Case reports

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Unexpected gallbladder cancer after laparoscopic cholecystectomy

An emerging problem? Reflections on four cases

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Abstract. Gallbladder cancer (GC) has been reported in 0.3–1.5% of cholecystectomies. Since the introduction of laparoscopic surgery, cholecystectomies have increased and occult GC may therefore be more frequent. Herein we analyze our own experience to determine whether there was an increase in GC. We also evaluate the risk factors for this outcome. Four patients with GC undiagnosed before surgery (four of 602 cases, or 0.66%) were submitted to laparoscopic cholecystectomy. The percentage in patients who underwent open surgery was 0.28% (two of 714 cases). Without reoperation, three patients died in the laparoscopic group and one is alive at 12 months. Trocar site metastasis was not observed. Although the percentage of GC (0.28% versus 0.66%) increased, the percentage is still in the referred average. Undiagnosed GC is on the increase. Examination of the gallbladder and a frozen section, if necessary, are recommended. Calcified gallbladders, age >70 years, a long history of stones, and a thickened gallbladder all represent significant risk factors.

Key words: Gallbladder cancer — Laparoscopic surgery — Cholecystectomy

Gallbladder cancer (GC) is a rare gastrointestinal condition that occurs in connection with ~0.3–1.5% of all cholecystectomies [15]. The prognosis is very poor if the cancer is diagnosed preoperatively. However, 15–30% of patients show no preoperative or intraoperative evidence of malignancy. Thus, they are not diagnosed until the typical histologic appearance is identified on postoperative microscopic evaluation. Theoretically, this group should have the best prognosis.

Since the introduction of laparoscopic cholecystectomy, the number of patients who undergo gallbladder removal has increased [15]; as a consequence, an increase in the number of unsuspected GC might be expected. As a matter of fact, several cases of incidental GC at laparoscopy have been reported [3, 7, 8, 10].

In our series of >600 laparoscopic cholecystectomies, we found four cases of GC that were totally unsuspected before and during operation (0.6%; four of 602 cases). We analyze these cases to determine whether the incidence of unexpected GC increased and to search for some predictive risk factors.

Case reports

Case 1

A 73-year-old woman with a 20-year history of gallstone disease underwent laparoscopic cholecystectomy. The gallbladder was very distended. An intraoperative cholangiogram showed a stone in the common bile duct. Because this case occurred early in our experience, we opted for an open approach. The cholecystectomy was performed, and the stone was extracted through a choledochotomy. A T-tube was left in the common bile duct.

The postoperative course was uneventful. Macroscopically, the wall of the gallbladder was thickened, apparently due to a chronic inflammation. Postoperative histology of the specimen showed adenocarcinoma of the gallbladder infiltrating all the wall's layers. Multiple small metastases in both lobes of the liver were observed 1 month after surgery via an ultrasound examination—a finding that inexplicably was not noted during or before surgery. The patient died 5 months later.

Case 2

A 75-year-old woman with a 15-year history of gallstone disease underwent laparoscopic cholecystectomy. At surgery, the gallbladder showed signs of chronic inflammation, but there was no macroscopic evidence of malignancy. The patient left the hospital 2 days after the operation. Surprisingly, histology showed an adenocarcinoma without invasion of the serosa (pT1). We decided not to reoperate. After 8 months, a liver metastasis was discovered on ultrasound. The patient died 13 months after surgery.

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Table 1. Reports of 24 unexpected gallbladder cancers after laparoscopic cholecystectomy

Author	Number	Age/sex	Stage	Follow-up
Gornish 1991 [10]	1	—	—	Trocar metastases at 15 wk
Drouard 1991 [6]	1	58/f	pT3	Trocar metastases at 3 mo
Barsoum & Windsor, 1992 [1]	1	73/f	pT3	Trocar metastases at 3 mo
Clair et al., 1993 [3]	1	66/f	pT3	Trocar metastases at 3 mo
O'Rourke et al., 1993 [20]	1	62/f	pT3	Trocar metastases at 3 wk
Fong et al. 1993 [8]	2	56/m	pT2	Reoperation: disease-free at 5 mo
		58/f	pT3	Peritoneal metastases after 47 days
Fligelstone et al., 1993 [7]	1	49/f	pT1B	Trocar metastases at 6 wk
Lucciarini et al. 1993 [16]	1	40/m	pT2	Peritoneal metastases at 5 mo
Lanford & Long, 1993 [14]	1	71/f	pT3	Not known
Landen SM [13]	1	40/f	pT2	Trocar metastases at 8 mo
Jacobi CA et al., 1995 [12]	1	73/f	pT2	Trocar metastases at 2 mo
Ishibashi & Magai, 1995 [11]	2	68/f	pT1A	Disease-free at 8 mo
		63/f	pT2	Disease-free at 6 mo
Ng et al., 1995 [19]	1	67/f	T3	Trocar metastases at 3 mo
Sandor et al., 1995 [21]	3	72/f	pT3	Trocar metastases at 8 mo
		65/f	—	Reoperation: disease-free at 10 mo
		69/f	pT3	Trocar metastases at 5 mo
Sorrentino et al. 1996 [23]	1	68/m	pT2	Peritoneal seeding at 1 mo
Contini 1997 [present study]	4	73/f	pT3	Died after 5 mo of liver metastases
		75/f	pT1	Died after 13 mo of liver metastases
		67/f	pT3	Died after 8 mo of liver metastases
		73/f	pT1	Alive at 8 mo

Case 3

A 67-year-old woman was admitted with a >10-year history of biliary colics. She underwent a laparoscopic cholecystectomy to remove a small, scarred, fibrotic gallbladder. Histology revealed adenocarcinoma of the gallbladder. The tumor spread to the serosal surface. As with our earlier cases, the tumor was unsuspected at surgery. The patient refused immediate reoperation; she was apparently well for 8 months after surgery, but subsequently her clinical condition deteriorated. Liver metastasis became apparent, and she died 12 months after surgery.

Case 4

A 73-year-old man with diabetes, proven gallstones, and a 15-year history of frequent biliary colic was admitted with jaundice. At ultrasound, a common bile duct stone was suspected. The patient was submitted to an ERCP, and the stone was extracted after an endoscopic papillotomy. After a few days, a laparoscopic cholecystectomy was performed. The gallbladder had a thick wall and showed signs of chronic inflammation.

The postoperative histological examination revealed a small adenocarcinoma of the fundus of the gallbladder that was limited to the mucosal and inner muscolar layer (pT1). Considering the limited invasion of the gallbladder wall, the relatively poor surgical risk of the patient, and the reluctance of the patient and his relatives to submit to a second surgery for resection of the liver bed of the gallbladder, a decision was taken to keep the patient for observation only. Eight months after surgery, he remains well. There are no signs of malignant relapse at ultrasound and no clinical signs of trocar site metastasis.

Discussion

Among patients undergoing cholecystectomy, GC has been reported in 0.3–1.5%. Given that the percentage of surgical treatment for gallbladder stones has increased in recent years from 29% to 59.3% [15], probably as a consequence of the enthusiastic application of laparoscopic surgery, theoretically we might expect a parallel increase of GC discovered at or after surgery. Several recent papers have reported cases of GC misdiagnosed or discovered as an unexpected finding at postoperative histology, especially after a laparoscopic approach (Table 1). Most of these neoplasms were locally advanced; nevertheless, they were not recognized. Moreover, peritoneal seedings and trocar metastases were consistently noted only a short time after surgery.

In our experience, the percentage of unsuspected cancers during laparoscopy in the last 4 years has been 0.6% (150 cholecystectomies per year). Conversely, an analysis of 714 open cholecystectomies performed at our center from 1979 to 1993 (at ~50 operations a year) yielded a percentage of unknown tumors at surgery of 0.28% (two cases); this percentage is similar to the rate of 0.3% reported by Bergdahl [2] in a series of 4600 cholecystectomies. Thus, we found an increased incidence of unknown GC that parallels the striking threefold increase in cholecystectomies coincident with the introduction of laparoscopic surgery. However, the small numbers do not allow any definite conclusion, and the percentage of 0.6% is still in the referred average of GC undiagnosed at surgery. In two of our patients, the neoplasm spread to the serosa of the gallbladder; whereas in the other two patients, the invasion of the wall was limited (pT1). Surprisingly, none of our cases showed trocar metastases, in spite of the fact that we did not use a plastic bag for extracting the gallbladder.

An obvious question is whether it is possible to obtain a more precise diagnosis preoperatively. In addition, we would like to establish whether there are risk factors that suggest the need for a more extensive preoperative or intraoperative assessment. Ultrasound and CT scans have been shown to be unreliable in the diagnosis of small carcinomas. The presence of gallbladder polyps at ultrasound—especially large polyps—should lead the physician to suspect cancer and to opt for an open cholecystectomy, considering that the incidence of cancer is 45% if the polyps are >15 mm [17]. Therefore, it would be wise to carefully palpate the gallbladder after the extraction. In cases where a polyp is present or a cancer is suspected, an immediate histology (frozen section) should be obtained. Calcified

gallbladders have a high incidence of associated gallbladder cancer; in these cases, a frozen section is recommended. The same procedure should be followed for patients >70 years old, and those with a long history of stones, or a thickened gallbladder wall. These conditions were present in most of the patients reported in Table 1 and in all of our patients. If malignancy is proved, conversion and a radical extended operation is recommended for most cases [21].

Is there any real difference between the open and the laparoscopic approaches in cases of occult GC? With either approach, the operative diagnosis is difficult to obtain if the cancer is small, and the flogistic changes of the gallbladder wall make the manual palpation less reliable. Moreover, tactile sensation is diminished during laparoscopy; thus, a palpable tumor may not be detected until after the gallbladder has been removed.

In addition, recent reports indicate that laparoscopic cholecystectomy may increase the risk of tumor implantation and dissemination in patients with gallbladder cancer [4], in spite of the reported lower depressive effect on cell-mediated immunity after laparoscopy. Metastasis after laparoscopy may occur at all trocar sites and is often evident at 1–6 months after surgery. In addition to this ''early'' type metastasis, a ''late'' type trocar metastasis [21] has been observed as late as 2 years after the laparoscopic procedure. Implant metastasis at trocar sites is especially common in tumors that invade the full thickness of the gallbladder wall. It has also been reported after intraoperative opening of the gallbladder. For these reasons, it is advisable to use a plastic bag to extract the gallbladder. Laser therapy, radiotherapy, or local excision [18] of the extraction sites are also indicated after a postoperative diagnosis of gallbladder cancer. Obviously, in cases where cancer is suspected, the open approach is preferable.

The therapeutic options are a matter of controversy for the <10% of GC amenable to surgical therapy. Although there have been a few long-term survivors, ''inapparent carcinoma'' of the gallbladder does not have a uniformly good prognosis, and many such patients die of recurrence [22]. If the cancer is limited to the first two internal layers, cholecystectomy is often considered to be the only therapy, because reresection offers no real advantage (and a considerable risk of complications) over the earlier operation. If the tumor invades the wall of the gallbladder and the liver bed, a reoperation for a more radical excision is suggested, especially if the patient is young and if the lesion is located on the wall, in contact with the liver.

In 1991, Gagner and Rossi [9] reported the United States experience with the use of radical operation for carcinoma of the gallbladder; no conclusions could be drawn from retrospective studies on the value of operations more radical than simple cholecystectomy. A recent survey [5] of 73 institutions, mainly in Europe, concluded that only patients with stage Tis disease have a real chance for cure following cholecystectomy; radical resection was not advocated for T3 and T4 disease. Another recent study [22] of unexpected gallbladder cancer found a 100% 5-year survival rate in the pT1 stage; the rate was 40% in the pT2 stage and 0% in the pT3 stage. In cases where a more radical operation was performed, the 5-year survival rate increased to 90% in the pT2 stage; it also increased somewhat in the pT3 and pT4 stages. These findings suggest that a more radical operation be performed in pT2 and even in more advanced cases. But though a more aggressive procedure could be useful for the early stages, the surgical decision must also take into consideration the age, surgical risk, and life expectancy of the patient.

In conclusion although it is not entirely clear whether there is an increase of ''inapparent'' GC, several cases have recently been reported after laparoscopy. These cases are probably related to the huge increase in the number of laparoscopic cholecystectomies being performed. These findings may reflect an emerging problem, with consequent diagnostic and therapeutic implications.

In order to identify unsuspected cancers, we recommend performing frozen sections in patients with gallbladder polyps, a calcified gallbladder, advanced age (>70 years), a long history of stones, or a thickened gallbladder wall. The use of a plastic bag to extract the gallbladder is mandatory in these cases.

The laparoscopic approach also brings with it some new problems, such as the presence of implant metastasis at the trocar sites and the potential for peritoneal diffusion. For these reasons, if cancer is suspected, open surgery should be preferred. At the moment, there is no agreement over surgical policy in the treatment of unsuspected GC. Whatever the treatment, the outlook for this disease is a dismal one. Therefore, its prevention is an important goal and should be based on the identification of risk factors. Removal of a gallbladder containing asymptomatic stones would be appropriate only if the risks of operation were less than the risk of cancer. More definite guidelines need to be followed for the treatment of unsuspected gallbladder cancer—a finding that is becoming more frequent in the laparoscopic era.

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