



Treatment of Accidentally Diagnosed Gallbladder Cancer after Laparoscopic Cholecystectomy

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Abstract

Introduction: The aim of the study was to retrospectively evaluate a group of 34 patients who underwent surgery due to incidental gallbladder carcinoma after laparoscopic cholecystectomy at the University Hospital Plzeň in 2005-2015.

Cohort: 34 patients after laparoscopic cholecystectomy with an accidental finding of gallbladder carcinoma in the definitive histological examination were included, not only at our site, but also at other sites in the Czech Republic. Radical cholecystectomy was performed at our site.

Results: Postoperative mortality in the group was 0%, morbidity was 24%. The most frequent complications included collection in the post-resection bed and right-side fluidothorax. The 5 year survival rate was 68% on average, but depended on the tumour staging.

Conclusion: Due to the early stages of incidental gallbladder cancer after LCHE, the patients have a very good prognosis in a specialized surgical centre after radical surgery.

Introduction

Laparoscopic cholecystectomy is one of the most commonly planned surgeries in the world and in our country. Chronic cholecystitis and its more severe stages cannot be reliably distinguished from a tumour - gall bladder carcinoma. No available examinations, such as ultrasound, computed tomography scan, magnetic resonance imaging, endosonographic examination with FNAB, or the use of ultrasound with contrast medium, can clearly distinguish a tumour from chronic cholecystitis. If preoperative examinations indicate a high risk that the gallbladder will be affected by a carcinoma, in our opinion, we should not operate laparoscopically, with the exception of laparoscopic staging in borderline operable findings or diagnostic laparoscopies for tumour staging.

However, "uncomplicated" cholelithiasis is increasingly more often managed laparoscopically, where the result of the biopsy may surprise us by malignancy in the gallbladder wall. If we do not find the tumour during the surgery and we do not immediately attempt a radical solution, we create a group of patients who are mostly discharged to home care after laparoscopic cholecystectomy, and the operating surgeon receives a biopsy result confirming gallbladder cancer only afterwards. The incidence of gallbladder carcinoma diagnosed in such manner ranges in the reports from 0.35% to 2% [1]. The prognosis of these accidentally found, incidental gall bladder carcinomas is significantly better than in pre-operatively confirmed tumours. Gallbladder cancer is two times more common in women than in men, but there are significant geographical differences. In Norway, the ratio of women to men is 2:1 while in Chile, the ratio of women to men is 2,7:1. In Europe, the highest incidence is in Central and Southern Europe - Germany, the Czech and Slovak Republics and Spain; in America the highest incidence is in Central and South America (Chile, Peru, Ecuador and Colombia), and in North America, a high incidence is stated in the indigenous Indian population. India, Japan, China and Korea are the Asian countries with the highest incidence [2].

In the case of incidental gallbladder cancer, it is necessary to consider the staging, *i.e.*, T1, T2 and T3, grading of the tumour and the overall condition of the patient, and decide quickly on complete radical-extended cholecystectomy - *i.e.*, bed resection, sometimes the entire S4 and S5 liver segments, including S1, and lymphadenectomy of the hepatoduodenal ligament, or careful monitoring of a T1a tumour. A preoperative evaluation of the spread through the ductus cysticus towards the bile ducts is necessary. The resection line must always be free of the tumour, so that it is a so-called "R0 resection".

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The surgeon should indicate re-operation in the shortest possible time after the primary surgery - laparoscopic cholecystectomy. The optimal time is within 1 week to 2 weeks after the primary surgery.

Often, we experience a delayed response from the operating surgeon and the site where the patient is referred to oncology after receiving the biopsy result, but the oncologist does not have any type of successful treatment and refers the patient for a complete radical procedure. This way, we are unnecessarily losing time before the radical surgery, sometimes up to 3 weeks to 4 weeks. The delay is undesirable especially in such an aggressive tumour as gallbladder cancer. Only 4% to 16% of the findings are suitable for radical surgery. The median 5-year survival rate of all stages of gallbladder cancer is only 5%.

Patient Group, Method

Patients who had undergone surgery at the department of surgery due to gallbladder cancer detected during laparoscopic cholecystectomy between 2005 and 2015 were not retrospectively included in the study if the primary surgery indication was not a carcinoma or a large gallbladder polyp (more than 1 cm), but cholelithiasis or chronic cholecystitis. Altogether, 34 patients after LCHE with gallbladder cancer confirmed in a definitive biopsy examination were referred to our department during this period. In 4 cases, the patient had already undergone primary cholecystectomy with the conversion to an open procedure, as it was not possible to complete cholecystectomy laparoscopically due to technical constraints. The completion of radical R0 resection with bed resection and lymphadenectomy was indicated in all stage T1b and T2 patients, part of T3 patients and T1a patients were indicated if the integrity of the gall bladder was not preserved or the biopsy finding was unambiguous.

We attempted to perform the procedure as soon as possible after the primary LCHE - optimally within 1 week, in our conditions within 14 days. The longest period after the primary surgery was 3 months due to the lack of discipline of the patient.

In the pre-operative examination, we usually require at least an ultrasound examination of the liver and computed tomography CT scan of the liver, the lungs in more phases to identify tumour residues, metastases in the liver, lymph nodes outside the hepatoduodenal ligaments, on the peritoneum or in the lungs. MRI, and PET-CT or PET-MR are preferable due to their greater ability to demonstrate extrahepatic affection. MRCP or ERCP can be used for visualisation of the biliary tract branches in case of a suspicion of biliary tract affection.

The procedure was performed from a subcostal incision in the right side. At that time, we started peroperative ultrasound examination. Further, bed resection and lymphadenectomy of the hepatoduodenal ligament were performed. The bed resection corresponded to the size of the infiltration mostly in the range of the S4 and S5 segments. Lymphadenectomy was radical, leaving only the structures of the arteries, portal vein and bile duct. The area of the nodes in the para-aortic area was not removed. On the contrary, the spread of the tumour to this area precluded radical management due to a very poor prognosis. Perioperative biopsy was used in suspicious objects or deposits outside of the resection area to exclude generalization. The intraoperative examination always focused also on the stub of the biliary duct or biliary tract to preserve a clean resection line. If the gallbladder had not been removed during LCHE,

Table 1: Numbers of patient according to tumour staging.

T1a with gallbladder wall affection	1 patient
T1b	18 patients
T2	10 patients
T3	06 patients

Table 2: Seventh edition of gallbladder carcinoma staging according to AJCC / used since 2010.

Stage I	T1N0M0
Stage II	T2N0M0
Stage IIIa	T3N0M0
Stage IIIb	T1-3N1M0
Stage IVa	T4N0-1M0
Stage IVb	T1-4N2M0 or T1-4N0M1 (7)

we also excised margins of the wound used to remove the gall bladder from the abdomen. Table 1 describes number of patients according the tumor staging (Table1, 2).

Results

No 30-day postoperative mortality was observed and morbidity was 24% in this group of 34 patients after radical cholecystectomy due to incidental carcinoma (24 women, 10 men). The most common complication was bile collection in the resection line (8 cases), which was addressed by the supplementation of drainage under CT navigation. The second most common complication was bronchopneumonia, in 2 cases. The median age of the patients in the group was 65.1 years. Recurrence was most commonly reported 6 months to 13 months after the radical surgery. In the monitoring of the group of patients after the radical surgery at our liver centre, we alternated between ultrasound and CT examinations. No patients after the radical surgery had adjuvant oncological treatment. Oncological treatment was only palliative after the discovery of an inoperable tumour recurrence. Careful follow-up was chosen in patients with an accidental finding of gallbladder carcinoma after uncomplicated LCHE in the Tis and T1a stage. Two patients were not included in the published cohort. The risk of metastatic disease in the T1a stage is very low - 0.0% to 2.5%, but node metastases have been described in this stage in the de-differentiated form of carcinoma [3].

We always attempted R0 resection, *i.e.*, complete removal of the tumour. However, we did not perform more extensive multi-visceral resections due to poor prognosis and high morbidity. Fortunately, these approaches were not necessary in this cohort.

In the case of peroperative detection of gallbladder carcinoma during the primary surgery, *i.e.*, laparoscopic cholecystectomy in the intra-operative biopsy, it was necessary to investigate the entire abdominal cavity, remove suspicious formations, have them immediately examined and perform intra-operative ultrasound. In the case of localized disease, we converted to an open procedure and performed radical surgery from a subcostal incision.

Recurrence was found in a total of 12 patients: 1 in 18 of the T1b patients after the surgery, 6 in 10 of T2 patients, and 5 in 6 of T3 patients after the surgery. The average 5-year survival rate in all stages of incidental gall bladder carcinoma after radical surgery was excellent in our team, higher than 50%.

A positive biopsy finding in the resection material during the

radical surgery was reported in 74% of cases in the gallbladder area and in 53% of cases in lymph nodes. No positive finding was reported from the incision of the port after laparoscopy.

Patient follow-up after radical surgery is provided by our department at the liver centre. For the first 2 years, patients are examined every 3 months, alternating between ultrasound and computed tomography or magnetic resonance imaging. It is advisable to carry out a PET MR Examination in case of a suspicion of tumour spread into the abdominal cavity after the radical surgery. This examination will completely describe and differentiate the condition of the tumour and determine the extent of the tumour.

After 2 years without gallbladder cancer recurrence, the time between visits to the liver office was extended to 6 months, and after 5 years, the follow-up of these patients was discontinued. We did not routinely use CIA or Ca19-9 oncomarkers in gallbladder monitoring.

Discussion

Gallbladder cancer is the most common biliary tract cancer. It is asymptomatic for a long time and late stages are preoperatively diagnosed in up to 60% of cases. Gallbladder cancer accidentally detected after LCHE is often of a lower, *i.e.*, earlier stage. For this reason, the prognosis for incidental carcinoma is good compared to a group of patients with preoperatively diagnosed gallbladder cancer.

Polyps with a size over 1 cm in diameter, chronic long-lasting inflammation, and possibly hormonal dependence (oestrogen and progesterone) affect the aetiology of gallbladder carcinoma. Thus, such tumour is 2 times more common in women than in men, and the number of pregnancies in women is also of interest, as gallbladder tissue is sensitive to these hormones and their high levels during pregnancy. Additionally, diabetes mellitus, smoking and alcohol consumption are suspected of affecting the development of gallbladder carcinoma. Chronic cholecystitis with gallbladder calcium salt incrustation - porcelain gallbladder - is considered to be a quite pronounced precancerosis where the risk of carcinoma development is 10% to 20%. Other risk groups include patients with pancreatic area maljunction, and patients with choledochus cysts, where chronic inflammation also likely contributes to the development of the carcinoma.

Symptoms in the group of patients with accidentally diagnosed carcinoma after LCHE do not differ from the lithiasis group. Significant weight loss was found in only 2 cases in our study (T2 stages and T3 stages). Icterus did not occur in the group of accidentally diagnosed gallbladder carcinomas.

Radical surgery, bed resection and lymphadenectomy of the hepatoduodenal ligament were first performed in 1954 by Glenn [4]. Since then, it has been used in the therapy as it can be curative and significantly affects the survival of patients with lower-stage gallbladder carcinoma. For a long time, there have been disputes as to whether to perform this radical intervention at the T1a stage. The gall bladder wall has only 3 layers – the mucosa, muscular layer and serous layer. Lamina muscularis mucosae and submucosa are missing. For this reason, node metastases have been described even in the T1a stage. However, the risk is very small and careful follow-up provides the same long-term results.

Another source of discussion is whether gallbladder carcinoma should be removed in an open or laparoscopic procedure. In our opinion, the procedure in a diagnosed carcinoma should always be

open. Laparoscopic management has recently been described in T1b stages, where radical procedure was performed laparoscopically [5].

The use of laparoscopy in the early stages of gallbladder cancer is, contrary to our position, supported by negative findings in all excised scars after ports performed in 7 patients in the T2 stage and T3 stage. The small number of these patients will probably be of some importance, although no cases of recurrence in the scar after radical cholecystectomy (N=34) were found in the follow-up period.

However, due to the metastases in the port and on the peritoneum after laparoscopy in gallbladder carcinoma reported in the literature, laparoscopic management is not recommended. Radical cholecystectomy in all stages of gallbladder cancer clearly shows better long-term outcomes than simple cholecystectomy [6].

Because of the poor prognosis of gallbladder cancer, the radical procedure should be performed as soon as possible and with utmost care and radicality. Other therapeutic modalities - adjuvant oncology therapy or radiotherapy, do not prolong life expectancy. Besides lymph nodes, it is also good to remove lymphatic vessels from the area of the ligament and hilum of the liver, so that only the portal vein, the left and right branch of the hepatic artery and biliary duct enter the liver. When exploring the nodes in this location, it is also advantageous to perform Kocher's manoeuvre. If we preserve the exposed biliary duct, we should try to preserve both small arteries together with the delicate pericholedochus vascular plexus that nourishes its wall. Their names are derived from their course - 3 o'clock and 9 o'clock artery.

Removal of these structures may lead to ischaemia and stenosis of the biliary duct. In our case, such a stenosis developed in one patient within 10 months of the radical surgery. The advantage was that this stenosis could be resolved endoscopically - dilatation and stenting.

With regard to the findings of submucosal infiltration, some authors (Shimitu, Japan) recommend a complete resection of the biliary tract, in addition to lymphadenectomy, in gallbladder carcinoma cases. On the other hand, other authors such as Makuuchi, Japan [2,7], do not recommend this radical approach. We incline to intra-operative biopsy of the cystic duct and, in the case of a positive finding, resect the biliary tract up to the microscopically healthy tissue.

In inoperable findings, which we encounter rather sporadically after LCHE, we indicate symptomatic treatment after consulting an oncologist - pain relief, endoscopic therapy of icterus, etc. Some literature reports from recent years suggest better gallbladder cancer survival when using the combination of 5-fluorouracil, doxorubicin and mitomycin C [8,9].

In the case of a relapse, it is possible to perform a repeated procedure with the removal of the affected area, unless the disease is generalized. However, the success rate of repeated surgeries due to the recurrence of gallbladder cancer is very low. In most cases, re-operations will find inoperable generalization of the tumour.

Conclusion

If gallbladder carcinoma is revealed in the definite histological examination after LCHE, the patient should always be referred to a specialized site for consideration of radical surgery as soon as possible after the primary surgery. Only radical surgery may be curative or can significantly prolong the survival of patients with a good quality

of life. However, the indication of radical extended cholecystectomy must be based on multiple factors. In addition to staging and grading the tumour, the patient's age and comorbidities must be seriously considered.

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