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Surgical Advances in the Treatment of Gallbladder Carcinoma at Different Stages

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Abstract

Gallbladder carcinoma remains the most common cancer originating from the biliary tract, which is associated with poor prognosis and poor survival rates. It is estimated that only one-third of patients with histopathological diagnostic of gallbladder cancer had been correctly diagnosed preoperatively, in the remaining cases the diagnostic being established intraoperatively or postoperatively, based on the histopathological examination. Moreover, although surgery remains the most appropriate therapeutic approach in order to improve survival, it is estimated that only 25% of cases with gallbladder carcinomas present resectable lesions. The current chapter reviews the most appropriate surgical options in patients diagnosed with both early stage and advanced stage gallbladder cancer, by minimally invasive as well as by open approach. In the meantime, the therapeutic strategies in incidentally diagnosed gallbladder cancer will be discussed.

Keywords: gallbladder cancer, atypical hepatic resection, bile duct resection, lymph node dissection, survival

1. Introduction

Gallbladder carcinoma represents the most frequently encountered malignant tumor originating from the biliary tract, with a low rate of diagnostic, a low rate of surgical treatment, and an extremely poor long-term prognostic [1, 2].

The global incidence of gallbladder cancer is low ($<2/100,000$ cases), but significant differences given by the regional and racial criteria have been reported [3].

Therefore, it has been demonstrated that women are more commonly affected by this malignancy; in regard to the patients' age, it seems that the incidence of gallbladder cancer significantly increases after the age of 40. In terms of race, it seems that the highest risk for gallbladder carcinoma has been reported among people from Chile, Poland, India, Japan, and Israel [4].

As for the risk factors incriminated for gallbladder cancer development, it seems that the presence and the dimensions of gallstones increased the body mass index as well as multiparity significantly influence it [5, 6].

2. Treatment options in gallbladder carcinoma

Surgery remains the most efficient therapeutic strategy in order to achieve long-term survival in gallbladder carcinoma patients. However, only a limited number of cases diagnosed with this pathology are amenable to surgery due to the extent of the disease. A generic observation pointed out that only one-third of gallbladder cancer patients are diagnosed preoperatively, and, among these cases, only one quart present resectable lesions [7, 8].

Incidental gallbladder carcinoma also represents a rare condition, ranging from less than 3% of all cases; however, it seems that that this situation is more common in female patients, over 65 years of age who are known with gallbladder stones or cholecystitis and originating from Asian or African descendants [9–11]. In order to provide a rapid diagnostic in such cases, intraoperative frozen section examinations have been proposed with good results [12]. As for the diagnostic criteria of incidental gallbladder carcinoma, certain authors proposed that in this category cases in which the diagnostic is not suspected during surgery or on gross examination of the specimen should be included, the neoplastic process being only detected at the histopathological examination [13].

When it comes to the extent of the resection, this parameter is dictated by the stage of the tumor; however, improvement of the surgical techniques in regard to liver resection and even liver transplantation as well as in regard to the perioperative management of these patients conducted to an increasing number of cases who can benefit from radical surgery for gallbladder carcinoma [14, 15]. Cases presenting advanced stage disease which is no longer amenable to surgery with curative intent can also benefit from palliative procedures in order to minimize the effects of gastrointestinal or biliary obstruction [2]. In selected cases adjuvant therapies such as chemotherapy or radiotherapy might be also associated in order to improve the overall outcomes [2].

3. Surgery as a therapeutic option in gallbladder carcinoma patients

The aggressivity of gallbladder cancer was maybe best defined by Alfred Blalock, an American surgeon who stated in 1924 that “in malignancy of the gallbladder, when a diagnosis can be made without exploration, no operation should be performed, inasmuch as it only shortens the patient’s life” [7]. This statement was unfortunately confirmed by a latter publication which demonstrated that on a group of 6222 patients, the cumulative survival rate was of 5–8 months, while the 5-year survival rate did not surpass 4% [16].

However, in the next decades, due to the improvement of the surgical techniques, more extended resections have been safely performed in order to cure this malignancy. This fact was maybe best demonstrated by a Canadian study which analyzed the outcomes of patients submitted to surgery for gallbladder cancer during a 12-year period; cases submitted to surgery in the second part of this interval reported an overall 5-year survival rate of 35%, significantly higher than the first period (in which the 5-year overall survival rate did not surpass 7%) [17].

Whenever gallbladder cancer is suspected, the therapeutic desiderate consists of complete tumoral resection with negative resection margins. In early stages of the disease, this desiderate is achieved if cholecystectomy en bloc with the surrounding liver bed and the regional lymph nodes are excised. In cases in which surgery is planned for a presumed benign disease and at the time of exploration the suspicion of malignancy is raised, hepatic resection should be associated; however, if the

surgical team is not prepared to perform liver resection, the patient should be transferred in a specialized center in order to be submitted to a complete surgical procedure. This sequencing of the surgical procedure seems not to influence the long-term survival of the patient [7, 18].

In cases diagnosed in early stages of the disease, it seems that a simple cholecystectomy is enough in order to achieve a good control of the disease; therefore, in stage T1a tumors, the rate of cure after simple cholecystectomy ranges between 85 and 100% [19, 20], while in stage T1b tumors, a more extended local resection should be performed in order to control the disease [21]. This extended resection usually refers to the necessity of associating a wedge hepatic resection [22].

Whenever a T2 gallbladder carcinoma is suspected, a more aggressive surgical procedure including adjacent liver resection involving the segments IVb and V and regional lymph node dissection should be added to improve the outcomes; therefore, it is estimated that, while in cases diagnosed with stage T2 gallbladder cancer, the 5-year overall survival reaches 80% if an extended surgical procedure is performed, significantly higher than simple cholecystectomy (in these cases, the 5-year overall survival ranges between 20 and 40%) [23, 24]. The necessity of resecting segments IVb/Vb is explained by the venous drainage of the gallbladder, which seems to be directed in this area [25].

An interesting study regarding the most appropriate surgical strategy in cases suspected for early gallbladder carcinoma diagnosed during or after cholecystectomy was conducted by Nitta et al. and was published in the *Annals of Medicine and Surgery* in 2018 [12]; the study included 529 patients submitted to cholecystectomy in Medico Shunju Shiroyama Hospital, Osaka, Japan, between April 2009 and December 2017. Among these cases, there were eight cases diagnosed with gallbladder cancer; five out of the eight cases were submitted to surgery for stones, while the remaining three cases were submitted to surgery for cholecystitis.

Whenever gallbladder cancer was proven at the frozen section, conversion to open surgery occurred, and the patient was submitted to gallbladder bed resection, liver resection of the segments IVb–Vb alone or in association with lymph node dissection; in the meantime if invasion of the cystic duct stump was found, prophylactic common bile duct excision was associated. After a median follow-up period of 17.9 months, five out of the eight patients were still alive; one patient initially diagnosed with stage IIIA gallbladder cancer died due to peritoneal carcinomatosis, while the other two cases died from other diseases [12].

Another interesting topic when it comes to incidental gallbladder carcinoma regards the timing of reoperation; therefore, if the patient is submitted to surgery for presumed benign pathology of the gallbladder and the histopathological studies demonstrate the presence of a malignant transformation at this level, it seems that the best outcomes are reported if early reoperation is performed. Therefore, in the study conducted by Muratore et al. on 11 patients with incidental gallbladder cancer, the authors demonstrated that the best long-term outcomes were seen if radical resection was performed within the first 2.2 months after cholecystectomy [26].

Moreover, the extent of the liver resection should be established in concordance with the local aspect: if the right portal pedicle seems to be involved, liver resection should consist of a right hepatectomy.

In cases suitable for both wedge resection and typical hepatectomy, the extent of liver resection should be carefully tailored due to the fact that in certain cases wedge resection might be insufficient (and associated with positive resection margins), while typical resection might be associated with increased morbidity rates; moreover, the decision of performing a right hepatectomy in patients associating cirrhosis should be taken after analyzing the risk of an insufficient liver remnant [25].

Study, year	No of cases	Stage at surgery	Type of surgery	Recurrence rate	Sites of recurrence	Lymph node metastasis rate	Survival rate	Gallbladder carcinoma related death	Factors influencing survival
Lee (review study) [32]	1266	T1a—706 cases T1b—560 cases	Laparoscopic cholecystectomy	1.1%	Common bile duct	2.5% (10.9% of T1b lesions and 1.8% of T1a lesions)	100% at 5-year follow-up	Eight cases with T1a lesions and 52 cases with T1b lesions died due to recurrent disease	
Nitta (single-center study) [12]	8	Tis—2 cases T1b—1 pt. T2—3 cases	Laparoscopic cholecystectomy—5 cases Open cholecystectomy—3 cases Wedge resection of the gallbladder bed—2 cases Segmental resection—1 case	12.5%	Peritoneal	NR	After a median follow-up period of 17.9 months, one case died due to the progression of the disease, while other two cases died due to other causes	One case— peritoneal carcinomatosis	
Aldossary (single-center study) [33]	76	Stage I—3 cases Stage IIA—13 cases Stage IIB—1 pt. Stage IIIB—2 cases Stage IVB—57 cases	21 cases—resection 55 cases—unresectable lesions	10.5%	NR	NR	20.5% for the entire cohort	71% of cases presented with unresectable lesions and died of disease	Resectability of the lesions Stage at diagnostic

Study, year	No of cases	Stage at surgery	Type of surgery	Recurrence rate	Sites of recurrence	Lymph node metastasis rate	Survival rate	Gallbladder carcinoma related death	Factors influencing survival
Shen (multicentric study) [2]	2379	Stage I—3.6% Stage II—7.3% Stage III A—341 cases Stage III B—333 cases Stage IV A—253 cases Stage IV B—838 cases NR—108 cases	Radical resection—641 cases Extended radical resection—82 cases Palliative surgery—499 cases Drainage—261 cases	NR	NR	29.7%	NR	NR	NR
Yildirim (single-center study) [34]	65	T1a—5 cases T1b—8 cases T2—34 cases T3—18 cases	Extended cholecystectomy—28 cases Simple cholecystectomy—37 cases	83.00%	NR	NR	Median survival—41 months 5-year overall survival rate—32%	45 cases	Lymph node status Tumor stage Type of surgery Vascular/neural invasion

Study, year	No of cases	Stage at surgery	Type of surgery	Recurrence rate	Sites of recurrence	Lymph node metastasis rate	Survival rate	Gallbladder carcinoma related death	Factors influencing survival
Jin (multicentric study) [35]	613	NR	Cholecystectomy—150 cases Partial hepatectomy—249 cases Extensive hepatectomy—25 cases Palliative/other procedures—108 cases Diagnostic—81 cases	NR	NR	NR	NR	NR	NR
Creasy, single-center study [36]	74	IIIA—2 cases IIIB—10 cases IVA—6 cases IVB—43 cases	Surgery with curative intent including resection of segments 4 and 5—6 cases Hemihepatectomy—2 cases Extended hepatectomy—2 cases Bile duct resection—10 cases	NR	NR	NR	Median overall survival—14.2 months	61 cases died due to the progression of the disease	Completeness of cytoreduction

Table 1.
The largest studies conducted on the theme of the role of surgical approach in gallbladder cancer patients.

Whenever extended liver resections are expected with a future liver remnant lesser than 25%, a portal vein embolization might be taken into consideration [27]. Another interesting subject is the one regarding the necessity of routinely association of caudate lobe resection; while the Japanese surgeons stand for routine caudate lobe resection, in the Western countries this practice is not part of the standard protocol [25, 28].

When it comes to the lymphatic spread of gallbladder cancer, anatomy studies demonstrated that the first involved lymph nodes are located along the biliary tree and represented by the cystic, common hepatic, and common bile duct lymph nodes; going further, the next involved stations are located along the pancreaticoduodenal, common hepatic artery, and coeliac axis nodes. The most distant lymph node stations are located at the level of the pancreatic body and tail; whenever tumoral cells are encountered at this level, the case is considered to have distant metastases [29].

As for the extent of the lymph node dissection, different opinions have been proposed so far: since certain authors recommended a local lymph node dissection involving the stations from the hepatoduodenal ligament, other surgeons routinely associate retropancreatic and celiac trunk lymph node dissection [7].

In cases presenting more advanced stages of the disease such as T3 gallbladder carcinomas, more extended upper abdominal resections might be taken into consideration; if the tumoral process involves the biliary duct, bile duct resection and anastomosis should be performed. Moreover if the adjacent organs (such as gastrointestinal tract or colon) are involved, segmental resections might be needed in order to achieve complete resection of the malignant process.

Special care should be provided for cases associating gallbladder cancer and stones; such patients might present local adhesions which might induce a difficult differentiation between the inflammatory and malignant transformations; therefore, a large resection is advisable in order to avoid incomplete resection. Whenever the desiderate of negative resection margins is achieved, long-term survival should be expected; in such cases the rate of 5-year overall survival ranges between 30 and 50% [30, 31].

Contrarily, patients diagnosed with stage T4 gallbladder lesions report a poor outcome, surgery with curative intent being suitable in rare cases. In such patients surgery is most commonly performed with palliative intent, while the overall survival remains extremely poor.

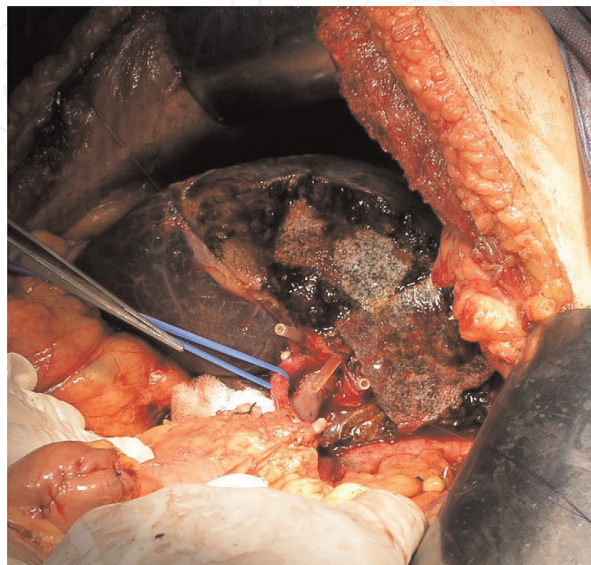


Figure 1.
Intraoperative aspect after right hepatectomy extended to the caudate lobe for locally advanced gallbladder carcinoma. Association of common bile duct resection was performed.

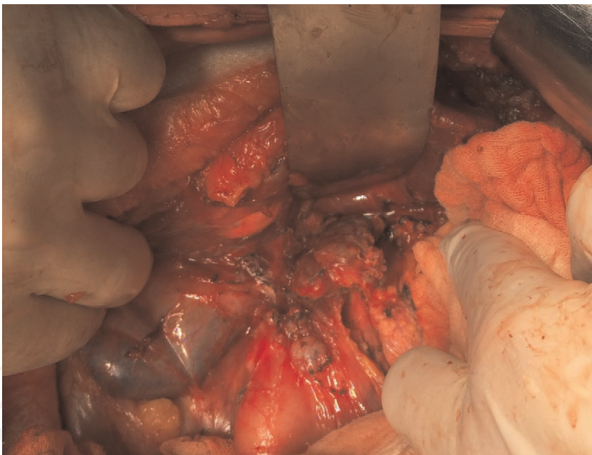


Figure 2.
Incidental finding—gallbladder carcinoma.

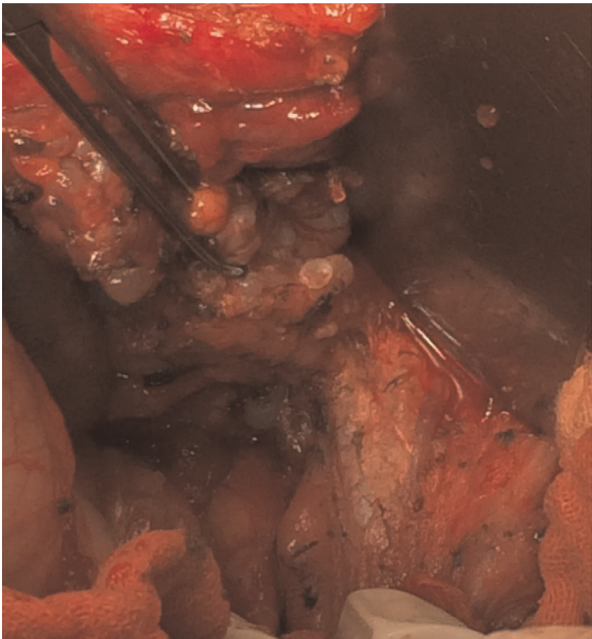


Figure 3.
Dissection of the cystic duct.



Figure 4.
The final aspect after cholecystectomy en bloc with lymph node excision.

The largest studies, which were focused on the role of surgery in gallbladder cancer patients, are summarized in **Table 1**.

Intraoperative aspects of patients submitted to surgery for gallbladder carcinoma are shown in **Figures 1–4**.

4. Laparoscopic versus open approach in gallbladder cancer patients

Although laparoscopic cholecystectomy represents one of the most facile to be performed minimally invasive procedures, there is still controversy regarding the feasibility and safety of the laparoscopic approach in gallbladder cancer patients. This fact is explained through the aspect that in such cases multiple upper abdominal resections might be needed in order to control the disease; moreover, another fact that should be taken into consideration when deciding for a minimally invasive approach in gallbladder patients is related to the risk of port-site metastases development.

One of the most recent studies which envisaged the efficacy and safety of the laparoscopic approach in gallbladder cancer patients has been recently published by the Chinese surgeons from Jiangsu [37]. The authors included in their study 102 patients with gallbladder carcinoma who were submitted to surgery between August 2008 and August 2017 in a minimally invasive manner, 41 cases, or via an open approach, 61 cases.

The authors demonstrated that there was no significant difference between the operative blood loss, operative time, postoperative complications, R0 resection, and tumor-related death between the two groups [37]. Moreover, the authors demonstrated an improved postoperative outcome for patients submitted to a minimally invasive procedure, while the long-term outcomes demonstrated similar overall survival rates at 1 year, 3 years, and 5 years postoperatively. Moreover, the authors analyzed the 5-year survival rate according to the stage at the initial diagnostic and demonstrated that there was no significant difference in terms of survival for patients submitted to surgery for Tis, T1b, T2, and T3 tumors in a minimally invasive or open approach.

In terms of recurrences and metastases, the authors reported that there was no difference in regard to the incisional site metastases between the two groups (4.9% in the laparoscopic group and 3.3% in the open approach group). However, the authors demonstrated that the risk of incisional metastases was increased in cases presenting gallbladder rupture.

When it came to the recurrence time, it seems that patients submitted to an open approach experienced relapsed disease earlier than those submitted to a minimally invasive approach; however, this aspect was rather related to the fact that among patients submitted to an open approach, a higher proportion of T3 tumors existed [37].

The subject of port-site metastases has been widely studied so far, in certain cases excision of the port sites being proposed in order to minimize this risk [38, 39].

One of the largest studies which debated the role of port-site resection in laparoscopically treated gallbladder cancer patients was conducted by Fuks et al. and was published in the *Journal of Visceral Surgery* [40]. The study included 218 patients with incidental gallbladder cancer who had been treated in a minimally invasive manner between 1998 and 2008 in 21 centers in France; among these cases, re-resection with curative intent was performed in 148 cases, 54 cases being also submitted to port-site excision.

Their results were compared to the ones reported in the remaining 94 patients who did not undergo to port-site excision. There was no significant difference between the two groups in terms of tumor stage or extent of resection. Port-site metastases were encountered in a single patient who had been previously submitted to port-site excision; it was the case of a patient who had been initially submitted to surgery for a T3 gallbladder carcinoma and who died 15 months after resection due to the development of peritoneal carcinomatosis.

However, the authors demonstrated that the 1-year, 3-year, and 5-year overall survival rates were similar between the two categories of patients; moreover, patients submitted to port-site excision developed an incisional hernia rate at the site of port excision of 8% [40].

Therefore, the authors concluded that port-site excision should not be routinely performed in such cases; an interesting aspect that was pointed out by the same study was the one regarding the possible protective role, which could be given by peritoneal frozen section surrounding the peritoneal trocar orifices in cases presenting greater or equal to T2 tumors [40].

5. Postoperative complications after surgery for gallbladder carcinoma

Whenever surgery with curative intent is performed in gallbladder carcinoma patients, the postoperative risk of developing complications seems to remain high at both 30 and 90 days postoperatively. Therefore, although most studies take into consideration the 30-day morbidity/mortality rate, it seems that maybe a more adequate tool in order to quantify the postoperative outcomes is represented by the 90-day morbidity/mortality rate. This fact seems to be true not only in gallbladder cancer patients but also in other malignancies such as pancreatic cancer and esophageal or gastric cancer [41, 42].

A recent study conducted on this theme by Goussous et al. and published in 2017 demonstrated that the postoperative mortality within the first 90 days postoperatively is 2.3-fold higher than the 30-day postoperative mortality [43]. Another interesting aspect underlined by this study was the one that the 30-day and 90-day mortality, respectively, was significantly correlated with the degree of tumoral differentiation, with the presence of vascular and lymphatic invasion, with the stage of the tumor, with incomplete resection, and with low-volume centers. Moreover, the authors demonstrated the fact that even in cases submitted to surgery in a minimally invasive manner, the 90-day mortality rate was significantly higher than the 30-day mortality rate [43].

6. Factors predicting survival after surgery for gallbladder cancer

It seems that the most important prognostic factors predicting the long-term outcomes after surgery for gallbladder carcinoma remain the stage of the disease at the time of diagnostic (including tumoral and lymph node status) as well as the completeness of resection [7, 18]. In the meantime, association of clinical signs as jaundice is most often a sign of locally advanced/unresectable disease and therefore is associated with poor rates of survival [44].

One of the most recent studies which were conducted on the theme of predictors of curative resection and long-term survival in patients with gallbladder cancer was published by Mishra et al. in the American Journal of Surgery [45]. The study included 385 patients diagnosed with gallbladder cancer between September 2003 and December 2014 in the Academic Block, GB Pant Hospital, New Delhi, India.

The authors demonstrated that cases presenting gastric outlet obstruction, weight loss, abdominal lump, and obstructive jaundice were more likely to present unresectable lesions.

Moreover, patients presenting at the time of initial diagnostic obstructive jaundice presented significantly lower rates of 1-year, 3-year and 5-year overall survival than those in whom jaundice had not been present at the time of diagnostic [45].

7. Palliative surgery for unresectable/metastatic gallbladder cancer

Due to the fact that a large proportion of patients with gallbladder cancer are diagnosed in advanced stages of the disease, when surgery with curative intent is no longer possible, palliative procedures might be needed in order to alleviate the symptoms. In such cases, the most frequently reported symptoms necessitating palliative procedures are represented by pruritus, cholangitis, jaundice, digestive obstruction, or pain. However, in this subgroup of patients, the goal of surgery is a pure palliative one, the overall survival ranging between 2 and 4 months [46, 47].

8. Conclusions

Gallbladder carcinoma remains an extremely aggressive malignancy which is rarely diagnosed in early stages of the disease; therefore the overall survival rates remain extremely poor, the most important predictors for long-term survival being related to the stage at diagnostic as well as to the completeness of resection. However, it should not be omitted the fact that most often extended upper abdominal resections might be needed in order to achieve an R0 resection; therefore such patients should be addressed in high-volume centers.

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