Background: Several reports claim that there is a risk that laparoscopic cholecystectomy (LC) might worsen the prognosis of unsuspected gallbladder cancer.

Hypothesis: Several factors rather than LC could influence prognosis.

Methods: A retrospective clinicopathologic study was performed on 20 patients, 9 patients (3 men and 6 women, aged from 36 to 75 years [mean age, 62.3 years]) undergoing LC and 11 patients (2 men and 9 women, aged from 53 to 91 years [mean age, 65.3 years]) undergoing open cholecystectomy (OC), with postoperatively diagnosed gallbladder cancer. The correlation was evaluated between cumulative survival rates and the following 7 prognostic factors: age, sex, histopathological grade, pathologic stage, occurrence of bile spillage, type of cholecystectomy (LC or OC), and additional surgical treatments.

Results: Seven patients (87%) after LC and 9 patients (82%) after OC had cancer recurrence: the difference is of no statistical significance ($P = .9$). There were no recurrences of cancer in the abdominal wall after either LC or OC. Survival rate was statistically correlated to tumor stage ($P = .007$) and to the occurrence of bile spillage ($P = .002$). Survival rate did not change according to whether the operation was carried out using LC or OC ($P = .60$).

Conclusion: These results would seem to lend support to the opinion that LC does not worsen the prognosis for unsuspected gallbladder cancer.

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WHEN EITHER open cholecystectomy (OC) or laparoscopic cholecystectomy (LC) is performed, there is a chance that gallbladder cancer may be revealed only at postoperative histologic examination of the removed gallbladder. Since Drouard et al first reported an early cutaneous seeding of gallbladder cancer after LC, several reports have alarmed laparoscopic surgeons by asserting that if the gallbladder harbors cancer, there is a high risk of port site or peritoneal early seeding. These potentially lethal complications would seem to occur more frequently after an LC than after an OC because of several oncological disadvantages of LC. Not all authors, however, share this opinion. Concern has been expressed that LC might adversely affect the prognosis of gallbladder cancer, although a recent multicenter evaluation suggested that the prognosis after LC was not significantly different from that reported in the literature after OC.

The reason for such a diversity of opinion can be explained by the extreme lack of homogeneity among the various evaluations. Most studies evaluate samples that are insufficiently large to be able to yield significant results, whereas others analyze large multicenter samples that are hampered by the difficulty to achieve homogeneity in the treatment and follow-up procedures. The objective of this study was to evaluate which factors influence the prognosis of gallbladder cancer diagnosed during or after surgery, and above all to evaluate whether the prognosis is worse after LC than after OC, using a series of 20 patients, a sufficiently large sample to allow for a statistical evaluation, and relating to a single center, to minimize the problem of homogeneity of treatment and follow-up.

RESULTS

Comparison between the 9 patients (3 men and 6 women) with unsuspected gallbladder cancer who underwent LC, aged 36 to 75 years (mean age, 62.3 years) and the
PATIENTS, MATERIALS, AND METHODS

In a series of 2300 consecutive LCs performed in the Department of Surgery at Parma University School of Medicine, Parma, Italy, from August 1992 to September 1999 on patients affected by cholelithiasis, histologic samples of the gallbladder revealed 9 cases (0.39%) of unsuspected gallbladder cancer. The medical records, imaging data, surgical records, and pathologic findings were reviewed in these patients and were compared with those relating to 11 cases (0.48%) of unsuspected cancer detected by histologic samples in a series of 2300 consecutive OCs performed at the same university unit from January 1986 to December 1999. For preoperative evaluation, all patients underwent ultrasonography and cholangiography; in none of these patients was gallbladder cancer detected by ultrasonography. A retrieval bag for gallbladder extraction was used during LC only when a perforation of the gallbladder caused or gave rise to suspicion of stone spillage. No adjunctive therapy (chemotherapy or radiotherapy) was given to any of these patients.

The recurrence of disease has been defined as any recurrence of cancer: distant metastasis, widespread or local peritoneal seeding, or scar recurrence. The presence of neoplastic tissue in the place of surgical wound was considered a scar recurrence.

Statistical analyses were carried out using statistical analysis procedures. The cumulative survival rate was calculated according to the Kaplan-Meier method. Correlation between survival rate and 7 prognostic factors (age, sex, histopathological grade, pathologic stage, occurrence of bile spillage, type of cholecystectomy (LC or OC), and additional surgical treatments) was examined using the log rank test. The analysis of variance (F test) was performed (with α = .05) for the statistical evaluation of the differences between the means in the 2 groups. The Fisher exact method was used for the statistical evaluation of differences between the percentage of frequencies. Multivariate analysis was carried out using the Cox multiple regression model to find independent variables correlated to survival rates.

11 patients (2 men and 9 women) who underwent OC, aged 53 to 91 years (mean age, 65.3 years) yielded no statistical differences between the 2 groups (Table). The preoperative diagnosis was chronic cholelithiasis in 16 patients and acute cholecystitis in the remaining 4 patients. In 1 patient malignancy was suspected directly during LC, in 3 patients malignancy was suspected directly during OC. Bile spillage occurred in 4 (22%) of 20 patients. In 2 patients (22%) who underwent LC, bile spillage was caused by gallbladder perforation during the dissection of the gallbladder bed. In 2 patients (20%) who underwent OC, it was caused by perforation of the gallbladder by the grasping forceps. Tumor stages in these patients are reported in the Table; in neither group was there a correlation between bile spillage and tumor stage. Laproscopic cholelithectomy was converted to OC in 2 patients in whom intraoperative cholangiography showed previously unsuspected stones in the common bile duct. Because these cases occurred early in our experience, we opted for an open approach. Cholecystectomy and choledochotomy were performed in one patient, cholecystectomy and hepaticojejunostomy in the other one. Common bile duct stones were also detected in 4 patients before or during OC; choledochotomy was performed in 2 of these patients and hepaticojejunostomy in the other 2.

No significant differences in tumor grading or tumor stage were found in the 2 groups (Table). No patient had pT4 disease. Invasion of the cut end of the cystic duct was found in 1 patient with pT3 disease, and metastasis of the cystic lymph node was seen in 2 patients with pT3 disease.

Four patients with pT2 disease were advised to undergo further surgery, and 3 of them who had undergone OC agreed. They underwent regional lymphadenectomy and excision of the liver bed. There were residual neoplastic foci in the resected tissue in 2 patients. The only patient with T2 disease who had undergone LC refused further surgery at first but agreed to it 2 months later. Only exploratory laparotomy was performed because of multiple small metastases around the gallbladder bed, metastases to the regional lymph nodes, and peritoneal carcinomatosis without tumor implant at the port site. Additional surgery was generally not proposed for patients with early cancer (T1) or for those with T3 or T4 cancer, with the exception of 3 patients. In 2 patients, a diagnosis was made on the initial pathology report (1 after OC and 1 after LC) of pT1b tumor invasion of the muscle layer near the liver bed. In these cases the surgeon decided to excise the liver bed and to perform regional lymphadenectomy. There were no residual neoplastic foci in the resected tissue. In 1 patient with pT3 disease, regional lymphadenectomy and excision of the liver bed were performed immediately after OC, since a small nodule on the gallbladder bed had given rise to the suspicion of cancer, a frozen-section examination was performed that resulted in the diagnosis of adenocarcinoma invading the muscle layer. Only definitive histologic examination showed pT3 disease.

There were no operative deaths, and data relating to follow-up were recorded for all patients. All of the patients in the study undergoing LC were followed-up by...
TABLE 1: Parameters Analyzed in 20 Patients With Unsuspected Gallbladder Cancer

<table>
<thead>
<tr>
<th>Patient Sex/ Age, y</th>
<th>Staging (TNM)</th>
<th>Grade</th>
<th>Type of Operation*</th>
<th>Bile Spillage</th>
<th>Postoperative Status</th>
<th>Patient Survival, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/73</td>
<td>pT1b</td>
<td>1</td>
<td>LC</td>
<td>No</td>
<td>No evidence of disease</td>
<td>45</td>
</tr>
<tr>
<td>F/75</td>
<td>pT1b</td>
<td>1</td>
<td>LC</td>
<td>No</td>
<td>Died of disease</td>
<td>13</td>
</tr>
<tr>
<td>F/49</td>
<td>pT2</td>
<td>2</td>
<td>LC</td>
<td>No</td>
<td>Died of disease</td>
<td>11</td>
</tr>
<tr>
<td>F/65</td>
<td>pT3</td>
<td>1</td>
<td>LC</td>
<td>No</td>
<td>Died of disease</td>
<td>18</td>
</tr>
<tr>
<td>M/62</td>
<td>pT3</td>
<td>1</td>
<td>LC</td>
<td>No</td>
<td>Died of disease</td>
<td>18</td>
</tr>
<tr>
<td>F/73</td>
<td>pT3</td>
<td>3</td>
<td>LC</td>
<td>Yes</td>
<td>Died of disease</td>
<td>6</td>
</tr>
<tr>
<td>F/67</td>
<td>pT3</td>
<td>1</td>
<td>LC</td>
<td>No</td>
<td>Died of disease</td>
<td>12</td>
</tr>
<tr>
<td>F/53</td>
<td>pTis</td>
<td>1</td>
<td>OC</td>
<td>No</td>
<td>No evidence of disease</td>
<td>103</td>
</tr>
<tr>
<td>F/63</td>
<td>pT1a</td>
<td>2</td>
<td>OC</td>
<td>No</td>
<td>No evidence of disease</td>
<td>151</td>
</tr>
<tr>
<td>F/68</td>
<td>pT1b</td>
<td>1</td>
<td>OC</td>
<td>No</td>
<td>Died of disease</td>
<td>32</td>
</tr>
<tr>
<td>F/57</td>
<td>pT2</td>
<td>1</td>
<td>OC</td>
<td>Yes</td>
<td>Died of disease</td>
<td>10</td>
</tr>
<tr>
<td>F/78</td>
<td>pT2</td>
<td>1</td>
<td>OC</td>
<td>No</td>
<td>Died of disease</td>
<td>18</td>
</tr>
<tr>
<td>F/63</td>
<td>pT2</td>
<td>1</td>
<td>OC</td>
<td>No</td>
<td>Died of disease</td>
<td>18</td>
</tr>
<tr>
<td>F/59</td>
<td>pT3</td>
<td>2</td>
<td>OC</td>
<td>Yes</td>
<td>Died of disease</td>
<td>10</td>
</tr>
<tr>
<td>M/67</td>
<td>pT3</td>
<td>1</td>
<td>OC</td>
<td>No</td>
<td>Died of disease</td>
<td>16</td>
</tr>
<tr>
<td>M/64</td>
<td>pT3</td>
<td>3</td>
<td>OC</td>
<td>No</td>
<td>Died of disease</td>
<td>12</td>
</tr>
<tr>
<td>F/91</td>
<td>pT3</td>
<td>1</td>
<td>OC</td>
<td>No</td>
<td>Died of disease</td>
<td>11</td>
</tr>
<tr>
<td>M/61</td>
<td>pT1b</td>
<td>2</td>
<td>LC</td>
<td>No</td>
<td>No evidence of disease</td>
<td>6</td>
</tr>
<tr>
<td>F/56</td>
<td>pT3</td>
<td>2</td>
<td>OC</td>
<td>No</td>
<td>Died of disease</td>
<td>6</td>
</tr>
</tbody>
</table>

*LC indicates laparoscopic cholecystectomy; OC, open cholecystectomy.

ultrasound and/or computed tomographic scan between 3 and 6 months after surgery, and again at 12 months (if alive). Only 6 (55%) of the 11 patients who submitted to OC had postoperative abdominal ultrasonography and/or computed tomographic scan: 2 within 6 months and 4 after 12 months or longer.

Recurrence of the disease was diagnosed in 16 patients: in 7 patients (77.7%) after LC, and in 9 patients (81.8%) after OC; the difference is not statistically significant (P = .90). Recurrences occurred after a mean of 5.7 months (recurrence range, 2-10 months) in patients who underwent LC, and after a mean of 13.4 months (recurrence range, 6-32 months) in patients who underwent OC; the difference between the means is statistically significant (P < .05). The diagnosis was affected when recurrence was still asymptomatic in 1 patient who underwent OC and in 6 patients who underwent LC. For 3 patients who underwent OC, the diagnosis of recurrence was an autopsy finding. No recurrences of cancer at the abdominal scars were found during follow-up and/or at autopsy examination either after LC or after OC.

Of the 7 patients with Tis or T1 disease, 4 patients were alive with no evidence of disease 5, 45, 103, and 151 months after surgery, and the other 3 patients died of cancer. All of the patients with T2 or T3 disease died of cancer 6 to 32 months after surgery (Table).

Survival rate was statistically correlated to tumor stage (P = .007) and to the occurrence of bile spillage (P = .002) (Figure 1). Also at multivariate analysis, tumor stage (P = .03) and bile spillage (P = .03) resulted as being independent variables correlated to survival rates.

There was no significant relation between survival rate and the other factors considered; in particular, there was no significant relation with LC or OC (P = .60) (Figure 2), or with additional surgery performed (P = .70).

Previously unexpected gallbladder cancer was found in 0.39% of our case series of patients who underwent LC. This percentage is similar to the rate of 0.35% reported in a series of 117840 cholecystectomies performed in Europe.8 The incidence of unsuspected malignancy of the gallbladder is so low that it is difficult to have in a monocentric study a sufficient number of cases to be able to identify with statistical reliability factors that could be correlated to the prognosis. However, those multicentric studies that allow for the collection of large samples inevitably suffer from lack of uniformity of diagnostic tools, treatment, and follow-up. We thus maintain that an experience such as ours, relating to 20 cases observed of 4600 cholecystectomies performed in 13 years, albeit not permitting us to draw certain conclusions, in any case provides an important piece of the puzzle.

The first observation to emerge from our results is that only 4 (20%) of the 20 patients under examination were still alive and with no evidence of the illness during follow-up. All 4 patients had stage T1 or stage Tis disease. This would seem to suggest, as has already been documented,37 that gallbladder cancer is a highly lethal malignancy unless diagnosed as an incidental finding at the early stage of disease.

The results of this case series support the hypothesis that the introduction of LC has no adverse effect on the outcome of patients with gallbladder cancer.12,14,18 Although recurrence of the disease was diagnosed earlier in the group of patients undergoing LC, no differences in survival rates were observed after LC and after OC. Possibly, earlier diagnosis of recurrence after LC was a consequence of a more intensive follow-up. Indeed, while all those patients undergoing LC had an early postoperative ultrasonographic examination or computed tomographic scan, only a few of those undergoing OC were...
followed up with an abdominal ultrasound. It can be hypothesized that abdominal wall recurrences after LC are detected earlier and more frequently only because they are more frequently and more precisely searched for. Since the rapid, worldwide success of laparoscopy has polarized the interest of the scientific literature, it is likely that anecdotal case reports of tumor implantation at trocar sites after laparoscopy had led the surgeons involved in this study to check more intensively their patients who underwent LC. This was not the case for those patients with gallbladder cancer diagnosed during OC; in fact, in 3 of these cases the diagnosis of recurrence was made at autopsy. In accord with the literature, prognosis was seen to depend on the depth of invasion.19,20

Another factor which, despite the few cases observed, resulted as being independently correlated to the prognosis of these patients was bile spillage during cholecystectomy. Wibbenmeyer et al23 have reported that gallbladder perforation during LC occurred more frequently in patients with cancer than in those with cholelithiasis. We observed bile spillage in 4 cases, 20% of the patients overall, 2 of these representing 22% of those who submitted to LC. This latter percentage is higher than the 11.6% we had found previously in a series of more than 1000 patients undergoing LC for nonneoplastic disease.21 The prognosis of those patients in whom this event occurred was significantly worse, independently of tumor stage. This is not surprising if we consider that recurrence of carcinoma of the rectum is higher in patients in whom the tumor is perforated,22 and that patients with gastric cancer have been shown to have viable cells in the peritoneal cavity when the serosa has been breached.23 If a bile spillage occurs during OC or LC in a patient with gallbladder cancer, a spillage of tumor cells may also occur, possibly accounting for the frequent rapid dissemination of this disease in many patients after cholecystectomy, both OC and LC. Also in the absence of bile spillage, a spillage of tumor cells invariably occurs if a cholecystectomy is done and the carcinomatous communication between gallbladder and liver is disrupted. This may explain the rapid peritoneal seeding in some cases observed by us in which bile spillage did not occur.

A spillage of tumor cells during LC, the contamination of surgical instruments, and the implantation of tumor cells in the subcutaneous tissue during the extraction procedure are among the factors called into question in the onset of recurrence at the trocar sites. To prevent trocar site seeding in the case of unsuspected gallbladder malignancy, some authors13,24 recommend the removal of the specimen in a retrieval bag in all cases of LC. In our opinion, the incidence of unsuspected malignancy of the gallbladder is so low at the time of LC that a general policy of extracting the gallbladder in a retrieval bag to avoid the occasional seeding of the wound is advised. The use of the retrieval bag may, however, be recommended in all cases of perforation of the gallbladder, since, besides limiting the damage of the rare event of a spillage of neoplastic cells, it prevents the more frequent event of stone spillage and the complications correlated to it.19 Surprisingly, none of our cases showed trocar metastases after LC, despite the fact that we used a plastic bag for extracting the gallbladder only in one case. We suspect that the extent of the problem after LC is nowadays overestimated, since the literature reports only those cases in which the event, which is rightly considered as being worthy of mention, actually happened. Recent articles report that the incidence of abdominal wall implantation does not increase with laparoscopic surgery but is more probably a manifestation of the aggressive nature of this tumor.12

Our results allow for some observations as to the indications for further surgery after the diagnosis of preoperatively unsuspected cancer. The literature is in agreement with the fact that patients with invasion confined to the mucosa do not need or benefit from further surgery.17,20 In the opinion of most, patients with serosal involvement do not benefit from further surgery because none of these survive for 5 years even when major resections, including hepatectomy, are performed.20,26,27 Some authors,19 however, have recently demonstrated the usefulness of major resections for T3 lesions, particularly if the cancer is minimally invasive in the liver. Resections result as being useful for T2 disease,19,20,28 although there is no consensus regarding stage T1b disease. In our series, patients with T1b disease who did not undergo radical resection died of the disease, in contrast with the only patient undergoing resection of the hepatic bed and local lymphadenectomy. These results, despite the limited number of cases observed, would seem to con-
firm the necessity for resection in the case of T1b disease.

Thus, although the limited number of cases observed does not allow for definite conclusions, the results of this study would seem to sustain the opinion that gallbladder cancer is a curable malignancy if diagnosed as an incidental finding at an early stage of a disease and that LC does not worsen the prognosis of unsuspected gallbladder cancer.

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REFERENCES


Quotation

Five things are proper to the duty of a Chirurgian: To take away that which is superfluous; to restore to their places such things as are displaced; to separate those things which are joined together; to join those that are separated; and to supply the defects of nature.

Ambrose Pare