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Early Gallbladder Cancer: Clinical, Morphological, Therapeutic and Evolutionary Aspects

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ABSTRACT

Introduction: The early cancer of gallbladder is an entity which is not well recognized currently. It is a cancer which does not extend beyond the muscularis layer of the gallbladder and it is characterized in almost of cases by the absence of lymph node and visceral invasion. **Patients and Method:** We have conducted this retrospective study of all our cases of early gallbladder cancer treated in our surgical unit. We have studied these through clinical, morphological, therapeutical and evolutionary aspects. **Results:** Of 202 gallbladder carcinoma, 33 cancers were classified as early cancer. 25 were females and 8 were males. The mean age was 56.4 years (41 - 70 years). All patients were free of gallbladder cancer symptoms and all except one had normal CEA and CA19.9. 2 patients had synchronous tumors (one colonic cancer and one rectal cancer). For 16 patients, the diagnosis was done by ultrasonography and 17 by histological examination of the specimen removed for biliary lithiasis. 8 patients had PT1a tumor (confined only to mucosa) and 25 had PT1b tumor (tumor infiltration of the muscular layer). For 19 patients who benefited from extensive lymphadenectomy, only one (5.3%) had lymph node infiltration. 16 patients had a simple cholecystectomy and in two cases, the cholecystectomy was associated with bile duct resection. 17 patients had hepatectomy with extensive lymphadenectomy. 2 patients had a simultaneous right colectomy and abdominoperineal resection and another one benefited from choledocal cyst resection. 3 patients benefited from stone removal from bile duct and two had tumor removal from bile duct (ruptured tumor in the bile duct). 1 patient (3.7%) died in postoperative course (hospital mortality). In the follow-up period, 4 patients died from intercurrent causes. Two patients presented a recurrence at 14 and 36 months and died respectively at 19 and 42 months. One patient presented a bile duct cancer at 66 months. She died at 78 months after palliative treatment. Currently, 22 patients (66.7%) are still alive without recurrence with mean and median survival of 53 and 31 months. **Conclusion:** Early gallbladder cancer is an entity which must be known by the radiologist and the surgeon. Recognized on time and well treated, early gallbladder cancer can be cured and its prognosis is excellent.

Keywords: Early Cancer; Gallbladder Cancer; Ultrasonography; Expert Radiologist; Surgical Treatment

1. Introduction

The early gallbladder cancer is an entity which is not well recognized currently. It is a tumor whose extension does not extend beyond the muscularis layer of the gallbladder and does not have frequent lymph node infiltration and metastatic spread [1]. Moreover, it represents a proportion of all gallbladder cancer which could be easily cured. In spite of modern morphologic examination and specifically an ultrasonography since twenty years, there is not a clear improvement in the diagnosis for this disease [2-4]. This form is often diagnosed after histological examination of specimen removed for biliary lithiasis. Making an exact diagnosis before surgery has an importance to improve the prognosis of this fatal disease in its invasive form. Surgery is debated when the muscular layer is invaded (pT1b) between cholecystectomy and radical resection whereas the cholecystectomy is the best treatment for the pT1a (tumor confined to mucosa). In this article, we present our experience of patients who were managed in our unit during the fifteen last years and to analyze immediate and long-term prognosis of this disease.

2. Patients and Method

We analyzed all cases of our patients treated for early gallbladder cancer. We reported the clinical, morpho-

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logical, biological, surgical and evolutionary features of these patients. The histological specimen was reanalyzed for the cancer discovered after cholecystectomy done for biliary lithiasis. All the following features were asked to the histologist: histological form and grade (differentiation), parietal extension, perineural, vascular and node infiltration. In our unit, pT1a tumor (confined to mucosa) is treated by cholecystectomy and pT1b (muscular infiltration) is treated by cholecystectomy alone for the patient above 70 years and by bisugmental IV-V with fatal associated disease and extensive lymphadenectomy for patients under 70 years and without fatal associated disease. On the postoperative course, the patient is followed clinically, biologically (Ca 19.9 and CEA) and morphologically (ultrasound) each 3 months during 2 years and each 6 months during the following 2 years. After 5 years, we propose only clinically follow up. If a recurrence is diagnosed, a CT scan or MRI is done to have an exact diagnosis and if the disease is curable we propose a new surgery for resection and in the contrary only diversion is practiced. If there is no need of surgery we propose palliative chemotherapy.

3. Results

Of 202 gallbladder cancer resected since 1996, we report 33 patients with early form (16.3%). There were 25 females and 8 males, with mean age of 56.4 years (41 - 70 years). No patient had any symptoms related to cancer before the surgery and physical examination were normal or related to lithiasis disease (pain, jaundice and palpable gallbladder in acute cholecystitis). 20 patients (60.6%) had associated biliary lithiasis. One patient had a history of choledocal cyst since 25 years. The diagnosis was done in the preoperative course in 16 cases (48.5%) by the radiologist with the ultrasonography and CT Scan. 3 last patients had an endoscopic ultrasonography. 17 cases were diagnosed on the histologist specimen. All of 24 carcino-embryonary antigen (CEA) and carbohydrate antigen 19.9 (CA19.9) measured out were normal except for one CA19.9 which was at 5618 UI/ml for patient with ruptured tumor in the bile duct and jaundice. One patient was treated for Hodgkin disease 10 years ago; 2 patients had their polypoid tumors known (diagnosed by ultrasonography) respectively 1year and ten years ago. The tumoral aspect was polypoid in 22 cases (66.7%), thickening wall in 6 cases (18%), unapparent form in 4 cases (12%) and nodular in 1 case. 2 patients had ruptured tumor in the bile duct (pT1a and pT1b). Microscopically, all these cases were adenocarcinoma. 8 cases (24.2%) were pT1a and 25 cases (75.8%) were pT1b (**Table 1**: characteristics of 27 cases). 1 patient had a choledocal cyst diagnosed and followed by a gastroenterologist during 16 years. 16 patients benefited from a cholecystectomy associated with bile duct resection in two cases for a tumoral related cause and another had her choledocal cyst removed with a gallbladder. 2 patients who have had a cholecystectomy benefited from a lymphadenectomy. For 17 patients, IV-V bisugmental hepatectomy with extensive lymphadenectomy was done. 2 patients had respectively colonic and rectal resection simultaneously. 3 patients benefited from stone removal from bile duct. Only one patient presented node infiltration between 19 who benefited from lymphadenectomy (5.3%). 24 patients (72.7%) had one operation and 9 (27.8%) two operations. The postoperative course was uneventful for 26 patients (78.8%) and complicated in 7 cases (21.2%). One patient (3%) died from myocardial infarction (**Table 2**: surgical treatment). Two patients benefited from systemic chemotherapy, one because she had had cystic infiltrative node and another had associated liver metastatic lesion. On the long term follow up, one patient received external beam therapy for uterine cervix cancer diagnosed 2 years after the cholecystectomy. One patient died from a colon cancer recurrence at 15 months without any evident gallbladder cancer recurrence. 2 patients (6%) presented a recurrence at respectively 14 and 36 months. They were initially treated by cholecystectomy. One benefited from bisugmental IV-V with lymphadenectomy and chemotherapy and died from a new recurrence at 19 months. The second patient had exploratory laparotomy and died at 42 months. One patient presented a bile duct cancer (upper part) at 66 months. She refused a surgery and died at 78 months. One patient died from acute diabetes complications at 56 months and other died from gastric hemorrhage secondary to gastric ulcus. One patient died from another disease at 67 months (portal high pressure). One was lost for follow up at 39 months. 22 patients (66.7%) are still alive with mean survival of 51 months and median survival of 32 months. The global 3 and 5 year survival are respectively 53% and 34%. 11 patients (33.3%) had more than 5 year survival and the two oldest had more than 10 years. No recurrence case occurred until nowadays for PTa tumor.

4. Discussion

The early cancer of gallbladder is a form which can be recognized by modern morphological examination but it is still diagnosed after surgery for biliary lithiasis. On clinical aspect, it is a silent disease (without any symptoms). This feature could explain this absence of diagnosis. Currently, it can be recognized in 2 situations:

- On preoperative course with ultrasonography [3-5].
- On the histological examination after cholecystectomy for biliary lithiasis [5-8].

For a clinician to make a diagnosis before a surgical step, he needs an expert radiologist who should be vigilant during ultrasound examination. There are two fundamentals lesions which are in favor of an early cancer:

Table 1. Characteristics of patients.

Case	Age	Sex	LB	D	M	M'	L	D (mm)	AP	CA19.9	CEA
1	56	F	No	HD	UNA	ADKNS	F	40	No	NA	NA
2	56	F	No	UD	P	ADK (MIXED)	C	30	No	NA	NA
3	62	F	Yes	HD	P	ADK (WD)	F + C	8 - 9	No	NA	NA
4	69	F	No	UD	P	ADK (NS)	F	30	No	NA	NA
5	65	F	No	UD	P	ADK (WD)	C	15	No	NA	NA
6	41	F	Yes	HD	TW	ADK (MD)	-	-	No	NA	NA
7	57	F	Yes	HD	P	ADK (MD)	F	12 - 15 - 20	No	NA	NA
8	61	M	No	UD	P	ADK (WD)	F + C	20	Synchronous Colon cancer	NA	NA
9	61	F	No	UD	P	ADK (WD) PAP	C	25	No	N	N
10	63	F	Yes	HD	TW	ADK (WD) PAP	F	30 - 10	No	N	N
11	68	M	Yes	UD	P	ADK(WD)	F	30	No	N	N
12	62	F	Yes	HD	P	ADK (WD)	Ne	8	No	E	N
13	48	F	Yes	HD	P	ADK (WD) PAP	NP	50	No	N	N
14	46	M	Yes	HD	TW	ADK (MIXED)	F	30	No	N	N
15	56	F	Yes	HD	P	ADK (WD)	UNA	30	No	N	N
16	70	F	No	UD	P	ADK (WD) PAP	F	40	No	N	N
17	58	F	Yes	HD	UNA	ADK (WD)	C	15	No	N	N
18	60	M	No	UD	P	ADK (WD) PAP	F	50	No	N	N
19	50	F	Yes	UD	P	ADK (WD) + CM	C	20	No	E	N
20	45	F	Yes	UD	P	ADK (WD)	F	-	BPM	N	N
21	45	M	Yes	HD	TW	ADK (MD)	Ne	30	No	N	N
22	58	M	No	UD	P	ADK (WD)	F	35	No	N	N
23	55	F	Yes	HD	P	ADK (WD)	Ne		No	N	N
24	60	F	Yes	HD	UNA	ADK (WD)	F	25	URC + rectal cancer	N	N
25	58	F	No	UD	P	ADK (WD)	F	15	No	N	N
26	47	M	Yes	HD	UNA	ADK (WD)	F	-	No	N	N
27	56	F	No	UD	P	ADK (WD)	Ne	-	No	N	N
28	46	M	No	UD	P	ADK (WD)	Ne	-	No	N	N
29	60	F	No	UD	P	ADK (WD)	NP	25	No	N	N
30*	47	F	Yes	HD	TW	ADKNS	TW	-	No	N	N
31	70	F	Yes	HD	NOD	ADK (WD)	NO	-	No	NA	NA
32	54	F	Yes	HD	P	ADK (WD)	P	20	No	N	N
33	56	F	Yes	HD		ADKWD	TW	-		N	N

BPM: biliary pancreatic maljunction; BL: biliary lithiasis; D: diagnosis; E: elevated; F: fundus; C: corpus; Ne: neck. HD: histological discovery; CC: choledocal cyst; ADKWD: adenocarcinoma well-differentiated, M: Macroscopic aspect. M': microscopy; AMD: adenocarcinoma mean differentiated, ADKNS: adenocarcinoma not specified; L: location; N: normal; AP: associated pathology; Ca19.9: carbohydrate antigen 19.9; CEA: carcino-embryonary antigen; P: polypoid lesion; TW: thickened wall; NOD: nodal aspect; UD: ultrasound discovery UN: unapparent; URC: ulcerative.

- The most easier form to be detected is a polypoid form (**Figure 1**).

It is an image which is appended to the gallbladder wall. It has the same ultrasound-structure than the liver. It is immobile at the patient positions changes and does not give an acoustic shadow. This polyp could be single or multiple, with or without a pedicle. Some features could orient to the malignant nature, but the strong element is the polyp diameter (**Table 2**: malignant criterion of gallbladder polyp). If the polypoid form is easily recognized in a gallbladder without stones by the radiologist, this last could misinterpret the diagnosis when the gallbladder contains several stones. In this case, the tumor lesion could be hidden by stones and this diagnosis become difficult if not impossible. For this reason, the ultrasonography should be done on 2 different positions (lying on the back and on the side). With the lithiasis, acute cholecystitis with the inflammatory changes induced could impede the polyp detection by the radiologist.

- The second image of the early cancer is represented by a thickening wall (infiltrative form). This abnormality could be localized or generalized in the gallbladder wall.

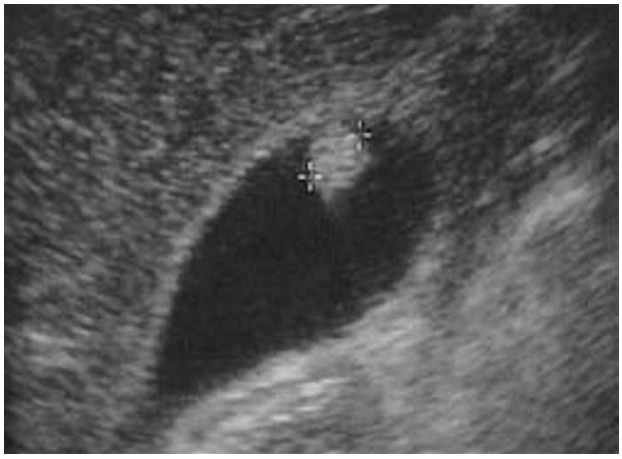

Figure 1. Image of polypoid lesion of the fundus of the gallbladder on ultrasound examination.

Table 2. Therapeutic and evolutionary aspects.

Case	Treatment	Postoperative course	Current status	Cause of death
1	CX	Simple	AWD at 120 months	
2	CX	Simple	AWD at 126 months	
3	IV-V+ lymphadenectomy	Simple	AWD at 156 months	
4	CX	Simple	DWD at 56 months*	
5	IV-V + lymphadenectomy	Simple	AWD at 140 months	
6	IV-V + lymphadenectomy	External biliary fistula	LOF at 39 months	
7	CX	Simple	AWD at 96 months	
8	CX + colonic resection	Simple	DWD at 15 months*	Died from colonic cancer recurrence
9	CX	Simple	DWD at 78 months	Bile duct cancer
10	CX	Simple	AWD at 81 months	
11	IV-V + lymphadenectomy + tumor removal from bile duct	Residual tumor in bile duct	Alive at 69 months	
12	CX	Simple	DOD at 19 months	Hepatic recurrence
13	CX + bile duct resection	Simple	AWD at 68 months	
14	CX	Simple	AWD at 72 months	
15	CX	Simple	DOD at 42 months	Hepatic recurrence
16	IV-V + lymphadenectomy + chemotherapy	Simple	DWD at 67 months	Hypertension portal?
17	CX + IV-V + lymphadenectomy	Lymphatic fistula	DWD at 20 months	Gastric ulcer Hemorrhage
18	CX+ IV-V + lymphadenectomy	Postoperative death	POD	Myocardial infarction
19	IV-V + lymphadenectomy + tumor removal from bile duct	External biliary fistula	AWD at 37 months	
21	IV-V + lymphadenectomy	Simple	AWD at 37 months	
20	CX + choledocal cyst resection	Simple	AWD at 36 months	
22	IV-V + lymphadenectomy	Wound sepsis	AWD at 28 months	
23	IV-V + lymphadenectomy	Hepatic necrosis	AWD at 28 months	
24	CX + abdominoperineal resection	Simple	AWD at 25 months	
25	IV-V + lymphadenectomy	Simple	AWD at 27 months	
26	CX	Simple	AWD at 25 months	
27	IV-V lymphadenectomy	Simple	AWD at 20 months	
28	CX+IV-V+ lymphadenectomy	Simple	AWD at 18 months	
29	IV-V+ lymphadenectomy + chemotherapy	Wound sepsis	AWD at 20 months	
32	CX+ IV-V+ lymphadenectomy	Simple	AWD at 10 months	
31	CX	Simple	AWD at 8 months	
30*	CX+ bile duct resection	Simple	AWD at 7 months	
33	CX + IV – V + lymphadenectomy	Acute renal failure	AWD at 4 months	

AWD: alive without disease; DWD: died without disease; DOD: died with disease; LOF: lost for follow up; POD: postoperative death; CX: cholecystectomy; IV-V: bisugmental hepatectomy.

For the radiologist, each lesion of this kind detected with a meticulous examination of the gallbladder wall should be considered as a malignant lesion especially when it is limited to one part of the wall. The difficulty is represented by the presence of the acute cholecystitis. Onoyama [3] had used the ultrasonography for 53 patients with an early cancer. He was able to do the diagnosis in 34% of all form of cases. For the polypoid form, the preoperative diagnosis had been done in 75% of cases in the absence of lithiasis whereas it was possible only in 38.1% of cases in presence of lithiasis. For the infiltrative form (thickening wall), the diagnosis was done respectively in 5.9% et 0%. Tsuchiya [5] founds the same difficulty in his series in presence of lithiasis and with the thickening wall. The early cancer of the gallbladder is suspected between the patients of the first group (INF0) of the Japanese Society of biliary surgery (JSBS) [9]. In our series and with the same examination (trans-cutaneous ultrasonography), the preoperative diagnosis have been done only in 16 cases (48.5%) and all these cases were

polypoid form. Between these, 5cases had lithiasis and 5 did not have. The contribution of the CT scan (**Figure 2**) for the diagnostic is good and the endoscopic ultrasonography seems also to be an excellent tool if well executed [4,10]. The endoscopic ultrasonography should be done after the trans-cutaneous ultrasonography (second intention). This examination could show the degree of parietal extension and then made a difference between an early form (pT1) and invasive form (pT2 and pT3) of gallbladder cancer [10]. But, few studies had been done with this examination currently. In our experience, we have started the practice of the endoscopic ultrasonography and the preliminary results are encouraging.

The second possibility to recognize this form of gallbladder cancer is represented by the histological examination of gallbladder specimen resected for biliary lithiasis and it is more common until nowadays. It is well known that in the almost cases, the surgeon can perfectly suspect this cancer after opening the gallbladder. It is macroscopically apparent on the mucosa of the gallbladder in almost cases [2,3,6,7,11,12]. In our series, it was the case (macroscopically visible) in 29 cases (87.8%) after the opening of the gallbladder by the surgeon. It was easy for a polypoid form and difficult for the thickening form especially when it is associated with cholecystitis. This fact is very important for the treatment and binds the surgeon to open the gallbladder at the end of the intervention and scrutinize the gallbladder mucosa and its wall [8] (**Figure 3**). 4 unapparent forms (mucosa apparently normal in case of acute cholecystitis) were encountered in our series (intraepithelial adenocarcinoma) and not recognized. For us, each resected gallbladder should be opened and carefully examined at the end of intervention and before the abdominal closure or port ablation by the surgeon. The specimen should have a histological ex-

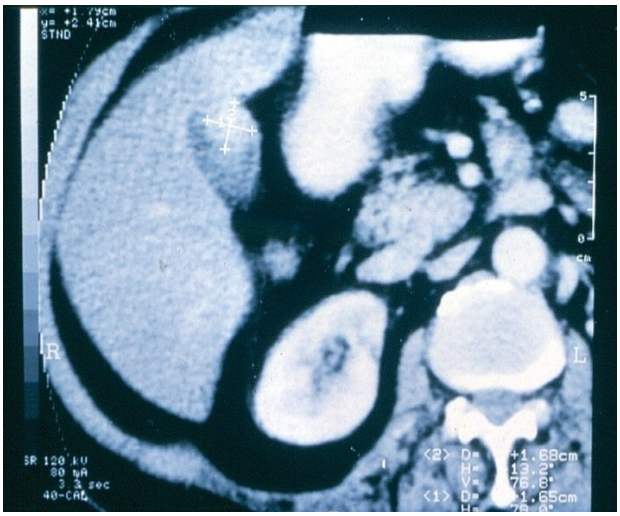

Figure 2. Image of polypoid lesion of the fundus of the gallbladder on CT scan examination.

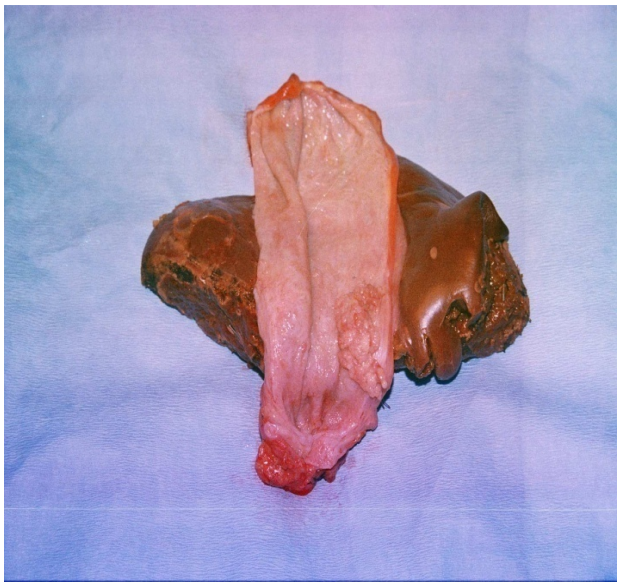

Figure 3. Specimen of PT1b gallbladder cancer.

amination in a short delay. All parts of the gallbladder must be examined. In this series, we encountered infiltrative cystic stump in which high degree of dysplasia was found after the second operation done 2 months later in patient who benefited from bile duct resection after a cholecystectomy.

The treatment of early gallbladder cancer is surgery [6,11-15]. The best treatment is cholecystectomy which is curative for the majority of the authors [8,16-19]. For others, the cholecystectomy is sufficient only for the pT1a form (mucosal tumor). A radical resection (cholecystectomy associated with hepatectomy and lymphadenectomy) is indicated for the pT1b form (involvement of the muscularis layer) [20-22]. This controversy seems to found its explanation in the fact that these authors find a node extension in the PT1b form [14,20]. For Shimizu *et al.* [23] and Shukla *et al.* [24], the best treatment for PT1b is a radical cholecystectomy and then the reoperation is recommended. In our series, two patients with pT1b tumor presented recurrence at 14 and 36 months (6%) after cholecystectomy alone and one have an infiltrative cystic node. No patient has presented any recurrence until now after radical resection for PT1b. Another explanation of this controversy could be the imperfection of the histological examination and some cases of the PT1b are in fact invasive form PT2 or even PT3 for which the cholecystectomy is insufficient. We have an example with patient who had 2 foci of tumor, one PT1b in the corpus of the gallbladder and another PT3 in the neck (data not shown). M. A. Abramson *et al.* [25] demonstrated that the greatest benefit in gained life-years is achieved for the youngest ages having radical resection. We agree with this view. For us, if the patient with pT1b tumor is 70-year-old or less and without a serious general disease and a long life

expectancy, the radical surgery (re-resection) is indicated but if the age is upon 70 years or the patient has a serious general disease or a short life expectancy, the radical surgery in must be avoided. It is what we have chosen for our patient. A recent and large study has reported a good prognosis with radical surgery which contains hepatectomy and lymphadenectomy [25].

If the diagnosis is done in the preoperative step, the radical approach is indicated for us when we do not know infiltrative degree in the gallbladder wall. We started recently the use of endoscopic ultrasonography after trans-cutaneous ultrasonography in the aim to explore the wall extension and to not misinterpret an invasive form (PT2 or PT3) and make a difference between PT1a and PT1b. In the opposite case, the decision is difficult. Should we do a simple cholecystectomy or a radical resection? During the intervention, the surgeon could lead himself on the aspect of the serous layer for the tumor located on peritoneal side of the gallbladder. If it is an early form, the serous layer is normal but if it is the contrary (retraction of serous surface and white color…), invasive form must be suspected. If the doubt persists, the surgeon could practice a radical cholecystectomy if the patient can support this surgery. If the diagnosis is done after the opening of the gallbladder at the end of the operation, it is wiser to wait the definitive histological examination. If it is a pT1a cancer the cholecystectomy is sufficient. The invasive form (PT2-T3) and PT1b needs a second operation [6,8]. The quality of the histological examination is fundamental. The histologist should verify with a multiple sections if there is not foci of invasive tumor or a lesion in the Rokitanski-Aschoff sinus and for a lesion near cystic channel (tumor of the neck) in which a surgeon would have cut in the tumor [8]. Others criterion are perineural infiltration and vascular embolus which must be noted in the histological report. If the patient presents a node infiltration, we advocate a systemic chemotherapy as adjuvant therapy. We have used systemic chemotherapy for two of our (one with infiltrative node and one with small liver metastasis).

The postoperative course is simple in almost cases. The prognosis of this form of gallbladder cancer is excellent with a cholecystectomy [2,11,14,16,18] and radical cholecystectomy. The 5 year survival fluctuates between 70% and 100% [2,7,8,11,14,16-21,26]. In our experience, we encountered one death (radical cholecystectomy) not related to the surgery (myocardial infarction). It is one of the favorable form in which we can talk about a complete recovery after a treatment, even if late recurrences have been reported in the literature [11,21].

5. Conclusion

There is a clear evidence through our experience and literature that the early gallbladder cancer could be recognized in the preoperative course with the modern morphologic examination (trans-cutaneous ultrasonography, CT scan, endoscopic ultrasonography…) and on histological specimen. This form is without gallbladder cancer symptoms, and tumor markers (CEA and CA19.9) are usually normal. A polypoid is the easy recognizable morphological form by the radiologist. The thickened wall form is more difficult to be diagnosed on ultrasonography. We focus on the fact that all the specialized teams (radiologist, surgeon, gastroenterologist, histologist…) are concerned in order to have a well conducted diagnosis approach and treatment. The radiologist is the key-element in this way. The trans-cutaneous ultrasonography examination (referential examination) should be done in minimally two positions in order to not misinterpret a tumoral lesion. Each infiltrative lesion (thick wall) must be addressed to a surgeon for a cholecystectomy. For the polypoid lesion, each polyp whose the diameter is above 10 mm is an indication of a cholecystectomy. Follow-up with ultrasonography for a lesion under 10 mm is indicated (**Figure 4**). The surgeon must do a simple cholecystectomy in case of PT1a and radical resection for the PT1b for the majority of cases. Well treated, almost of these patients will be cured.

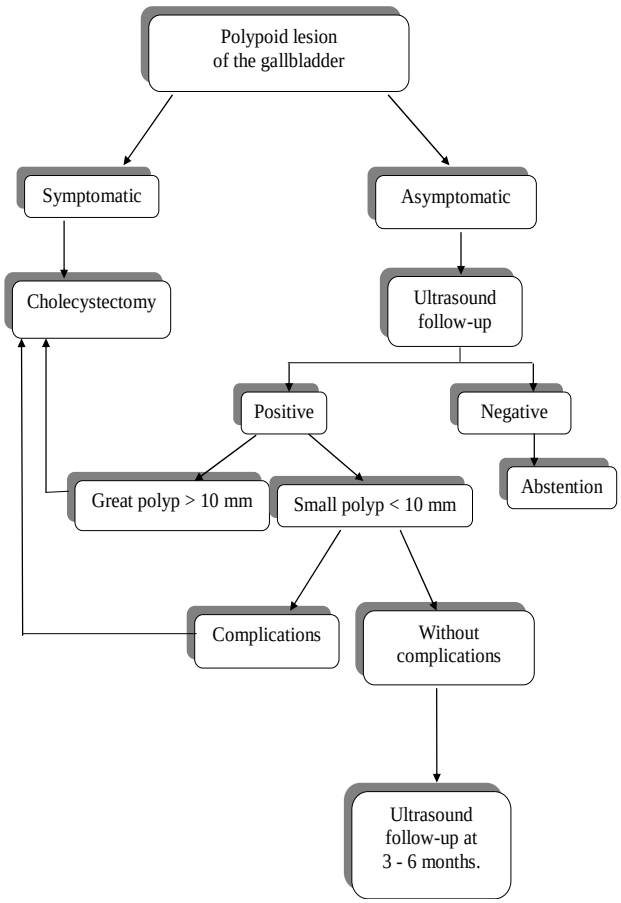

Figure 4. Algorithm of gallbladder polyp follow-up.

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