Editorial

Bile spillage should be avoided in elective cholecystectomy

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We read with great interest the article entitled "Adverse Outcomes After Bile Spillage in Incidental Gallbladder Cancers: A Population-based Study" by Michael J. Horkoff *et al.*, which was e-published the 13th of April, 2019 in *Annals of Surgery* (1). This retrospective study was conducted by the University of Calgary and included all cholecystectomies performed from 2001–2015 in the region of Alberta, Canada. The aim of the study was to evaluate if bile spillage during the index operation for presumed benign gallstone disease would affect survival in the group of patients found to have incidental gallbladder cancer.

Gallbladder cancer is a rare cancer disease with a dismal prognosis. So far, radical resection is the only curative treatment, and for T1b and more advanced stages this should at least include resection of the gallbladder fossa and regional lymph nodes (2). Incidental gallbladder cancer, found in specimens after cholecystectomy for expected benign gallstone disease, stage T1b and above should therefore be restaged and offered reresection in order to increase the chance for cure. Risk factors for not proceeding to reresection are non-radical primary surgery and advanced tumour stage. Previous study, from the German incidental gallbladder cancer registry, regarding biliary spillage have shown that this increases the risk of tumour recurrence even if a retrieval bag was used, and this was also reported from a recent review (3,4). One retrospective study has shown a negative impact on overall survival after bile spillage but could not show increased risk of peritoneal carcinomatos (5). Furthermore, reduced recurrence free survival has been found when spillage of bile occurs (6).

In this large retrospective study by Horkoff *et al.*, 115,484 cholecystectomies were performed between 2001–2015 and 129 (0.11%) incidental gallbladder cancers were found. Out of these, 47 were excluded due to missed cholecystectomy report (n=17), other cancer forms (n=4), early stages Tis (n=10), T1a (n=2), and metastatic tumours (n=14). Therefore, 82 patients with gallbladder adenocarcinomas were included in the analysis. Fifty-five (67%) had bile spillage during the index cholecystectomy, the majority of these, n=32 (58%), were due to accidental perforation, in 16 cases (29%) gallbladder decompression was performed to facilitate manipulation of the gallbladder during the operation, and in 7 cases (13%), cholangiography was performed and may have caused some bile spillage. No one of the cholangiography patients developed carcinomatosis, which may indicate that no major bile leak occurred but the number of patients were too low know.

In the bile spillage group increased rate of peritoneal carcinomatosis was found, 24% (13/55) *vs.* 4% (1/27) among patients that did not have bile leak (P=0.0287). The carcinomatosis was identified at different stages during the follow up. One patient (1.2%) developed a port site metastasis, 6 patients (7.3%) were identified at the staging CT scan. In two patients, diagnostic laparoscopy encountered the disease and four were found at laparotomy for reresection. The final two later developed carcinomatosis after radical reresection.

The study also showed a reduced likelihood to go to reresection in the bile spillage group [25% (14/55) *vs.* 56% (15/27); P=0.0131]. This reduction in reresection rate was also shown to be an independent factor in multivariable analysis where T-stage, gender, and age were included, strengthening the bile spillage as the reason for lower resection rate.

The reduced reresection rate, increased risk of peritoneal carcinomatosis and reduced R0 rate in the resected patients also translated into a shorter median disease free survival (7.67 *vs.* 22.33 months; P=0.0389). Cox proportional modeling adjusted for age, sex, and tumor T stage demonstrated bile spillage to be the strongest independent predictor, of shorter DFS, but not median overall survival (15.83 *vs.* 31.27 months; P=0.0742). Taken together these data indicate that bile spillage may also impact on overall survival but the study may have been underpowered for this endpoint.

During follow up, patients with bile spillage had a significantly higher risk of recurrence and a different pattern of recurrence. They showed both an increased risk of peritoneal carcinomatosis but also an increased risk of liver metastases. If these were solitary nodules in the liver or carcinomatosis on the liver surface was not possible to analyze due to the retrospective nature of the study.

These findings are new and emphasis the risk that the bile may contain tumour cells as reported by Tanaka *et al*. in a small case series (7) in patients with bile duct cancer. Studies analyzing tumor cells in bile from patients with gallbladder cancer are rare. One small case series showed that C-Ki-ras point mutations at codon 12 was present in the bile in 5 out of 8 patients with gallbladder adenocarcinoma (8), and this mutation as well as mutation of the *p53* gene has been found in both bile, and in tumour biopsies in patients with gallbladder cancer (9).

Only one patient (4%) in the group without bile spillage developed peritoneal carcinomatosis during the follow up, further emphasis the role of bile as the source for the development of peritoneal carcinomatosis.

This study clearly strengthens the results of previous studies regarding the negative oncological impact of bile spillage. From a gallbladder surgical point of view, performing cholecystectomies in the daily praxis, the results of this study are not easy to follow but may impact on the way cholecystectomies are performed. Bile spillage during cholecystectomy is either due to accidental perforation with a risk of 25–50% in different materials, or perioperative draining to facilitate and improve vision during cholecystectomy. The third risk, spillage of bile during a perioperative cholangiography, if correctly performed, is very low and is not a reason to abandon this procedure.

Accidental bile spillage during cholecystectomy, is not only a negative factor in incidental gallbladder cancer. It is also negative in benign disease, with increased risk of lost stones and collections of bile in the abdomen with increased risk of abscess formations. For these reasons, laparoscopic cholecystectomy should always be performed with the goal of not causing biliary spillage. In cases where perioperative drainage is needed to be able to perform a laparoscopic procedure, one should make sure that there is no suspicion at all for gallbladder cancer. In these cases the operation should be abandoned and referred to a liver surgical center.

The authors recommend starting the reresection with staging laparoscopy in cases where there had been bile spillage during the index operation due to the increased risk of peritoneal carcinomatosis. This approach would in this material lead to that about 10 patients (26%) would only have had staging laparoscopy with an expected faster recovery and earlier start of palliative chemotherapy.

In summary, spillage of bile in cases of incidental gallbladder cancer reduces the chances for curative reresection, increases the risk of peritoneal carcinomatosis and reduces recurrence free survival. For these reasons, all precautions should be made to reduce the risk of gallbladder perforation during cholecystectomy for presumed benign gallstone disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Horkoff MJ, Ahmed Z, Xu Y, et al. Adverse Outcomes After Bile Spillage in Incidental Gallbladder Cancers: A Population-based Study. Ann Surg 2019. [Epub ahead of print].
2. Sternby Eilard M, Lundgren L, Cahlin C, et al. Surgical treatment for gallbladder cancer - a systematic literature review. Scand J Gastroenterol 2017;52:505-14.
3. Goetze TO, Paolucci V. Use of retrieval bags in incidental gallbladder cancer cases. World J Surg 2009;33:2161-5.
4. Soreide K, Guest RV, Harrison EM, et al. Systematic

review of management of incidental gallbladder cancer after cholecystectomy. Br J Surg 2019;106:32-45.
5. Ouchi K, Mikuni J, Kakugawa Y. Laparoscopic cholecystectomy for gallbladder carcinoma: results of a Japanese survey of 498 patients. J Hepatobiliary Pancreat Surg 2002;9:256-60.
6. Lee JM, Kim BW, Kim WH, et al. Clinical implication of bile spillage in patients undergoing laparoscopic cholecystectomy for gallbladder cancer. Am Surg 2011;77:697-701.
7. Tanaka N, Nobori M, Suzuki Y. Does bile spillage during an operation present a risk for peritoneal metastasis in bile duct carcinoma? Surg Today 1997;27:1010-4.
8. Cariati A, Piromalli E, Cetta F. Gallbladder cancers: associated conditions, histological types, prognosis, and prevention. Eur J Gastroenterol Hepatol 2014;26:562-9.
9. Itoi T, Takei K, Shinohara Y, et al. K-ras codon 12 and p53 mutations in biopsy specimens and bile from biliary tract cancers. Pathol Int 1999;49:30-7.

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