]

39 **Cancer Genome Atlas Research Network**. Comprehensive genomic characterization of squamous cell lung cancers. *Nature* 2012; **489**: 519-525 [PMID: 22960745]

40 **Goetze TO**, Paolucci V. Benefits of reoperation of T2 and more advanced incidental gallbladder carcinoma: analysis of the German registry. *Ann Surg* 2008; **247**: 104-108 [PMID: 18156929]

41 **Goetze TO**, Paolucci V. [Incidental T1b-T3 gallbladder carcinoma. Extended cholecystectomy as an underestimated prognostic factor-results of the German registry]. *Chirurg* 2014; **85**: 131-138 [PMID: 24005717 DOI: 10.1007/s00104-013-2587-8]

42 **Misra S**, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. *Lancet Oncol* 2003; **4**: 167-176 [PMID: 12623362]

43 **Sun CD**, Zhang BY, Wu LQ, Lee WJ. Laparoscopic cholecystectomy for treatment of unexpected early-stage gallbladder cancer. *J Surg Oncol* 2005; **91**: 253-257 [PMID: 16121343]

44 **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**: 160-165 [PMID: 14708053]

45 **Goetze T**, Paolucci V. Does laparoscopy worsen the prognosis for incidental gallbladder cancer? *Surg Endosc* 2006; **20**: 286-293 [PMID: 16362480]

46 **Clair DG**, Lautz DB, Brooks DC. Rapid development of umbilical metastases after laparoscopic cholecystectomy for unsuspected gallbladder carcinoma. *Surgery* 1993; **113**: 355-358 [PMID: 7772085]

47 **Braghetto I**, Bastias J, Csendes A, Chiong H, Compan A, Valladares H, Rojas J. Gallbladder carcinoma during laparoscopic cholecystectomy: is it associated with bad prognosis? *Int Surg* 1999; **84**: 344-349 [PMID: 10667815]

48 **Shirai Y**, Ohtani T, Hatakeyama K. Laparoscopic cholecystectomy may disseminate gallbladder carcinoma. *Hepatogastroenterology* 1998; **45**: 81-82 [PMID: 9496492]

49 **Goetze TO**, Paolucci V. Influence of high- and low-volume liver surgery in gallbladder carcinoma. *World J Gastroenterol* 2014; **20**: 18445-18451 [PMID: 25561815 DOI: 10.3748/wjg.v20.i48.18445]

50 **Cho JY**, Han HS, Yoon YS, Ahn KS, Kim YH, Lee KH. Laparoscopic approach for suspected early-stage gallbladder carcinoma. *Arch Surg* 2010; **145**: 128-133 [PMID: 20157079 DOI: 10.1001/archsurg.2009.261]

51 **Benson AB**, Abrams TA, Ben-Josef E, Bloomston PM, Botha JF, Clary BM, Covey A, Curley SA, D'Angelica MI, Davila R, Ensminger WD, Gibbs JF, Laheru D, Malafa MP, Marrero J, Meranze SG, Mulvihill SJ, Park JO, Posey JA, Sachdev J, Salem R, Sigurdson ER, Sofocleous C, Vauthey JN, Venook AP, Goff LW, Yen Y, Zhu AX. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. *J Natl Compr Canc Netw* 2009; **7**: 350-391 [PMID: 19406039]

52 **Nagai H**, Kuroda A, Morioka Y, Shimada H, Ezaki I. Modes of spread of gallbladder carcinoma: a study of autopsied cases (in Japanese). *Tan to Sui* 1983; (**4**): 1227

53 **Ogura Y**, Tabata M, Kawarada Y, Mizumoto R. Effect of hepatic invasion on the choice of hepatic resection for advanced carcinoma of the gallbladder: histologic analysis of 32 surgical cases. *World J Surg* 1998; **22**: 262-266; discussion 266-267 [PMID: 9494418]

54 **Endo I**, Shimada H, Takimoto A, Fujii Y, Miura Y, Sugita M, Morioka D, Masunari H, Tanaka K, Sekido H, Togo S. Microscopic liver metastasis: prognostic factor for patients with pT2 gallbladder carcinoma. *World J Surg* 2004; **28**: 692-696 [PMID: 15175901]

55 **Boerma EJ**. Towards an oncological resection of gall bladder cancer. *Eur J Surg Oncol* 1994; **20**: 537-544 [PMID: 7926055]

56 **Fahim RB**, Mcdonald JR, Richards JC, Ferris DO. Carcinoma of the gallbladder: a study of its modes of spread. *Ann Surg* 1962; **156**: 114-124 [PMID: 13891308]

57 **Ito M**, Mishima Y, Sato T. An anatomical study of the lymphatic drainage of the gallbladder. *Surg Radiol Anat* 1991; **13**: 89-104 [PMID: 1925922]

58 **Shirai Y**, Yoshida K, Tsukada K, Ohtani T, Muto T. Identification of the regional lymphatic system of the gallbladder by vital staining. *Br J Surg* 1992; **79**: 659-662 [PMID: 1643479]

59 **Uesaka K**, Yasui K, Morimoto T, Torii A, Yamamura Y, Kodera Y, Hirai T, Kato T, Kito T. Visualization of routes of lymphatic drainage of the gallbladder with a carbon particle suspension. *J Am Coll Surg* 1996; **183**: 345-350 [PMID: 8843263]

60 **Sasaki R**, Itabashi H, Fujita T, Takeda Y, Hoshikawa K, Takahashi M, Funato O, Nitta H, Kanno 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 [PMID: 16369715]

61 **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**: 418-422 [PMID: 10759735]

62 **Kondo S**, Nimura Y, Kamiya J, Nagino M, Kanai M, Uesaka K, Hayakawa N. Mode of tumor spread and surgical strategy in gallbladder carcinoma. *Langenbecks Arch Surg* 2002; **387**: 222-228 [PMID: 12410358]

63 **You DD**, Lee HG, Paik KY, Heo JS, Choi SH, Choi DW. What is an adequate extent of resection for T1 gallbladder cancers? *Ann Surg* 2008; **247**: 835-838 [PMID: 18438121 DOI: 10.1097/SLA.0b013e3181675842]

64 **Cavallaro A**, Piccolo G, Panebianco V, Lo Menzo E, Berretta M, Zanghì A, Di Vita M, Cappellani A. Incidental gallbladder cancer during laparoscopic cholecystectomy: managing an unexpected finding. *World J Gastroenterol* 2012; **18**: 4019-4027 [PMID: 22912553 DOI: 10.3748/wjg.v18.i30.4019]

65 **D'Angelica M**, Dalal KM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Analysis of the extent of resection for adenocarcinoma of the gallbladder. *Ann Surg Oncol* 2009; **16**: 806-816 [PMID: 18985272 DOI: 10.1245/s10434-008-0189-3]

66 **Jayaraman S**, Jarnagin WR. Management of gallbladder cancer. *Gastroenterol Clin North Am* 2010; **39**: 331-342, x [PMID: 20478489 DOI: 10.1016/j.gtc.2010.02.006]

67 **Fuks D**, Regimbeau JM, Le Treut YP, Bachellier P, Raventos A, Pruvot FR, Chiche L, Farges O. Incidental gallbladder cancer by the AFC-GBC-2009 Study Group. *World J Surg* 2011; **35**: 1887-1897 [PMID: 21547420 DOI: 10.1007/s00268-011-1134-3]

68 **Yi X**, Long X, Zai H, Xiao D, Li W, Li Y. Unsuspected gallbladder carcinoma discovered during or after cholecystectomy: focus on appropriate radical re-resection according to the T-stage. *Clin Transl Oncol* 2013; **15**: 652-658 [PMID: 23359177 DOI: 10.1007/s12094-012-0988-7]

69 **D'Hondt M**, Lapointe R, Benamira Z, Pottel H, Plasse M, Letourneau R, Roy A, Dagenais M, Vandenbroucke-Menu F. Carcinoma of the gallbladder: patterns of presentation, prognostic factors and survival rate. An 11-year single centre experience. *Eur J Surg Oncol* 2013; **39**: 548-553 [PMID: 23522952 DOI: 10.1016/j.ejso.2013.02.010]

70 **Åndrén-Sandberg A**, Deng Y. Aspects on gallbladder cancer in 2014. *Curr Opin Gastroenterol* 2014; **30**: 326-331 [PMID: 24686434 DOI: 10.1097/MOG.0000000000000068]

71 **Hari DM**, Howard JH, Leung AM, Chui CG, Sim MS, Bilchik AJ. A 21-year analysis of stage I gallbladder carcinoma: is cholecystectomy alone adequate? *HPB* (Oxford) 2013; **15**: 40-48 [PMID: 23216778 DOI: 10.1111/j.1477-2574.2012.00559.x]

72 **Goetze TO**, Paolucci V. [Immediate radical re-resection of incidental T1b gallbladder cancer and the problem of an adequate extent of resection (results of the German Registry "Incidental Gallbladder Cancer")]. *Zentralbl Chir* 2014; **139** Suppl 2: e43-e48 [PMID: 21365537 DOI: 10.1055/s-0030-1262698]

73 **Goetze TO**, Paolucci V. Immediate re-resection of T1 incidental gallbladder carcinomas: a survival analysis of the German Registry. *Surg Endosc* 2008; **22**: 2462-2465 [PMID: 18247090 DOI: 10.1007/s00464-008-9747-9]

74 **Horiguchi A**, Miyakawa S, Ishihara S, Miyazaki M, Ohtsuka M, Shimizu H, Sano K, Miura F, Ohta T, Kayahara M, Nagino M, Igami T, Hirano S, Yamaue H, Tani M, Yamamoto M, Ota T, Shimada M, Morine Y, Kinoshita H, Yasunaga M, Takada T. Gallbladder bed resection or hepatectomy of segments 4a and 5 for pT2 gallbladder carcinoma: analysis of Japanese registration cases by the study group for biliary surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci* 2013; **20**: 518-524 [PMID: 23430053 DOI: 10.1007/s00534-012-0584-9]

75 **Goetze TO**, Paolucci V. The prognostic impact of positive lymph nodes in stages T1 to T3 incidental gallbladder carcinoma: results of the German Registry. *Surg Endosc* 2012; **26**: 1382-1389 [PMID: 22089259 DOI: 10.1007/s00464-011-2044-z]

P- Reviewer: Beltran MA, Gao Y **S- Editor**: Ma YJ
L- Editor: A **E- Editor**: Liu XM

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327