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Ruptured Gallbladder Cancer in the Bile Ducts Does Not Always Have a Poor Prognosis

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Abstract

The rupture of hepatobiliary malignancy in the main bile duct is a situation described as very bad and sign of an outdated tumor as hepatocellular carcinoma. Gallbladder cancer rupture in the main bile duct is yet not well-known condition. We report here eleven cases of patients who presented this complication. Casuistic: These are twelve patients with eight females and four males with an average age of 55.6 years (40 - 77 years).The jaundice and cholangitis are the most symptoms presented by the patients. Only in one case, diagnosis was suspected before the surgery. Macroscopically, the tumor was either polypoid and/or diffuse. Microscopically, eleven case were adenocarcinoma and one epidermoid carcinoma. Two tumors were classified pT1, 3cases had invasive form but localized to gallbladder (p T2 and pT3), and seven were extended to neighboring viscera or metastatic (pT4). The rupture recognizes three mechanisms: the first was free (tumor debris or mucin conglomerate), the second was infiltrative form (invading gradually the biliary wall) and the third was the association of the previous mechanisms. We carried out a curative treatment with total extraction of the tumor debris or bile resection for elevenpatients. One patient benefited from diversion by prosthesis. One patient presented postoperative residual tumor debris successfully extracted by endoscopic sphincterotomy. One patient died from a digestive hemorrhage and another died from an undetermined cause. On long-term follow-up, four patients are alive without disease at 240, 127, 120 and 48months.Six patients died of their disease at 5 months, 22 months, 22 months, 35months, 44 months and 45months. Conclusion: Gallbladder cancer rupture in the main bile duct is not always the result of advanced cancers and treatment for curative purposes should always be attempted. The most favorable case is the presence of free tumor debris in the bile duct, the extraction of which associated with radical treatment of the disease can give rise to long-term survival.

Keywords: *Tumor rupture - Main bile duct –free rupture – infiltrative rupture – long-term survival*

Introduction

The rupture of hepatobiliary tumors malignancies in the main bile duct constitutes a serious condition and is a sign of an advanced tumor as for hepatocellular carcinoma [1]. This situation is not well known for the gallbladder cancer. P. Rudstom reported the first two cases in 1951 [2]. This tumor rupture in the main bile duct may also concern intrahepatic bile ducts and have more than one of mechanisms since the tumor can rupture in the main bile duct and release free debris in the latter or rupture and invades gradually its wall. The rupture constitutes a pejorative turning point of the disease with a poor prognosis like ruptured hepato cellular carcinoma[3]. Fahim et al have recognized the main bile duct disseminationas a route of spread for gallbladder cancer in the sixties [4]. In order to recognize the mechanism, the treatment and the prognosis of this type of complication, we carried out this retrospective study. We analyzed all chapters of this complication as clinic aspects, the mechanism of the tumor rupture, the surgical therapy, immediate and distant consequences of gallbladder cancer rupture in the main bile duct. The main purpose among this study is to know if radical treatment is possible, and what is the survival after this treatment.

Material and Method

All the files of patients with ruptured gallbladder cancer were included in this retrospective study. We analyzed all this following parameters:

- Age, sex, clinic, diagnosis of rupture, whether done or not, carbohydrate antigen 19.9 (Ca19.9), carcinoembryonic antigen (CEA), macroscopy and location of the tumor, tumor status, histological type, caliber of the main bile duct (VBP), hepatobiliary ultrasound (HBU), computed tomography (CT scan), cholangio-MRI (C-MRI), TNM.

Surgical gesture on the tumor, gesture on the tumor debris and/or the infiltrated wall, morbidity, mortality, long-term survival.

The rupture mechanism was defined as follow:

A- Free tumor rupture: it is the presence of free tumor debris in the main bile duct.

B- The infiltrative form: rupture takes place gradually at the level of the mucous membrane of the bile duct.

C- Mixed form: the above mechanisms are associated with each other.

Patients who survived the operative procedure benefited from adjuvant chemotherapy when the tumor was invasive and with lymph nodes infiltrated (pT2, T3, T4) and / or associated with metastases.

Briefly, our surgical approach is conducted on the TNM classification as follow:

For the located tumor to gallbladder bisegmental IV-V resection associated to extended lymphadenectomy is performed.

When tumor invades neighboring organs and resection possible, bisegmental IV-V is enlarged to these organs.

For the **A form**, only tumor debris are removed from the main bile duct associated at the end of surgery by external biliary drainage if the dilation of main bile duct or without this external biliary drainage.

For the form B and C, the resection of main bile is performed if possible after extraction of the free debris and lavage of the bile duct.

For the tumor invading the neighboring viscera and resection possible, we extend the surgery to these concerned viscera.

-The long-term follow-up was as follows:

Physical examination, dosing Ca 19.9, CEA, and abdominal ultrasound (AU) every 3 months for 2 years. Beyond two years, the same sequence is performed up to 5 years every 6months.

After 5years, only clinical follow-up is conducted and no patient was lost of this follow-up.

Beyond 5 years, only clinical monitoring is carried out.

Results

we collected twelve cases out of eight-hundred gallbladder cancer patients treated, i.e. a frequency of 1.6%. These are eight women and four men with an average age of 55.6 years (40 - 77 years). The mechanism was free form in ten patients and mixed in two others. Macroscopically, these were eight polyps and four diffuse tumors. The average tumor size was 55.5 mm on average (23 - 110 mm). The clinic was primarily dominated by jaundice and acute cholangitis (8 out of 12 patients). Morphological examination revealed images of dilation of the bile ducts without making a positive diagnosis of the rupture (**Table 1**). It should be noted that free form(A) rupture was associated with all type of wall invasion (**from pT1 to pT4**) were encountered in this series. Two patients with **mucosal (pT1a) and muscular (pT1b)** presented with free tumoral rupture, 3cases had invasive form but localized to gallbladder **(pT2 and pT3),** and seven were extended to neighboring viscera or metastatic **(pT4)**. The sixth patient presented with jaundice associated with a gallbladder polyp without infiltration of neighboring viscera. The preoperative diagnosis for her was a ruptured tumor in the main bile duct or a bile duct stone. For two other patients, the retained diagnosis was the presence of stones associated to a tumor in the main bile duct (patient 10 and 11). **Tables 2 and 3,** show the anatomical and biological characteristics of the 12 tumors and their consequences on neighboring organs.

Table1. *Clinical and radiological aspects*

CASE	SEX	AGE	SYMPTOMS	ECT	CT.	MRI	DR
1	M	46	Obstructif jaundice	Dilation main bile duct and +intrahepatic bile duct	Dilation main bile duct + intrahepatic + tumoral gallbladder	-	NM
2	M	40	Cholangitis	Gallbladderpolyp	Gallbladderpolyp + liver metastasis	-	NM
3	F	46	Cholangitis	Subhepatic fluid formation	Tumorof IV-V	-	NM
4	F	61	Cholangitis	Gallbladder tumor of 80mm +stones	Tumor of gallbladder bed	-	NM
5	M	68	Obstructif jaundice	Polype du fond de la VB + lithiases	-	-	NM
6	F	50	Obstructif jaundice	Gallbladder polyp + dilation of main bile duct	Dilation main bile duct + intrahepatic bile duct + tumoral gallbladder	Dilation main bile duct + defect in main bile duct + gallbladder poylp	Suspected
7	F	77	Cholangitis	Enlarged gallbladder with hyperechoic content with stones + dilation main bile duct	Gallbladder polyp +infiltration of hilum	Enlarged gallbladder +stones +polyp	NM
8	F	47	Pains	Tumoral gallbladder (irregular wall)	Thikhened and irregular gallbladder wall	-	NM
9	F	68	Obstructif jaundice	-	Gallbladder tumor invading main bile duct or Merizzi syndrome	Gallbladder tumor invading hilum	NM
10	M	38	Pains	Polyp	Polyp + main bile duct stones		NM
11	F	61	Pains	Polyp	Gallbladder polyp + tumor of main bile duct	Gallbladder polyp + Main bile duct stones Gallbladder polyp + Main bile duct stones	NM
12	F	75	Pains	Dilation main bile duct+ stones	Dilation main bile duct + intrahepatic bile duct with no visible obstacle	-	NM

CT: Computed tomography; MRI: magnetic resonance imaging; DR: Diagnosed rupture at preoperative period

Table2: *Tumor macroscopic aspects, tumor site, caliber of the main bile duct and rupture mechanism.*

Case	Tumor site	Macroscopic aspect of tumor	Size of tumor	Rupture mechanism	Bile duct caliber	Tumor status
1	Diffuse	Diffuse	50	C	Dilated	LR
2	Body	Polyp	40	A	Fine	LR+MET
3	Diffuse	Diffuse	23	L	Dilated	LR+MET
4	Corps	Polyp	90	A	Fine	LR+MET
5	Fundus	Polyp	30	A	Fine	L
6	Body	Polyp	40	A	Dilated	L
7	Body	Polyp	110	A	Fine	LR
8	Diffuse	Diffuse	45	C	Dilated	LR+MET
9	Diffuse	Polyp	60	A	Dilated	LR
10	Body	Polyp	40	A	Dilated	L
11	Fundus + body	Polyp	40	A	Dilated	L
12	Diffuse	Diffuse	85	A	Dilated	L

LR: locoregional status, MET: metastatic status

Table3. *Biologic and histologic aspects TNM and stage*

Case	Microscopy	Ca19.9	CEA	Microscopy of tumor debris	TNM	TNM stage
1	NA	-	-	-	T4NXM0	IVA
2	EC	-	-	P	T4N2M+h	IVB
3	ADKNS	52	2	P	T4N0M+h	IVB
4	ADKMD	0,6	2.34	-	T4N1M+h	IVB
5	ADKWD	6.37	0.8	P	T1aN0M0	I
6	ADKWD+MC	5618	4.1	-	T1bN0M0	I
7	ADKMD	0,5	1,43	P	T4N1M0	IVA
8	ADKWDPAP	232,2	2,29	-	T3N2M0	IVB
9	ADKNS+MC	5	50	-	T4N2M0	IVB
10	ADKNS+MC	26,54	14,8	P	T3N3M0	IVB
11	ADKWD+PAP	22,2	1,8	P	T2N2M0	IVB
10	ADKNS+MC	131,9	18,66	P	T3N2M0	IVB
11	ADKWD+PAP	22,2	1,8	P	T2N2M0	IVB
12	ADKNS+MC	131,9	18,66	P	T4N3M0	IVB

ADK: Adenocarcinoma; EC: Epidermoïd carcinoma; NA: not available; NS: not specified; MD: moderately differentiated; WD: well differentiated; MC: mucoïd contingent; PAP: Papillary; P: Positive; CEA: Carcinoembryonnary antigen, Ca19.9: Carbohydrate antigen.

Intraoperatively and before opening the cystic duct or the main bile duct, the diagnosis was not done. Thus, the diagnosis was confirmedon the sight of tumor debris leaving the bile duct at the time of the opening of the cystic duct or the main bile duct. Therapeutically, eleven patients underwent radical surgery associated with the extraction of tumor debris and two of them had resection of the main bile duct. One patient had an extraction of the tumor debris associated with a transtumoral prosthesis (palliative surgery) (**Table 4**). One patient underwent postoperative endoscopic sphincterotomy for residual tumor debris in the main bile duct. At a distance, we have four patients alive, including three beyond 5 years and 6our patients who died of their disease at 5 months, 22 months, 22 months, 35months, 44 months and 45months. The forth-surviving patients had the form A of tumor rupture in the main bile duct. No surviving-patient was noted for the form B avec three of them had a survival beyond 24months **(Table 4**).

Table4. *Surgical gestures against the tumor, immediate and long term follow-up*

Case	Hepatic resection	Gestures on main bile duct	Immediate follow-up	Long term follow-up
1	No	Extraction of tumoral debris through main bile duct + biliary prothesis	Postoperative death	-
2	LH +V + Met + Lym	Extraction of tumoral debris through cystic duct + EBD	Parietal dehiscence + Pleural effusion	AWD 240months
3	IV-V +Lym	Extraction of tumoral debris Extraction débris tumoraux through main bile duct + bile ductresection	Unventfull	DOD 22mois
4	IV-V-VI +C + E + Met + Lym	Extraction of tumoral debris Extraction des débris des débris tumoraux par le cystique + EBD	Postoperative death	-
5	IV-V + Lym	Extraction of tumoral debris through cystic duct + EBD	Residual tumoral debris extrated by endoscopic sphincterotomy	DOC 120months
6	IV-V + Lym	Extraction of tumoral through main bile duct + EBD	Uneventfull	AWD 127months
7	IV-V+ C+ Lym	Extraction of tumoral debris through cystic duct	Pulmonary embolism + external bile fistula	DOD 5months
8	IV-V + Lym	Extraction of tumoral debris through cystic duct +EBD	Pulmonary embolism	AWD 48months
9	IV-V + Lym	Extraction of tumoral debris through main bile duct + Resectionof main bile duct	Uneventfull	DOD 44months
10	IV-V+Lym	Extraction of tumoral debris through main bile duct + EBD	Uneventfull	DOD 35months
11	IV-V+Lym	Extraction of tumoral debris through main bile duct + EBD	CVA	DOD 45months
12	IV-V+Lym	Extraction of tumoral debris through cystic duct + EBD	Uneventfull	DOD 22months

IV-V: bisegmentectomy IV-V; Met: metastasectomy; LH: Left hepatectomy, EBD: External bile duct drainage; AWD: Alive without disease; DOD: Died of disease; DOC: Died of other cause; PE: Pulmonary embolism; ES: endoscopic sphincterotomy; Lym: Lympahdenectomy; CVA: cerebrovascular accident

Table5. *Clinical aspects in the literature.*

Author	Year	Number	Jaundice	Fever	Palpable mass	Modern exams: ERCP, MRI,..	Diagnosis of rupture
J.J. Verbanck	1986	1	-	-	-	-	-
RA. Prinz	1993	2	Yes Yes	-	-	Dilation + Defect main bile duct	No
M.S. El-Qudah	1996	1	Yes	-	-	Dilation + Defect main bile duct	Yes
OD.Hughes	1997	1	-	-	-	-	-
C.Rau	2000	1	Yes	-	-	Dilation + Defect main bile duct	Yes
Y.Midorikawa	2000	1	Yes	-	-	-	Yes
Y.Wang	2013	1	Yes	Yes			No
Y. Xin-Wei	2013	3	Yes No Yes	No No No	No Yes No	Dilation + Defect main bile duct Dilation + Defect main bile duct Dilatation main bile duct	No No No
Presentseries	2020	12	Yes No Yes Yes No Yes No No No No No	No Yes Yes Yes No Yes Yes No No No No	No Yes Yes No No Yes Yes Yes No No No	Dilation main bile duct No No No No Dilation + Defect main bile duct Yes No Yes Dilation + Defect VBP No Dilation + defect main bile duct	No No No No No Suspected No No No No No No
Total		23					4/10

ERCP: endoscopic retrograd cholangiography and pancreatography

Discussion

The rupture of gallbladder cancer in the main bile duct is an evolution or a form of complication little reported in the literature and unknown. It is a way of spreading cancer described by Fahim et al [4]. This is a rare event for the gallbladder cancer. In the present series, it represents 1.6%. It is impossible to know the true frequency of this complication because we did not operate all patients with gallbladder cancer whom we received in our unit. To our knowledge, only 11 cases have been reported in the world literature and

devoted to this pathology, since the first case reported by P Rudstom [2]. It is very difficult to recognize the rupture before the surgery. However, like our patients, it is possible to suspect this complication whenever there is obstructive jaundice without a usual and obvious cause in this tumor context or acute cholangitis. Two diagnoses were mentioned in this tumor context: stones of the main bile duct or an invasion of the latter by the tumor of the gallbladder. El-Qudah [5] and Mirodikawa [6] were able to diagnose a rupture before the intervention thanks to ERCP and cholangiography associated with cholangioscopy, respectively. The most common symptomatology is jaundice, the flare-up of typical or atypical cholangitis (fever). The diagnosis is possible thanks to the modern means at our disposal. To achieve this,once a dilation of the intrahepatic or extrahepatic bile ducts is observed on ultrasound, it is necessary to pass to MRI or ERCP. These exams can show images which are interpreted as defect suggestive of lithiasis of the main bile duct which.We think that is the same cases, tumor rupture has to be evocated as the stones. Radiologist must scrutinize these defects and not interpret easily as stones. Intraoperatively and before preoperative images in favor of a pathology of the main bile duct, an exploration must be carried out by intraoperative cholangiography and the opening of the common bile duct confirms the diagnosis.The palpation due to the softness of the debris, cannot feltthe latter. This was the case for three of our patients. For the rest of the patients, it is when the cystic duct is opened that the debris leaves the bile duct. Different authors report the same data. We have encountered adenocarcinoma and squamous cell carcinoma in our patient series. Prinz et al [7] reported two cases of gallbladder tumor rupture in a series of six cases. In addition to the adenocarcinoma, which is, most often histological form reported by the literature, other histological types have also been encountered such as melanoma [8] and adenosarcoma [9]. Besides cancer, Prinz et al [7] reported in their series of six cases, the rupture of an adenomyosis. Yamamoto et al [10] reported a ruptured tubulopapillary adenoma. It is noted through the cases of the literature and our series that all stages of gallbladder cancer can be encountered during rupture from pT1 to pT4. This is important when deciding on therapy. The rupture mechanism is also important to know. The free rupture mechanism **(A)** is the most common and the easiest to treat. The free rupture need only, the complete removal of tumor debris is involved with lavage of the main bile duct. The obstruction by a conglomerate of mucin or gelatin, as reported by Hugues et al [11] and in our 10th case with this mechanism, is easy to treat. The infiltrating type mechanism **(B and C)** remains difficult to treat if it extends down or up the bile duct (confluence or intrahepatic duct) and requires resection, which is not always possible. This mechanism has been encountered twice in our series **(Case 1 and 9)**.

In our opinion and on the analysis of the present series and literature, the surgery in curative intent must established on the TNM classification of the gallbladder tumor and not on the fact of the rupture itself. The goal of the resection is to treat the tumor in a radical way whenever possible while clearing the main bile duct. Eight of eleven cases reported in the literature underwent radical surgery. For our twelve patients, tenhad radical surgery because R0 resection was possible. The issue of bile duct clearance, in our opinion, dependent on the mechanism of the rupture. When the latter is a free rupture of debris in the bile duct, the whole objective is to remove tumor debris from the bile duct. The remove of tumoral thrombi through cystic duct or bile duct is a simple gesture that allows the extraction of tumor debris as a surgeon would do for stones of the main bile duct. Even if a surgical or endoscopic sphinctérotomie is needed, it must be done for the complete clearance of the main bile duct.

The situation is quite different when the rupture is an infiltration by gradual invasion. This type of rupture limits the indication of radical surgery according to its importance.We recommend an extemporaneous examination to ensure that the resection has passed into a non-tumor area. We performed radical surgery on one of our patients **(Case 9)** because involvement of the main bile duct was limited to the path of its pedicle part only. Another patient with an infiltrative type rupture (Observation n°1) and due to the infiltration of this rupture towards the hilum and the pedicle bile duct underwent palliative surgery. Wang et al [9], Midorikawa et al [6], Rau et al [12] and Xing et al [13] performed a resection of the main line even if the clearance of the latter was possible by simple extraction (**Table 6**).

Table6. *Histology, TNM stage, surgery and long follow-up*

Author	Histology	pTNM	Stage	Surger	Long-term follow-up
J.J. Verbanck	MEM	-	-	-	-
RA. Prinz	ADK	T4N0M0 TXNXM0	IVA -	1-Whipple 1 CX+ CDA	AWD 48mnths DOD 10months
M.S. El-Qudah	ADK	T4NXM0	IVA	1 CX + EBD	DOD 6months
OD.Hughes	-	T1NXM0	I	Radical surgery	AWD 18 months
C.Rau	ADK	-		IV-V + main bile duct résection	AWD 6months
Y.Midorikawa	ADK	T2N0XM0	II	RH + main bile duct résection	AWD 24months
Y. Wang	ADK+ AS	-		IV-V + main bile ductresection + Lym	-
Y. Xin-Wei	ADK ADK ADK	-		IV-V+ main bile duct résection +Lym CX + EBD CX + EBD	AWD 30months AWD 17months AWD 23months
Presentseries	11ADK 1 EC	T4NXM0 T3N2M+h T4N0M+h T4N1M+h T1aN0M0 T1bN0M0 T4N1M0 T3N2M0 T4N2M0 T3N3M0 T2N2M0 T3N3M0	IVA IVB IVB IVB I I IVA IVB IVB IVB IVB IVB	Main bile duct prothesis LH + Met +EBD IV-V + Main bile duct resection+ Lym IV-V + C + Lym + EBD IV-V + Lym +EBD IV-V + Lym + EBD IV-V + Lym IV-V + EBD+ Lym IV-V+ main bile duct resection +Lym IV-V+ EBD+ lym IV-V+EBD+ Lym IV-V+ EBD+ Lym	Postoperative death AWD 240months DOD 22months Postoperative death DOC 120months AWD 120months DOD5months AWD 48months DOD 44 months DOD 35months DOD 45months DOD 22months

ADK: Adenocarcinoma; SMA: Sarcoma; MEM; ADK: adenocarcinoma; Melanoma; AS: adenosarcoma; CX: cholecystectomy; IV-V: bisegmentectomy IV-V; Met: metastasectomy; LH: Left hepatectomy, RH: right hepatectomy; EBD: External bile duct drainage; AWD: Alive without disease; DOD: Died of disease; DOC: Died of other cause; PE: Pulmonary embolism; Lym: Lympahdenectomy; CDA: Choledoco-duodenal-anastomosis.

The long-term prognosis depend on the stage of the neoplastic disease and completeness of resection (Complete resection with R0). Indeed, patients who have undergone radical surgery with removal of all tumoraldebris have an interesting survival as evidenced by the literature and our patients. This survival can reach even 5 to 10 years. When the surgery is palliative, survival is on average 6 to 8 months. For the palliative treatment, we advocate that if the clearance of the main bile duct cannot be obtained, then the diversion is the most adapted choice even if the stage of the gallbladder cancer is not advanced. It is the case of diffuse rupture to the top and low bile duct.

We propose a classification for therapeutic purposes, which allows the surgeon to adapt the gesture to the lesions encountered on the tumor level and in terms of rupture with the main objective of removing all tumor foci.This classification takes into account the form of rupture, the site of the latter and possibly their association **(Tables7 and figure 1).** This classification underline the fact that form A does not need bile duct resection and only extraction of tumoral debris, while form B and C, need bile duct resection. It underline also that from the type I to type IV, surgical resection becomes more difficult and then long survival may be impossible.

Table7. *Proposed classification (for therapeutic and prognosis goal)*

Stage	Mechanism	Diagram
I	Free rupture	
	Ia : Free rupture in main bile duct	A – Low free form
	Ib : Free rupture in intrahepatic bile duct	B – C – High free form
	Ic : Free rupture in main bile duct and intrahepatic bile duct	E – High and low free form
II	Mixed rupture (Free + infiltrative of the low)	A + F – Mixed form
	Free rupture + infiltration of main bile duct (low)	B - C - D + F – Low mixed form
III	Mixed rupture mixte (Free + infiltrative of intrahepatic bile duct)	A + F – High mixed form
	IIIa : Free rupture + unilateral infiltration of intrahepatic bile duct	A + F – Unilateral high mixed form
	IIIb : Free rupture + bilateral infiltration of intrahepatic bile duct	A + F – Bilateral high mixed form
IV	Infiltrative rupture (main bile duct + intrahepatic bile duct)	F – Infiltrativeform
	IVa :pure infiltrative rupture in main bile duct + unilateral intrahepaticbile duct	F – Unilateral high and low infiltrative form
	IVb : Infiltration of main bile duct and bilateral intrahepatic bile duct	F – Bilateral low and high infiltrative form

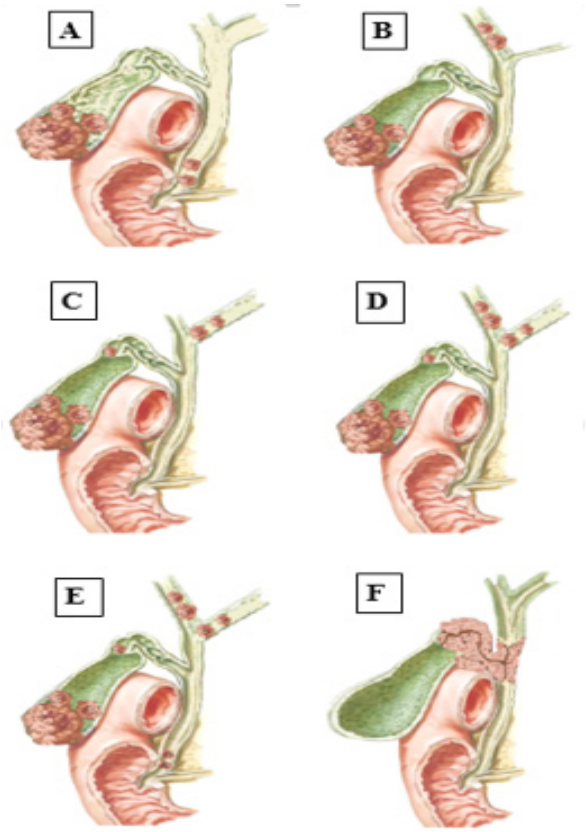

Figure1. *Classification of rupture form.*

Finally, as already reported above, the prognosis depends on the nature of the surgery and the latter depends on the tumor rupture mechanism and TNM classification.Conclusion: tumor rupture of gallbladder cancer in the main bile duct is not the preserve of advanced forms only. The diagnosis of this rupture is currently possible thanks to the modern examinations available to us as abdominal ultrasound, computed tomography and magnetic resonance imaging. The therapy should be adapted to the stage of gallbladder cancer and classification proposed if an R0 type resection could be obtained. Infiltrative form of tumor rupture can be difficult or impossible to treat. The free form of tumor rupture is perfectly compatible with radical surgery. If the latter is applied, gallbladder cancer ruptured in the main bile duct can have a real chance of survival at 5 years.

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