

## How to Ameliorate the Gallbladder Cancer Prognosis?

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### Abstract

*Cancer of the gallbladder is a serious condition. In the majority of cases, it is conventional to say that making the diagnosis of this cancer is practically announcing the death very close to the patient. However, it seems that this remains incompletely true and that various advances have emerged in diagnostic and the therapeutic management. With advances in imaging (transcutaneous ultrasound, computed tomography, endoscopy, magnetic resonance imaging, etc.), those in liver surgery, anesthesia-resuscitation, chemotherapy and radiotherapy, some prognostic improvements are emerging. This presentation is intended to be as complete as possible of the diagnostic and therapeutic possibilities that will allow better management of a patient with cancer of the gallbladder. We will review diagnostic means with some definitions. The essential surgical therapeutic indications, the non-surgical therapies which have given some results. This update also emphasizes the combination of effective therapies such as radical surgery and chemotherapy*

**Keywords:** *gallbladder cancer - early diagnosis - radical surgery - prognostic improvement*

### INTRODUCTION

Gallbladder cancer remains a lethal pathology to date in the short term and 5-year survival in all stages combined hardly exceeds 5% [1,2]. The main reason for this is due to late diagnosis. Eighty percent of patients have their tumor recognized at the locoregional and / or metastatic invasion stage. Surgery, the basic treatment for this cancer, can only be offered to a small number of patients at this stage. This surgery most often has a palliative nature [3]. Moreover, several other reasons contribute to this state of affairs :

- 1-The ignorance of the useful stages (cancers confined to the gallbladder) [4].
- 2- The inadequacy of surgical therapy in the face of so-called histological discoveries.
- 3- An unsuitable surgical attitude towards advanced cases.
- 4- The difficulty of diagnosis at a useful stage (forms localized to the gallbladder).
- 5- The role of effectiveness of adjuvant treatments such as chemotherapy or radiotherapy.

In this update, we will review all of these situations and give certain indications so that the intervener in the overall care of the patient can offer the patient the most effective therapy. We will not use the TNM staging but the following terms : localised gallbladder cancer, advanced gallbladder cancer and metastatic gallbladder cancer.

### ESTABLISHING THE DIAGNOSIS

The diagnosis of gallbladder cancer is made in the majority of cases at an advanced stage when the tumor has invaded the neighboring organs represented by the liver, the digestive tract and especially the main bile duct [5]. In addition, this contiguity invasion is frequently associated with metastatic localizations represented essentially by hepatic metastases and peritoneal carcinosis [6, 7]. Consequently, radical resection surgery is rarely indicated in these locally advanced and / or metastatic forms [8]. Thus, it is more profitable to make the diagnosis at the useful stage for which the surgery is operative with resection rates and appreciable survival [9,10]. Making diagnosis at the stage on which the tumor does not invade the neighboring viscera is the first goal for the clinicians

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to offer the chance to surgeon to eradicate the tumor with curative intent

You should know that making the diagnosis at the stage is possible with modern means of exploration.

### ESTABLISHING THE DIAGNOSIS AT THE USEFUL STAGE (CANCER CONFINED TO THE GALLBLADDER)

This must be a challenge for the clinician and especially the radiologist. At this stage, the tumor must be asymptomatic apart from the clinical signs of associated vesicular lithiasis. The clinician must rely on imagery to arrive at the diagnosis. The radiologist has a very important role to play thanks to the performance of a hepatobiliary and vesicular echotomography (ECT). You should know that at this stage the tumor has 2 macroscopic aspects can evoke a cancer of the gallbladder.

### THE POLYPOID FORM AND THE INFILTRATING FORM [11]

In this batch of tumors, we find early cancers [12]. We must say tumors whose transparietal extension does not extend beyond the muscularis of the organ or the the forms affecting the mucosa (pT1a), the muscularis (pT1b) and invasive cancers, which are tumors that have reached the subserosa (pT2) and serosa (pT3). The issue here is important since patients with early tumors recover by simple cholecystectomy (pT1a ) or radical resection for pT1b [publications in favor of radical surgery for pT1b] when tumors while pT2 and pT3 radical surgery is necessary [13].

Some of the histological discoveries belong to this

**Table1.** *Criteria for malignancy of gallbladder polyp*

Author	Year	Diameter >10mm	Sessile	Uniqc	Age over than 60 years	Quick growth
Koga	1988	+			+	
Chijiwa	1994	+	+	+	+	
Kubota	1995	+	+			+
Toda	1995	+				

For localized thickening that is easy to recognize, it is easy for us to offer surgery adapted to the lesion quickly. It should be emphasized that this type of cancer represents between 20 to 30% of all cancers and unfortunately the majority of them are subcontracted since only a simple cholecystectomy is performed when they are discovered.

group too. The radiologist plays a big role thanks to the practice of echotomography. The latter must carefully examine the thickness of the wall. The examination should be done in at least 2 different patient positions. The polyp is a structure with the same echostructure as the liver. It is immobile when the patient's position changes and does not give the image of a shadow cone [14]. These characters differentiate it from the calculation. But if the isolated polyp is easy to recognize, the presence of several calculations hinders the recognition of the latter which is somehow hidden by the lithiasis.

### THE INFILTRATING FORM IS RECOGNIZED BY THE RADIOLOGIST

in the form of localized or generalized wall thickening. When the thickening is localized, it should be taken for cancer until histological proof to the contrary [15].

When diffuse, thickening is a differential diagnosis with acute cholecystitis first. Other conditions can be discussed such as adenomyosis but which is easy to recognize.

In the case of a polyp image, the diameter remains to this day the central element of the decision [Table 1]. The frequency of cancer is low below 10mm while it is believed to be from this dimension. Some authors have found a frequency of 100% of cancers from 18mm in diameter [16]. So from a practical point of view, any image of thickening or polyp whose diameter is greater than 10mm must direct the patient to the surgeon So from a practical point of view, any image of thickening or polyp whose diameter is greater than 10mm must direct the patient to the surgeon.

Cancer in the form of generalized thickening, which causes acute cholecystitis to be discussed, remains difficult to remember or eliminate and only the histological evidence will decide [17, 18]. Finally, it should also be noted that the latter may be associated with cancer and the problem not resolved is : overtreat the benign lesion and undertreat the malignant disease.

### **ESTABLISHING THE DIAGNOSIS IN ADVANCED FORMS (CANCER WITH INVASION OF NEIGHBORING ORGANS)**

These forms are symptomatic and it should be noted that cancer of the symptomatic gallbladder is most often advanced. The clinical signs sign of an extension of the disease to the neighboring organs and / or a metastatic spread. Contrary to a traditional notion, palpation of the tumor mass is not always pejorative [19]. In our experience, 40% of patients with this sign have been able to benefit from curative surgery. Only the presence of jaundice still retains a pejorative character. According to Miyazaki [20], no icteric patient survived 5 years after curative surgery as in our experience. In this group of patients with advanced disease, the contribution of the ultrasound-CT scan couple has a privileged place. Generally speaking, hepatobiliary ultrasound visualizes well the invasion of the liver, the neighboring digestive tract and that of the main bile duct. The main interest of computed tomography is the study of the tumor extension towards the digestive tract (colon, duodenum, stomach) and the pancreas. In these forms, the most important is to differentiate between a locoregional and metastatic extension. Currently, cholangio-MRI is an increasingly important examination in the exploration of jaundiced patients [21].

The differential diagnosis is also constituted by acute pseudotumoral cholecystitis (xanthogranulomatous cholecystitis) [22]. The latter can simulate in all points a vesicular cancer as well by its clinical aspects, as morphological (radiological and intraoperative). In our experience, we have had diagnostic difficulties in 40 patients in whom the final histological diagnosis was in favor of cholecystitis. 16 of them have had gallbladder cancer treatment. In the literature, cases with hepatic excision have also been reported in patients with pseudotumoral cholecystitis [20]. Doppler ultrasound seems to be an interesting test to differentiate between cholecystitis and cancer [23]. It is imperative before these advanced cases to select the patients well for a surgical gesture with curative aim or failing this with palliative aim. Overall, patients with good general condition, without tare or with a minor or balanced tare and with a tumor without metastatic extension are good candidates for curative surgery. Extension to the liver is the one that responds the most to radical resection with an interesting resection rate and survival [20].

In the event of metastatic diffusion, patients in good general condition can benefit from radical surgery in selected patients [7].

### **THE APPROACH TO TAKE IN FRONT OF SO-CALLED HISTOLOGICAL DISCOVERY FORMS**

You should know that this notion of histological discovery defined by itself the notion of insufficient diagnosis of these forms which at the time of cholecystectomy were pT1b, pT2 and pT3 tumors. After 1 to 3 months later, these forms will have a locoregional extension and / or metastatic. These are in fact cancers that went unnoticed by preoperative ultrasound scanning of these lithiasic gallbladders. Indeed, these histological discoveries are cancers confined to the gallbladder and for the majority of them invasive cancers [23,24]. Eighty percent of these cancers are invasive. In our experience, 90% of these forms are invasive.

If we start from the principle that all these forms are recognized before cholecystectomy then they will be treated before the alteration of their stage [25 Special Issue]. The prognosis will be worsen after the cholecystectomy secondary to tumoral dissemination by surgeon gestures. Improving the management of these forms requires improvement in preoperative diagnostics (this is what we developed in the previous chapter) and adequate surgery. Out of 100 cholecystectomies for cholelithiasis, 1 to 2 cancers are found after histological reading of the operating room. In our casuistry, the proportion of histological discoveries is 180 out of 990 gallbladder cancers (18%). The treatment of choice is radical surgery. The latter combines a hepatectomy of variable importance with a lymphadenectomy both of variable importance [26, 27,28].

On the other hand, these forms are to some extent recognizable intraoperatively. The surgeon must be very vigilant in front of a whitish or retracted appearance of the serous vesicular (therefore visible on the serous side) which are in favor of a pT3 tumor already. Thus, any suspicion of an intraoperative tumor must make the surgeon think and act. On the other hand, any resected vesicle must be opened and examined by the surgeon before the laparotomy is closed. 90% of the histological discovery lesions in our series presented a macroscopic lesion visible at the opening of the gallbladder. Any suspicious lesion must be subjected to a histological examination in

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extemporaneous or cold. Reoperation for additional surgery should be performed as soon as possible. In our experience, this delay in surgical recovery is 1 month. Indeed, the rate of additional excision is 100% at one month, then decreases to less than 10% beyond 3 months and practically disappears thereafter. In the literature, some authors also advise to re-operate the patient within the month as well. This resumption of surgery has, for some, the same long-term results as an intervention made immediately [29].

There are 3 levels to improve their diagnosis and therefore their prognosis of these forms

### Recognize them Before Cholecystectomy

In our view, this is a big part of diagnostic and prognostic improvement through the practice of careful echotomographic exploration. The radiologist must be alert. He has to scrutinize the gallbladder wall for a localized or generalized polyp or thickening. The examination to properly highlight a polyp must be done by changing the patient's position (dorsal decubitus and right and left lateral decubitus). In this way, we can advance that the diagnostic improvement for these asymptomatic forms or drowned in the symptomatology of the lithiasic disease.

On another level, with the advent of magnetic resonance imaging, the radiologist there too must look for the presence of a biliopancreatic junction anomaly. Its diagnosis must lead to prophylactic cholecystectomy given the great risk of cancer of the gallbladder and the main bile duct [30, 31].

### Recognize it During Cholecystectomy

During surgery for cholelithiasis, if a parietal abnormality is detected by the surgeon, the latter must have the following 2 attitudes :

- a- If he has the competence of the radical surgery of the gallbladder cancer and after an extemporaneous histological examination of confirmation, he will carry out the radical gesture.
- b- If he does not have the competence of the radical surgery of the gallbladder cancer and / or in the absence of possibilities of histological examination in extemporaneous, he must do nothing, close the laparotomy or remove the trocars. The patient should be explored secondarily and radical surgery performed after this exploration

### Examine the Cholecystectomy Part Systematically and Immediately

after cholecystectomy and adopt the same attitudes as for the previous chapter .

### HOW TO DEAL WITH ADVANCED FORMS OF CANCER (INFILTRATION OF NEIGHBORING VISCERA AND/OR METASTATIC FORMS) WHEN WE USE RADICAL SURGERY

Eighty gallbladder cancers are currently recognized at this stage. The key issue is to identify patients who may be undergoing radical excision surgery. The latter is retained in patients with absence of hepatic, peritoneal, pulmonary metastases and having a good general condition. This surgery has produced interesting results for many authors in terms of morbidity and mortality and long-term survival [32, 33, 34, 35, 36]. This type of advanced tumor therefore seems to benefit from a radical approach even in the elderly [37]. In our practice, we carried out 110 radical resection with a mortality of 17%, a morbidity of 40% and a 5-year survival excluding postoperative mortality of 16% [38].

### THE BEHAVIOR TO BE FOLLOWED IN FRONT OF THE ADVANCED FORMS IS OFTEN PALLIATIVE BUT A RADICAL RESECTION CAN BE RETAINED AFTER A PRECISE SELECTION OF THE PATIENTS

Radical surgery ranges from IV-V bisegmentectomy to cephalic hepatoduodenopancreatectomy which is the heaviest surgery in this case [39, 40]. Significant survival can be obtained from these forms when adequate surgery is performed in an expert center. It is for this reason that the surgical teams invested in the management of this disease must be alert and measure the indication. If a team cannot perform a very heavy surgery, it must pass the hand to another more expert.

The lymphadenectomy is the second aspect of radical surgery and in our view the extended technic is the appropriate one for this disease. A minimally of 16 nodes must be removed to better stage the patients. Removing a lot of nodes could have a therapeutic role. Some Japanese surgeons had published good results on this aspect [41, 42, 43].

Faced with these forms, the possibility of palliative surgical treatment should be considered in patients whose life expectancy is greater than 3 months and who cannot benefit from radical surgery. For us, a palliative treatment is a palliative excision or a double

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biliary and digestive diversion. Patients aged 75 and over, with severe or unbalanced tare, very advanced disease (multiple and bilateral metastases to the liver, massive peritoneal carcinosis and multiple loco-regional invasion), are not good candidates for surgery with radical excision [44, 45].

### THE CONTRIBUTION OF NON-SURGICAL TREATMENTS

Contrary to popular belief, gallbladder cancer appears to be chemosensitive and radiosensitive. Indeed, several authors have reported interesting results [46, 47, 48].

Since 2017, a simple regimen with oral 5fluoro-uracil is the standard regime in adjuvant view after radical surgery [49].

In our experience, systemic chemotherapy based on Gemcitabine and Cisplatin gave us a response rate of 28.5% with secondary excision of tumors initially unresectable in 12 out of 84 patients (14.3%). The average overall survival was 12 months (03—50 months). Survival after curative resection is 24 months and only 12 months without resection. [50]. In the literature, the objective response rate of systemic chemotherapy varies between 10% and 40% [51,52]. For radiotherapy, various publications have reported interesting results in both the adjuvant and palliative setting [53,54]. It is towards these 2 directions that efforts must also be made in order to better consolidate the operative act whether it is for curative or palliative aim.

We must emphasize that any patient who presents an objective response after palliative chemotherapy must be discussed for a possible secondary surgical

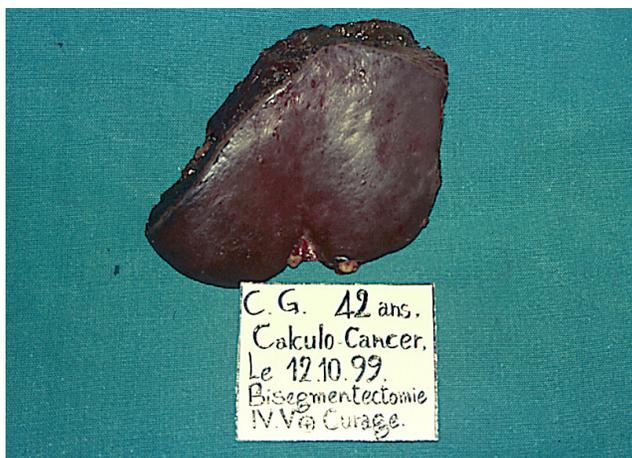
procedure [55, 56].

### ESTABLISHING A FOLLOW-UP OF TREATED PATIENTS

Monitoring patients after curative surgery is very important. And even if the overwhelming majority of recurrences reported to date in the literature are not curable [57] and rare are the favorable responses in the face of a recurrence of vesicular cancer [56]. In our experience, out of 54 cases of recurrence we performed a new excision in 4 patients (8%) with a respective survival of 04 months and 22 months and palliative surgery in 20 patients (40%) with a survival of 3 months medium [58]. We also performed 3 iterative hepatectomies for gallbladder cancer recurred to date in 2 patients who had strict follow-up at the 17th and 24th month postoperative. Monitoring therefore seems to be one of the means to improve the prognosis of this disease.

### CONCLUSION

these are the points that seem important to us in the management of gallbladder cancer. They help improve the prognosis of this dreaded condition. The involvement of the various stakeholders (general practitioner, surgeon, medical oncologist, radiotherapists, gastroenterologists, anatomopathologist and radiologist) is one of the conditions for this. We must offer each patient the appropriate therapy, curative or palliative that allows him to live in a comfortable and as long as possible. The surgeon remains to this day the essential element of this care and it is his responsibility not to abandon the game and to encourage other stakeholders to better care and greater commitment through diagnostic means and therapeutics that exist today.



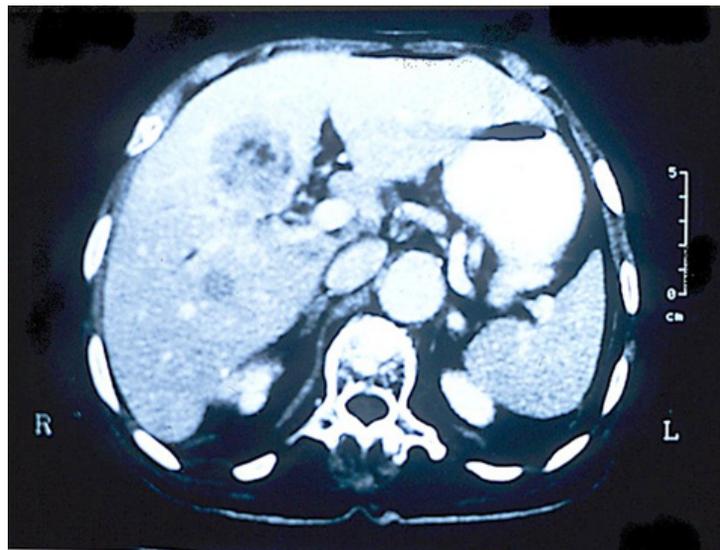
**Fig1.** Bisegmentectomy IV-V for adenocarcinoma discovered on specimen. Patient alive after without recurrence at 248 months.



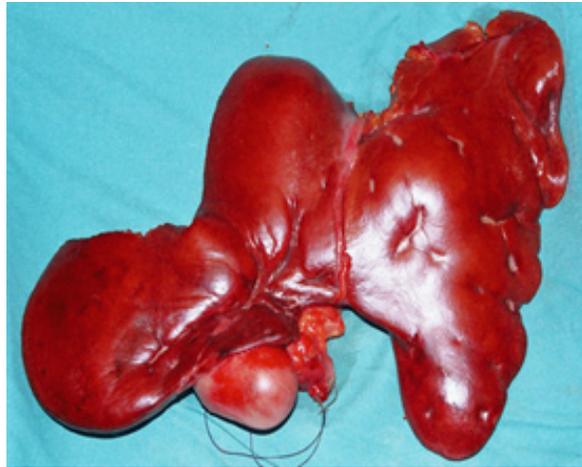
**Fig2.** Bisegmentectomy IV-V. Patient alive at 100months.



**Fig3.** Polyp of fundus. Bisegmentectomy IV-V with lymphadenectomy. Patient alive at 150months.



**Fig4.** CT scan. Metastasis of segments IV and VII. Patient died from recurrence at 8months



**Fig5.** Left hepatectomy extended to segment V. Hepatectomy done after neoadjuvant chemotherapy for metastatic gallbladder cancer. We note the umbilicated foci which are scars of hepatic metastases.

**Summary table for improving prognosis of gallbladder cancer :**

**The six axes**

**1- Diagnosis :**

**Alert radiologist → Alert radiologist who scrutinizes the  
gallbladder wall**

**2- Decrease of the number of histological discovery :**

**Alert radiologist → Alert radiologist who scrutinizes the  
gallbladder wall**

**Surgeon aware about macroscopic form of cancer**

**3- Optimal surgery for localized forms:**

**Minimal of bisegmentectomy IV-V**

**Lymphadenectomy at 2stages steps or 3steps**

**(Extensive lymphadenectomy to remove maximal nodes  
even in inter-aorto-caval area)**

**4- Optimal surgery associated ith chemotherapy :**

**Locoregional forms :**

**First surgery if total resection if possible + chemotherapy**

**Neoadjuvant approach followed by surgery and chemotherapy**

**Metastatic forms :**

**First surgery if total resection ispossible + chemotherapy**

**Neoadjuvant approach followed by surgery and chemotherapy**

**5- Optimal approach for not resectable forms :**

**Biliary diversion and/or dogestive diversion**

**Chemotherapy**

### Secondary discussion of the patient's case with objective

#### Response

#### 6- Optimal approach for the palliative approach :

Palliative surgery associated with chemotherapy

Instrumental diversion associated with chemotherapy

Supportive care for very advanced diseases and patients with major visceral defects

### ANNEX

#### Definitions

##### *Early Cancer*

tumor whose extension does not extend beyond the muscularis of the organ.

##### *Confined Cancer*

tumor of the gallbladder that has not protruded from the gallbladder.

##### *Invasive Cancer*

tumor whose extension has exceeded the muscularis.

##### *Advanced Cancer*

cancer whose extension affects neighboring organs and / or is accompanied by hepatic or peritoneal metastases or both.

##### *Histological Discoveries*

tumor the diagnosis of which is made by the histologist after reading the operating room.

##### *Radical Surgery*

surgery which removes the gallbladder, a more or less important part of the liver and the lymph-ganglionic structures which may be interested in tumor spread.

##### *Palliative Surgery*

surgery that removes the tumor without curative claim or that performs a biliary and / or digestive bypass to treat a symptom.

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