

Unexpected gallbladder cancer: Surgical strategies and prognostic factors

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Author contributions: Clemente G contributed all to this paper.

Conflict-of-interest statement: Clemente G declares no conflict of interest related to this publication.

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Manuscript source: Invited manuscript

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Received: March 19, 2016

Peer-review started: March 22, 2016

First decision: April 11, 2016

Revised: May 7, 2016

Accepted: June 14, 2016

Article in press: June 16, 2016

Published online: August 27, 2016

Abstract

Gallbladder cancer is the most common tumor of the biliary tract and it is associated with a poor prognosis. Unexpected gallbladder cancer is a cancer incidentally discovered, as a surprise, at the histological examination after cholecystectomy for gallstones or other indications. It is a potentially curable disease, with an intermediate

or good prognosis in most cases. An adequate surgical strategy is mandatory to improve the prognosis and an adjunctive radical resection may be required depending on the depth of invasion. If the cancer discovered after cholecystectomy is a pTis or a pT1a, a second surgical procedure is not mandatory. In the other cases (pT1b, pT2 and pT3 cancer) a re-resection (4b + 5 liver segmentectomy, lymphadenectomy and port-sites excision in some cases) is required to obtain a radical excision of the tumor and an accurate disease staging. The operative specimens of re-resection should be examined by the pathologist to find any "residual" tumor. The "residual disease" is the most important prognostic factor, significantly reducing median disease-free survival and disease-specific survival. The other factors include depth of parietal invasion, metastatic nodal disease, surgical margin status, cholecystectomy for acute cholecystitis, histological differentiation, lymphatic, vascular and perineural invasion and overall TNM-stage.

Key words: Gallbladder cancer; Laparoscopic cholecystectomy; Liver resection; Lymphadenectomy; Incidental gallbladder cancer; Unexpected gallbladder cancer

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Core tip: Unexpected gallbladder cancer is diagnosed, as a surprise, after cholecystectomy for gallstones. A second surgical procedure consisting in a re-resection may be required depending on the depth of invasion. The discovery of cancer represents a challenge for the surgeon who must inform the patient many days after cholecystectomy and must evaluate the indication for a re-resection. The presence of a residual disease in the operative specimen after re-resection is the most important prognostic factor.

Clemente G. Unexpected gallbladder cancer: Surgical strategies and prognostic factors. *World J Gastrointest Surg* 2016; 8(8): 541-544 Available from: URL: <http://www.wjgnet.com>

INTRODUCTION

Gallbladder cancer (GBC) is the most common tumor of the biliary tract and it is recognized as one of the most aggressive cancers^[1]. It is generally associated with a poor prognosis with a reported 5-year survival rate of 5%^[2,3]. The delay in diagnosis is considered the main cause of the high mortality. GBC is a relatively rare disease in Western countries: In the United States an incidence of 1.2/100.000 is reported^[4] but, in some countries (Chile, Northern India), the incidence is ten times higher. Unexpected GBC (UGBC) can be defined as a cancer incidentally discovered, as a surprise, at the histological examination after cholecystectomy for gallstones or other indications. In recent years, the widespread diffusion of laparoscopic techniques has caused an increase in the number of laparoscopic cholecystectomies and therefore an increase of diagnoses of UGBC. Today, between 0.2% and 3% of patients undergoing cholecystectomy has a diagnosis of UGBC, depending on regional prevalence. In some tertiary centers such as Johns Hopkins University^[1] and the Memorial Sloan-Kettering Cancer Center^[4], UGBCs account for about half of all GBCs. Unlike the GBC, UGBC is a potentially curable disease with an intermediate or good prognosis in most cases. The adoption of an adequate surgical strategy is mandatory to improve the prognosis and an adjunctive radical resection may be required depending on the depth of invasion. However, UGBC represents a challenge for the surgeon who must inform the patient many days after cholecystectomy and must evaluate the indication for a re-resection.

DIAGNOSIS AND TREATMENT

After histological confirmation of the diagnosis, the first step is to obtain, as much as possible, all the information regarding the first surgical procedure. Circumstances and operative details of cholecystectomy must be accurately reviewed: Emergency or elective surgery, opening and emptying of the gallbladder, occurrence of bile spillage and method of gallbladder extraction (with or without bag). If possible, the original specimen could be re-reviewed by an experienced pathologist to more accurately define the exact site of the tumor, the depth of parietal invasion, the cystic duct involvement and the presence of metastatic lymph nodes. Unfortunately, as reported in a multicenter French survey, we are not always able to obtain all relevant information^[5].

In any case, if the cancer is a pTis or a pT1a, and the operation was rightly performed without loss of bile or stones, a second, revisional, surgical procedure is not mandatory. However, in these cases, a close

surveillance is still required. Unfortunately, in most cases pathology shows a muscular layer involvement (pT1b), a perimuscular tissue involvement (pT2) or a serosal involvement (pT3). A CT evaluation is required to detect any macroscopic residual disease or distant metastases; indeed, in these cases, a second surgical procedure is contraindicated. On the contrary, if any residual disease is absent, a second, radical surgical procedure can be planned. Re-resection for gallbladder carcinoma incidentally discovered after cholecystectomy is considered safe and effective^[6] and it is routinely advocated in the majority of cases^[7].

Although some authors consider unnecessary a second procedure in patients with T1b cancer, the majority performs a re-resection also in this indication. The aim of re-resection is to obtain a radical excision of the tumor and an accurate disease staging. Usually, this include a 4b + 5 segmentectomy, because a more extensive hepatectomy is not associated with a more favourable prognosis. Nevertheless, as the aim is to achieve a margin free resection, a right extended hepatectomy may be required in some cases^[8]. Lymphadenectomy should include the regional lymph nodes (gallbladder, hepatic pedicle, hepatic artery and periportal). Some topics of this surgical treatment are still under discussion: (1) the role of a preliminary laparoscopy before definitive treatment; (2) indications for CBD excision with hepatico-jejunostomy; and (3) port-sites excision. A preliminary laparoscopy could be useful in pT3 tumors to avoid an unnecessary laparotomy in cases with peritoneal carcinomatosis or liver metastases not detected by CT or MRI. The removal of the CBD with a hepatico-jejunostomy was emphasized in the past in order to obtain a more extensive lymphadenectomy. At present, there is no evidence to support prophylactic common bile duct excision^[9]. However, this maneuver, if routinely performed, increases the morbidity without any benefit on survival; therefore, it should be reserved for cases with cystic duct involvement^[10]. The routine port-sites excision is not associated with improved survival or disease recurrence^[11]. Today, this maneuver is not considered mandatory and could be reserved for cases in which the frozen-sections show residual disease on peritoneal surface at the level of the trocar-sites. However, it is advisable to excise the port-sites if the gallbladder was extracted without bag during cholecystectomy, or when this information is not available. Finally, the re-resection and lymphadenectomy can be performed by laparoscopy, as recently reported by Machado *et al*^[12]. Obviously, this approach can be pursued only in centers with extensive experience in hepatobiliary and advanced laparoscopic surgery.

PROGNOSTIC FACTORS

The operative specimens of re-resection should be examined by the pathologist to find any "residual" tumor. The "residual disease" can be found on the liver,

at the level of the gallbladder bed, on the lymph nodes or at the level of the trocar-sites excised. The presence of residual disease is found in about 50%-70% of cases and it can be predicted by the pT stage after cholecystectomy. Pawlik *et al*^[7] reported a risk of residual disease within the liver and to loco-regional lymph nodes of 0% and 12.5%, respectively, for cancers pT1, of 10.4% and 31.3% for pT2, of 36.4% and 45.5% for pT3. The residual disease is the most important prognostic factor, significantly reducing median disease-free survival and disease-specific survival^[13]. The other factors include depth of parietal invasion, metastatic nodal disease, surgical margin status (R0 resection), cholecystectomy for acute cholecystitis, histological differentiation, lymphatic, vascular and perineural invasion and overall TNM-stage^[14-16]. On the contrary, the time interval between cholecystectomy and re-resection is not significant for the prognosis^[13]. This fact allows, when the discovery of cancer occurs during the operation, to refer the re-resection to a later date. It also allows to refer the patient for re-resection in a tertiary center if the cholecystectomy was performed in a non-specialized hospital.

With regard to the prognosis after radical surgery, it is very favorable in patients with pT1b cancer with a 10-year survival up to 90%-100%^[6,17]. Re-resection significantly increases survival in patients with carcinoma pT2 and pT3. A 5-year survival rates ranging from 49.8% to 78.3% for pT2 cancers and from 0% to 23% for pT3 cancers was reported in the literature^[6,17,18]. In the same way, an increase in 5-year survival rate up to 62% for patients with pT2 cancer and up to 19% for patients with pT3 was reported in a multicenter French study^[16]. On the contrary, poor 5-year survival rates, ranging from 10% to 22%, were reported after simple cholecystectomy for pT2 cancers^[17,19]. In conclusion, radical re-resection, including liver resection and lymph node dissection, is the operation of choice for the treatment of pT2 and pT3 unexpected gallbladder cancers; it allows to obtain a significant survival benefit compared with simple cholecystectomy^[19,20].

CONCLUSION

A second, radical surgical procedure, when possible, improves prognosis in patients with UGBC. The possible occurrence of UGBC after cholecystectomy for gallstones allows some considerations. Firstly, laparoscopic cholecystectomy is a procedure that must be correctly performed in all cases, without loss of stones and bile: The occurrence of "spillage", in case of unexpected cancer, significantly worsens the prognosis. In case of acute cholecystitis, or in any technically difficult case, as in the elderly, the surgeon should be cautious and eventually can convert the laparoscopy in a traditional laparotomy rather than possibly causing a tumor dissemination with inadequate maneuvers. The patients with UGBC should be treated by an experienced surgeon, preferably in a tertiary center specialized in hepatobiliary

surgery.

REFERENCES

- 1 **Shih SP**, Schulick RD, Cameron JL, Lillemoe KD, Pitt HA, Choti MA, Campbell KA, Yeo CJ, Talamini MA. Gallbladder cancer: the role of laparoscopy and radical resection. *Ann Surg* 2007; **245**: 893-901 [PMID: 17522515 DOI: 10.1097/SLA.0b013e31806beec2]
- 2 **Piehler JM**, Crichlow RW. Primary carcinoma of the gallbladder. *Surg Gynecol Obstet* 1978; **147**: 929-942 [PMID: 362580]
- 3 **Cubertafoond P**, Gainant A, Cucchiario G. Surgical treatment of 724 carcinomas of the gallbladder. Results of the French Surgical Association Survey. *Ann Surg* 1994; **219**: 275-280 [PMID: 8147608 DOI: 10.1097/00000658-199403000-00007]
- 4 **Duffy A**, Capanu M, Abou-Alfa GK, Huitzil D, Jarnagin W, Fong Y, D'Angelica M, Dematteo RP, Blumgart LH, O'Reilly EM. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). *J Surg Oncol* 2008; **98**: 485-489 [PMID: 18802958 DOI: 10.1002/jso.21141]
- 5 **Chatelain D**, Fuks D, Farges O, Attencourt C, Pruvot FR, Regimbeau JM. Pathology report assessment of incidental gallbladder carcinoma diagnosed from cholecystectomy specimens: results of a French multicentre survey. *Dig Liver Dis* 2013; **45**: 1056-1060 [PMID: 23948233 DOI: 10.1016/j.dld.2013.07.004]
- 6 **Fong Y**, Heffernan N, Blumgart LH. Gallbladder carcinoma discovered during laparoscopic cholecystectomy: aggressive re-resection is beneficial. *Cancer* 1998; **83**: 423-427 [DOI: 10.1002/(SICI)1097-0142(19980801)83]
- 7 **Pawlik TM**, Gleisner AL, Vigano L, Kooby DA, Bauer TW, Frilling A, Adams RB, Staley CA, Trindade EN, Schulick RD, Choti MA, Capussotti L. Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection. *J Gastrointest Surg* 2007; **11**: 1478-1486; discussion 1486-1487 [PMID: 17846848 DOI: 10.1007/s11605-007-0309-6]
- 8 **Garg PK**, Pandey D, Sharma J. The surgical management of gallbladder cancer. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 155-166 [PMID: 25155211 DOI: 10.1586/1474124.2014.943188]
- 9 **Pandey D**, Garg PK, Manjunath NM, Sharma J. Extra-Hepatic Bile Duct Resection: an Insight in the Management of Gallbladder Cancer. *J Gastrointest Cancer* 2015; **46**: 291-296 [PMID: 26049726 DOI: 10.1007/s12029-015-9737-9]
- 10 **Regimbeau JM**, Farges O, Pruvot FF. Chirurgie des cholangiocarcinomes intrahépatiques, hilaires et vésiculaires. Monographie de l'Association Française de Chirurgie. Paris, Verlag: Springer, 2009
- 11 **Maker AV**, Butte JM, Oxenberg J, Kuk D, Gonen M, Fong Y, Dematteo RP, D'Angelica MI, Allen PJ, Jarnagin WR. Is port site resection necessary in the surgical management of gallbladder cancer? *Ann Surg Oncol* 2012; **19**: 409-417 [PMID: 21698501 DOI: 10.1245/s10434-011-1850]
- 12 **Machado MA**, Makdissi FF, Surjan RC. Totally Laparoscopic Hepatic Bisegmentectomy (s4b+s5) and Hilar Lymphadenectomy for Incidental Gallbladder Cancer. *Ann Surg Oncol* 2015; **22** Suppl 3: S336-S339 [PMID: 26059653 DOI: 10.1245/s10434-015-4650-9]
- 13 **Butte JM**, Kingham TP, Gönen M, D'Angelica MI, Allen PJ, Fong Y, DeMatteo RP, Jarnagin WR. Residual disease predicts outcomes after definitive resection for incidental gallbladder cancer. *J Am Coll Surg* 2014; **219**: 416-429 [PMID: 25087941]
- 14 **Clemente G**, Nuzzo G, De Rose AM, Giovannini I, La Torre G, Ardito F, Giuliante F. Unexpected gallbladder cancer after laparoscopic cholecystectomy for acute cholecystitis: a worrisome picture. *J Gastrointest Surg* 2012; **16**: 1462-1468 [PMID: 22653330 DOI: 10.1007/s11605-012-1915-5]
- 15 **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]
- 16 **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]

- 17 **Choi SB**, Han HJ, Kim CY, Kim WB, Song TJ, Suh SO, Kim YC, Choi SY. Incidental gallbladder cancer diagnosed following laparoscopic cholecystectomy. *World J Surg* 2009; **33**: 2657-2663 [PMID: 19823903 DOI: 10.1007/s00268-009-0249-2]
- 18 **Yagi H**, Shimazu M, Kawachi S, Tanabe M, Aiura K, Wakabayashi G, Ueda M, Nakamura Y, Kitajima M. Retrospective analysis of outcome in 63 gallbladder carcinoma patients after radical resection. *J Hepatobiliary Pancreat Surg* 2006; **13**: 530-536 [PMID: 17139427 DOI: 10.1007/s00534-006-1104-6]
- 19 **Chijiwa K**, Nakano K, Ueda J, 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**: 600-607 [PMID: 11333097 DOI: 10.1016/S1072-7515(01)00814-6]
- 20 **Kohya N**, Miyazaki K. Hepatectomy 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 [PMID: 18314875 DOI: 10.1002/jso.20982]

P- Reviewer: Aloia TA, Garg PK, Machado MAC **S- Editor:** Qi Y
L- Editor: A **E- Editor:** Wu HL





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