

## Research Article

# Video Laparoscopic Cholecystectomy: The Last Diagnostic Step or the First Surgical Procedure to Prevent Cancer? A Review of Incidental Gallbladder Cancer

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### Abstract

**Aim:** Incidental gallbladder cancer (GBC) is a more and more frequent medical entity discovered on the specimen after a cholecystectomy. The aim of our study is to value the importance of cholecystectomy as last diagnostic step or surgical procedure to prevent invasive gallbladder cancer. Histological/routine examination of surgical specimen could discover a lot of hidden gallbladder cancer.

**Material and methods:** We collected data on patients treated with video laparoscopic cholecystectomy (VLC) for lithiasis, from January 2000 to December 2015. We selected 477 patients, who underwent VLC after a preoperative gallstones positive US, and who had histologic analysis of gallbladder specimens. Our outcomes were retrospectively analyzed and compared to international results for a global review.

**Results:** VLC has been realized in all patients with a rate of conversion of 5%. In 4 of these patients (0.9%) was incidentally discovered a GBC during pathological exam of specimens. All the samples showed adenocarcinoma-type lesions.

**Discussion:** The incidental finding of gallbladder cancer during VLC is a quite rare event; incidence goes from 0.2 to 2.9% (0.9% in our personal experience). Good results in term of overall survival were obtained for pTis and pT1a, while higher stages are related to a poor prognosis, especially in elderly population (due to comorbidities and less therapeutic choices). Most severe stages are related to an extremely high mortality rate.

**Conclusions:** VLC has an important role in diagnosing and treating gallbladder cancer. Lesions Tis and T1a can be efficiently treated with the only VLC approach, while more severe stages require further procedures. For this reason, we suggest the importance of a preventive cholecystectomy in high risk patients, followed by histological examination in selected cases.

**Keywords:** Gallbladder carcinoma; Lithiasis; Histological examination; Elective approach; Prevention; Videolaparoscopic cholecystectomy.

## Background

### Epidemiology

Gallbladder carcinoma is the most frequent malignancy of the biliary tract and the fourth most common biliary tract neoplasia [1]. It is a relatively rare cancer that affects only approximately

2500 patients yearly in the United States with an annual incidence estimated to be 1 to 2 people per 100.000 [2].

Gallbladder carcinoma represents the 0.5% of all the deaths for cancer. Furthermore, among other malignancies its incidence is 0.9% (up to 2.1% in patients with gallstones); this kind of cancer represents the 4% of gastroenteric tumors and it induces the 47.9% of deaths for extrahepatic biliary tract neoplasia, with a prevalence in women (with a male/female rate among 1 - 2,2) and in the over 60 population. Gallbladder cancer represents only the 0,009-0.3%

of hospitalizations or surgical procedures. Preoperative suspicion is only present in 30% of patients, while the remaining 70% is identified by pathologists later. The percentage of gallbladder removed for other reasons, which reveals the presence of cancer, ranges from 0.2% to 2.9% [3,4].

Currently is still alive the habit of avoiding the execution of a routine histological examination of gallbladder samples. International guidelines recommend histological routine in high risk areas, while in the western countries a histological evaluation should be practiced at least in the high risk population according to economic burdens [5, 6].

The incidence of gallbladder cancer in Italy is different depending on the region. The ratio between areas with the highest rates and those with the lowest rates is about 3. Besides, incidence and mortality for gallbladder cancer tend to increase in both sexes. The overall survival rate for advanced stage patients is six months, while the 5-year survival rate is about 5%. Finally, more than 80% of cancers is an adenocarcinoma and originates from the fundus (60%), the body (30%) or neck (10%) of the gallbladder. Symptoms related to gallbladder cancer are nonspecific, mimicking those of the much more common cholelithiasis, that is present in 90% of GBC.

GBC is suspected preoperatively only in 30% of the patients, whereas in the remaining 70% of cases, carcinoma is discovered during or after cholecystectomy and represent the correct definition of "incidental" GBC. Generally, the prognosis of GBC is poor and the depth of tumor penetration and the presence of lymph node metastasis have been reported as important prognostic factors. Radical surgical resection is the best chance to cure and long-term survival, but only an early diagnosis at the first stages could ensure this treatment [5, 7-9]. As the number of patients who have undergone VLC has increased worldwide, the number of cases of incidental GBC has increased too. Therefore, in the clinical setting of incidental GBC detected after VLC, surgeons might be confronted with difficulties of performing a second operation to get radicality, according to the depth or extension of the tumor [10-15].

The recurrent dilemma is about the extension of additional radical surgery. Actually, simple cholecystectomy appears to be an adequate treatment for T1a tumors, radical re-resection is necessary for other stages [16-23].

### Physiopathology

Worldwide, it has been proved that GBC incidence and prevalence rates have regional trends (highest rates in Chile, Bolivia, Peru, Ecuador, India and Poland) and it's probably due to interactions between genetic background and environmental agents. The risk increases with age, and women are affected 2-6 times more than men [24]. The main risk factor for the GBC is biliary lithiasis (BL) [25]. The association between GBC and biliary lithiasis (BL) is supported by level IIA of evidence. In patients affected by BL, GBC risk increases from 21 to 57 times [26].

Then, biliary lithiasis has been strongly associated with gallbladder cancerogenesis. Therefore, the presence of gallstones (specially stones > 2 cm) is considered a risk factor for cancer. Several risk factors have been connected to gallstones formation. They can be summed up with "5F": female, fat, fertile, forty, family.

Among the risk factors, geography and in particular ethnicity play a huge role in the BL prevalence, influencing also the type of stones formed. Cholesterol stones predominate in the Western world and developed countries while biliary pigments stones are common in Asia. The ethnic group with the highest rate of cholelithiasis is the North American Indian population (i.e. Pima Indian Population): 29.5% of men and 64.1% women are affected. In fact, these data reflect also the prevalence of Salmonella carriers (high Prevalence in American Indians). Higher Incidences in Europe are observed in Poland, Czech Republic and Slovakia [27,28]. Family history and genetic susceptibility are also key factor in the lithiasis progression. Well-known genes involved are: APOE, APOB, CEPT, CCAR, LDLR, ABCG 8. However, it should be emphasized that the cholelithiasis has a polygenic disease etiology [29-31].

Besides, cholelithiasis prevalence increases directly with aging. After 40 years the risk grows from 4 up to 10 times. Even the quality of stones varies according to the age range. Cholesterol gallstones are common in younger patients, while biliary pigments stones are found in the older ones [32].

Female sex, in particular during the childbearing age, is more than twice prone to have stones. Estrogens increase the share of cholesterol in bile composition. Progesterone, instead, works by slowing down gallbladder emptying, supporting biliary stasis [33-35]. Obesity (in particular visceral fat), metabolic syndrome, dyslipidemia and diabetes are frequently involved in the formation of stones. A loss of weight greater than 1 kg/week, increase enormously the cholelithiasis risk. This condition is frequently observed in the first 6 weeks follow-up after bariatric surgery [36,37].

Total parenteral nutrition is a known risk factor for the formation of biliary sludge [38], probably due to the suspension of the enteric stimulation on gallbladder and to the subsequent biliary stasis. Furthermore, another important risk factor for GBC is Salmonella Typhi carrier condition (Odds Ratio 4.0). Endemic regions for such condition are South Central Asia and Southeast Asia [39]. Recent findings underline a strong correlation between chronic inflammation Salmonella induced and GBC [40], supporting the possible role of this bacterium in cancerogenesis. Besides, other conditions such as primary sclerosing cholangitis (PSC), anatomic variations of the pancreatic duct and bacterial infections, are linked to the BL and GBC occurrence. All this conditions share a strong inflammatory drive [41-44].

### Material and Methods

From January 2000 to December 2015, 477 patients underwent VLC for cholelithiasis in the Clinical and Surgical Medicine

Department of the University of Naples. Patients admitted for lithiasis were retrospectively analyzed, in order to value the importance of incidental diagnosis of gallbladder cancer. We chose as inclusive criteria: age between 35 and 80, cholelithiasis diagnosed by US, and histological analysis report of the specimen obtained during VLC. Every patient has been checked-up during the hospitalization and examined with US before surgery. During US, quality, number and dimension of the stones has been collected. Gallbladder specimens obtained during VLC were processed and analyzed by pathologists, and the report was matched with the rest of the data for each patient. Tumor stage was defined according to pTNM classification proposed by the American Joint Committee on Cancer (AJCC). VLC has been realized in all patients with a rate of conversion of 5%. In all cases, precautions were taken to reduce cancer spreading even if not suspected: use of endobag, CO2 drainage through trocars and avoidance, when possible, to open gallbladder reducing bile spillage. Adjuvant therapy, after surgical resection, was administered when surgical treatment was not radical and with patients in satisfying general condition. Follow-up data were taken from medical records and telephone interviews. Patients follow-up was completed when death occurred or until May 31, 2015.

## Results

We examined a group of 477 patients (M=186 F=291), with a median age of 59.5 years (range: 35-80 years). All patients had been submitted to preoperative ultrasonography that was positive for gallstones in 66% (n=315), in 2.8% (n=9) polyps were present but not suggestive of malignancy; so patients were operated, without any suspicion, laparoscopically. About 85% (n=404) of patients had symptoms at the time of recovery or had a positive anamnesis for pain in right hypochondrium, dyspepsia, nausea, an-

orexia or jaundice; only 15% (n=48) were asymptomatic and the gallbladder disease was found during a medical check-up. In 4 of these patients (0.9%) gallbladder cancer was incidentally discovered during histopathological examination of specimens, and adenocarcinoma was recognized. According to AJCC Cancer Staging Manual, they were stages pT1b, pTis e pT3; besides, gallstones were present in all cases and margin of resection were disease-free in the first two ones.

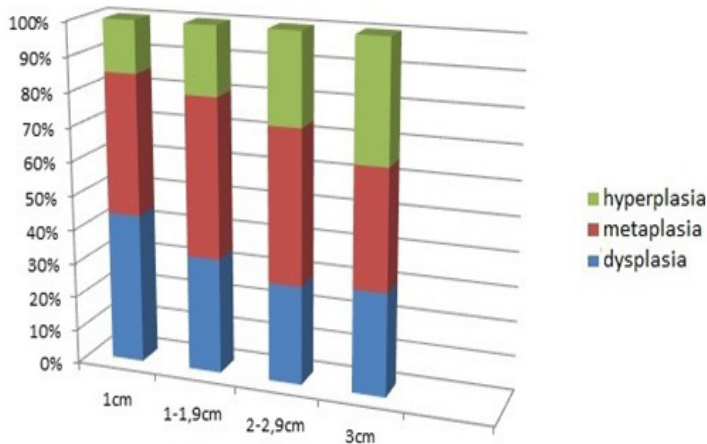
The first patient had a pT1b GBC and we decided to proceed with an extended cholecystectomy (resection including 4b+5 segmentectomy, lymphadenectomy, port-sites excision).

By contrast, two patients had a pTis GBC, so, as simple cholecystectomy ensured radical resection, no further surgical procedures were needed, but now are still followed up. The last patient had a pT3 GBC, but re-resection was not possible because of comorbidities (cirrhosis HCV-related at stage Child B, decompensated diabetes mellitus and cardiovascular disease). After VLC surgery, patient refused to begin chemotherapy. After two years of free disease survival he developed metastasis at the umbilical trocar site. It was surgically excised, but it recurred in a month. After further eight months of survival, during which patient accepted to begin therapy with 5-fluorouracil, he developed peritoneal carcinosis, three months later he was lost at the follow-up. The disease-free survival for all patients has been at least two years, while global survival has been longer than three years.

Most of the patients (99,1%) involved in this study had not malignant lesion according with pathological exam results. Between 477 patients with stones, we found: in almost all cases a chronic organ wall inflammation; in 32% hyperplasia; in 47.8% of metaplasia and dysplasia in 15% (Table 1 and 2).

	No Alterations	Hyperplasia	Metaplasia	Low Grade Dysplasia	High Grade Dysplasia
<b>Diameter</b>					
<1 cm	63	64	60	22	-
1-1,9 cm	39	34	47	20	-
2-2,9 cm	17	25	39	13	10
>3 cm	4	6	7	3	4
<b>Total: 447</b>	<b>123</b>	<b>129</b>	<b>153</b>	<b>58</b>	<b>14</b>
<b>%</b>	<b>26</b>	<b>27</b>	<b>32</b>	<b>12</b>	<b>3</b>

**Table 1:** Histological findings related to stone size.



**Table 2:** Graphic representation of Table 1.

Nevertheless, examining all the data collected, it is really clear how most severe lesions (low grade-high grade dysplasia) were present in patient with specific features, such as: stone/s bigger than 1,5 cm, several gallbladder acute inflammation and painful episodes, gallstones asymptomatic carrier for long time (15 years).

## Discussion

Our series, as retrospective study, has obvious limitation of heterogeneity bias that must be taken into consideration when interpreting the results. Therefore, one of the main problem of our study has been to create a valid population. Our data could be not representative of the real prevalence of GBC in Italy, due to poor number of cases. This is mainly due to the rarity of this kind of neoplasia, which, as told several times, represents only the 4% of gastrointestinal tumors. We choose to select 477 patients with positive US for lithiasis or polyps and with an abnormal histological exam. Despite the small number, our result seems to be comparable in term of incidence and prevalence to Western World rates [5].

Since low incidence of Incidental Gallbladder Cancers (IGBC), it is necessary to start multicentric studies to evaluate the influence of a selective histologic approach based on the various criteria presented (age, intraoperative macroscopic appearance, ethnic origin). Such studies could eliminate the heterogeneity and properly evaluate the sensitivity and specificity of each factor, either alone or in combination, to predict the risk of IGBC and indicate the histologic analysis [45-47,21]. Since laparoscopic cholecystectomy (VLC) for cholelithiasis is the third most frequent procedure in gastrointestinal surgery, incidental gallbladder carcinoma (GBC) is going to become more and more frequent medical entity. The importance of incidental diagnosis is related to possibility that it gives to surgeons to treat a very aggressive disease in early stage, thus improving significantly the prognosis. Among other things, for the implementation of VLC it is always necessary to follow precautions to reduce the spread of cancer,

even if it is not suspected preoperatively [17,18,48-51]. Indeed, some rules should be always applied to reduce damages in cases of cancer not diagnosed even during VLC, such using endobag to pull out gallbladder (in order to avoid to contaminate near organs and abdominal wall), to avoid to open gallbladder or to drain CO2 from trocars (to avert a close contact of organs and cells in suspension in gas).

Moreover, VLC is also associated with a reduction of post-operative complications, such as infections or bile duct injuries, in particular if compared to open surgery [52-57,48,49]. The incidental gallbladder carcinoma (GBC) represent from 0.2% to 2.9% of the cholecystectomies performed for gallstones and from 27% to 72% of diagnosed tumors. Despite the low prevalence of this malignancy, international guidelines further underline the need of a routine histological examination performed on surgical specimens, in order to diagnose early-stage carcinomas of the gallbladder. And this is even more significant today, since it is still common that some specimen are not histologically examined, because of both surgeon imprudence or inexperience and an irrational optimization of health care spending.

Elshaer et al. calculated the cost of conducting identification of any GBC through a histological examination of the surgical specimen and it was of £15 for each slide examined. This study analyzed 3330 gallbladders: 13 showed GBC at the histological examination. The cost to diagnose a GBC with histological routine was then estimated around £5,437.50 per case. They suggest that a more selective approach would reduce significantly the cost. In their series, the costs to detect an IGC are estimated between £2,664.0 and £3,842.30 per case using the routine histologic analysis and between £1,492.80 and £2,153.0 with a selective approach based on the age cutoff of 51 years.

In the past they had been proposed several selective approaches for histological examination. Most of them, have been based on criteria such as intraoperative macroscopic appearance of the organ and a difficulty in dissecting gallbladder from liver. It was a common belief that such gallbladder harbored more easily a cancer, considering that a longstanding lithiasis it is often associated with organ wall thickening and fibrosis. However, this is not always true, because a long history of gallstones frequently produces a thickening of the gallbladder wall in the absence of neoplasia. In fact, in a study of Panebianco et al., a suspicious intraoperative aspect was histologically correlated to GBC in only one case. Then, routine histological examination is essential to diagnose the presence of cancer, but it has serious economic implications.

In the study by Elshaer et al., it was shown that the GBC did not occur in people under 51 years of age. This age could be used as a significant discrimination factor, alone or with others (such as the macroscopic appearance of the gallbladder or the patient's native land), to help to select cases in which histological analysis

could be required [45]. Despite the small number, our population shows a very similar trend to that of the Elshaer study. Indeed, median age in our study was of 59 years. Also we observed higher grade lesions in patient who had story of “stones carrier” for at least 15 years and/or stone size > 2 cm. Those patients would be definitively included in the elective approach leading to histological examination after VLC.

With this approach could be gained both a cost optimization and adequate coverage, at least for high risk population for GBC. Thus, early GBC diagnosing through histological examination, although the economic burdens, allows to save important resources in terms of second-look surgeries, chemotherapeutic protocols and social load, which all represent an important and burdensome cause for healthcare spending. Eventually, it is necessary to underline that this elective approach could bring to a clear improvement of patient’s prognosis. In fact, in cases greater than T1a stages, histological examination has crucial role guiding the therapeutic choice and considering necessity and extension of a second look surgery. In these patients, radical surgery (in one or two steps according to the stage) provides a 5-year survival, ranging from 35 to 38% of cases. Lymph node involvement (LNI) and bile ducts infiltration (BDInf) are important prognostic factors too. Effectively, 3-year survival ranges from 65.6% in patient LNI-BDInf-, to 35.3% for LNI+BDInf-, 14.3% for LNI-BDInf+, 5.9% to LNI+BDInf+. This requires a careful histological, immunohistochemical and molecular lymph node assessment to exclude micrometastases already present in unrecognized cancers.

Postoperative prognosis is closely related to the correct approach in the first instance. Although, surgery is the only technique capable of ensuring a radical intervention in not advanced stages. Intervention aggressiveness is not related to efficacy. It has been proven that tumor biology and stage, rather than the extent of resection, are key predictors of GBC patient’s prognosis. On the other hand, an extremely aggressive resection may worsen the prognosis [58, 12, 19, 59, 60- 63].

## Conclusions

VLC for gallstone disease is the second or the third most frequent surgical procedure in gastrointestinal surgery. Therefore, IGBC is going to become an increasingly frequent medical entity. Then, incidental diagnosis importance is related to the possibility it gives to surgeon to treat a very aggressive disease at an earlier stage, improving the prognosis. VLC requires always to follow precautions (use of endobag, draining CO2 through trocars to avert chimney effect, avoid to open gallbladder reducing bile spillage) in order to reduce cancer spreading, even if it is not suspected. We retain that VLC in all patient with gallstones is a good screening method, capable of modifying the survival in GBC. Moreover, it is a definitive treatment in pT1a and a good first step procedure in all other stages. Histological examination affects both diagnosis and prognosis. Thus, we suggest elective histologic approach based on

the various criteria presented (age > 51, gallstones diameter > 2 cm, intraoperative macroscopic appearance, ethnic origin).

Based on our experience and comparing it with data found in literature, VLC should be performed in all patients with symptomatic and asymptomatic BL with other risk factors for GBC such as: female, over forty, fertile patients, with central obesity, familiarity for GBC or BL and large size gallstones (> 2cm). The best surgical treatment is prevention. VLC is the gold standard in prophylactic cholecystectomies of cholelithiasis patients, with anomalous junction of the biliary tract and polypoid lesions greater than 1 cm [64, 65] and it should be followed by histological examination of the surgical specimen, especially in the high risk population. However, other types of study are needed to confirm the elective approach role in IGBC management.

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