

Profile and Number of Residual Tumor Worsen the Prognosis of Incidental Gallbladder Cancer

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Abstract

Introduction: Incidental gallbladder cancer (IGC) has an overall 5-year survival of around 40% but this figure concerns patients with secondary resection. The pT1b, pT2 and pT3 tumors especially require a surgical revision in order to resect the tumor residue left in place after cholecystectomy. The latter represents on average 48% depending on the series. The chances of secondary resection depend mainly on the tumor residue and the majority of patients will not benefit from it. The aim of this work is to analyze the impact of the tumor residue (sites and its profile) on the prognosis of a histological finding of IGC treated by secondary radical surgery.

Material and Method: Retrospective study of all pT1b, pT2 and pT3 tumors which benefited from radical secondary resection and we analyzed the tumor residue in them and divided the patients into 4 groups. Group A (Without visceral residue or lymph node), group B (patients with only lymph node tumor residue), group C (patients with visceral tumor residue only) and group D (patients with visceral and lymph node tumor residue).

Results: Ninety-nine women and 13 men, with a mean age of 57 years (26 - 75 years) were included. The time of surgical revision was 93.5 days (30 - 387 days). Fifty-two patients (46.4%) presented with tumor residue. Dissemination of the disease was noted in 23 patients (20.5%). The first 3 tumor sites are the lymph nodes, the liver and the peritoneal serosa. The patients are divided into 60 for the group A (53.6%), 18 for the group B (16%), 19 for the group C (17%) and 15 for the group D (13.4%). It should also be noted that the presence of double and triple tumor foci mainly concerns the group D (double and triple foci only) while for the group C, single foci are more frequent than double and triple foci. Overall survival at 5 years in group A is 66.7%, that of groups B and C is respectively 33.3% and 31.6% while it is zero in group D. Moreover and beyond of a tumor residue equal or greater than 2 residual tumor foci, survival is zero.

Conclusion: The profile and number of the tumor residue is a good indicator of survival in patients with IGC. These result could help oncological team to choose patients for secondary radical surgery.

Keywords: Gallbladder Cancer; Residual Tumor; Radical Surgery

Introduction

Gallbladder cancer (GC) is classically recognized as having a poor prognosis in all stages, with an overall 5-year survival of 5%

[1]. It is also classic to say that incidental gallbladder cancer (IGC) have a good prognosis compared to those diagnosed mainly thanks to morphological examinations [2]. This relative better 5-year sur-

vival is mainly due to the fact that tumors in this form are diagnosed at an earlier stage [3,4]. On the other hand, the 5-year overall survival of IGC ranges from 40.8% to 42.8% [5,6]. If for pT1b the radical surgery is still debated, It has been demonstrated for over 20 years that a tumor classified as pT2 and pT3 must undergo surgical revision in order to resect the tumor residue left in place after cholecystectomy [7]. The latter ranges from 41.7% [8] to 56% [9] depending on the series. We must not lose sight of the fact that a certain proportion of patients do not benefit from surgical revision either because of their physiological state, advanced age and especially of a tumor residue considered unresectable [10]. Finally, some patients, even operated on, will not be able to benefit from a radical resection because of the non-resectability of the tumor residue. Overall, 50% of patients with IGC will not have life-saving radical surgery due to dissemination of the patient after the cholecystectomy. For patients who receive radical resection, at least half of them will relapse [11]. In total, the proportion of patients who will have a deterioration in the prognosis of their disease is high for tumors originally classified as pT2 and pT3 or localized in the gallbladder. The aim of this work is to analyze the impact of the tumor residue (profil and sites) on the prognosis of IGC treated by secondary radical surgery.

Material and Method

We included in this retrospective study, all patients with IGC in whom additional radical surgery was performed secondarily with curative intent and all resected specimen were by standard histology.

Radical surgery was retained on the following elements:

- Absence of diffuse and bilateral hepatic metastases.
- Absence of diffuse peritoneal carcinoma.
- Absence of pulmonary metastases.
- Diffuse and unresectable lymph node infiltration.

Radical surgery consists of minimal resection of segments IVa and V associated with extensive lymphadenectomy. The latter consists of the extirpation of the lymphoganglionic structures of the hepatic pedicle, of the common hepatic artery, of the retroduodenopancreatic region, of the right flac of the celiac trunk and of the inter-aortico-caval area.

This is the basic intervention that can be extended to one or

more infiltrated neighborhood organs. If there is a few hepatic metastasis or peritoneal foci, the radical surgery is realized.

Before undertaking the additional surgery (reoperation), a request for re-reading of the surgical specimen (gallbladder) is requested for the following details: the macroscopy of the tumor; the site of the tumor, pT, histological type, the grade tumor, vascular emboli, perinervous sheaths and slice of cystic duct.

We systematically ask for the operative report of the cholecystectomy to have the following elements: classic or laparoscopic cholecystectomy, the exact diagnosis (simple gallstone disease, chronic cholecystitis or acute cholecystitis), operating difficulties, opening of the gallbladder during cholecystectomy, bile spillage, extraction gallbladder in a bag or not, opening of the gallbladder at the end of the operation with examination of the gallbladder.

A thoraco-abdominopelvic tomodensitometry and if necessary an MRI in case of obstructive jaundice were performed.

A request for an operative assessment with the realization of the hepatic functions assay, renal function, blood crase, the assay of tumor markers: carbohydrate antigen (Ca19.9) and embryonic carcinoma antigen (ACE), the assay of the albuminemia and total proteins. Performing a chest x-ray, electrocardiogram and echocardiography to control the main functions of patient's body.

Intraoperatively and postoperatively, the following elements are systematically noted:

- Morbidity, mortality, tumor residue and its site, lymph node and visceral involvement, procedure performed, time to reoperation, TNM 1 and TNM 2 stages, 5-year survival.
- Patients are classified according to tumor residue and its location (s) and tumor spread.
- The tumor residue is defined as the presence of tumor foci at the level of a viscera (bed of the gall bladder, liver, duodenum, stomach, etc.) and/or at the level of the lymph nodes and/or peritoneal serosa and/or outside the peritoneal cavity.

Tumor dissemination is defined as the discovery at surgical resection, tumor foci absent at the time of cholecystectomy such as peritoneal carcinoma, multiple liver metastases and infiltration of neighboring organs (which develop in the free interval between

cholecystectomy and reoperation). All the tumor foci reported in this study were proven by histological examination of the parts resected by the surgeon.

The patients were classified into 4 groups according to the profile of the tumor residue:

- A: V0N0 (patients without any residue).
- B: V0N+ (patients without visceral residue but with lymph node residue).
- C: V+N0 (patients with visceral residue and without lymph node residue).
- D: V+N+ (patients with visceral and lymph node residues).
- Survival is recorded from cholecystectomy until the completion of this study.

Results

Out of a total of 262 patients, 112 met the criteria for inclusion in the study (see chart flow) (Figure 1). These are 99 women and 13 men, with an average age of 57 (26-75). These are 111 adenocarcinomas (99%). The delay of the surgical revision time was 93.5days (30 - 387days). Fifty-two patients (46.4%) presented a tumor residue at the start of the operation while the overall tumor residue rate for the entire series is 67,5% (1778/262). The dissemination of the disease was noted in 23 patients (20.5%). The first 3 tumor sites are the lymph nodes, the liver and the peritoneal serosa (Table 1). The patients are divided into 60 in group A (53.6%), 18 in group B (16%), 19 in group C (17%) and 15 in group D (13.4%). Overall morbidity and mortality in the 112 patients is 35.7% and 04.5% respectively. It is noted that the tumor dissemination concerns groups C and D and not the 2 other groups. We also note that the presence of double and triple tumor foci mainly concerns group D (double and triple foci only) while for group C single foci are more frequent than double and triple foci (Figure 2). the most frequent site of dissemination is the peritoneal serosa. It should be remembered that the various peritoneal carcinomas resected in our patients, regardless of the groups, were limited. The patients in group D presented only double and triple tumor residue (Table 2). Overall 5-year survival in group A is 66.7% and 46 patients in this group are currently alive (76.7%). The 3 patients who died from their disease in this group had infiltration of the Mascagni ganglion (cervix) at the time of cholecystectomy. Two of them presented with hepatic recurrence as liver metastases and

had repeated liver resection and who again had recurrence as liver metastases. The 3rd patient presented with a recurrence in the form of an umbilical nodule (trocar opening) which required reoperation with resection for curative purposes. He relapsed again in the form of diffuse peritoneal carcinoma. These 3 patients died of their disease at 18, 30 and 31 months. One patient in this group is alive with recurrence and is benefiting from chemotherapy. A total of 4 patients (06,7%), presented a recurrence in this group. Overall survival in groups B and C is 33.3% and 31.6%, respectively. No patient in group D is alive at 5 years (Table 3 and figure 3). The mean survival in the last group is 23.3 months of mean survival (03-28months). The number of tumor residue (tumor foci) is also essential since, in its absence, survival is that of group A, therefore 66.7%. It drops to 38.7% for a single residue and becomes zero for the double and triple residues (Figure 4).

Discussion

Our series shows that the tumor residue is an essential and determining element at the time of reoperation for histological discovery. Several authors currently insist on the tumor residue [12,13]. We have even reported that the tumor residue was greater than the

Flow Chart

Variables	Number	Percentage
Total of patients	112	83,3%
Females	99	16,7%
Males	13	
Age	57years (26 - 75 years)	
T1	17	15,2%
T2	21	18,8%
T3	74	66%
Histology		
ADKWD	76	67,8%
ADKMD	22	19,6%
ADK+ peyorative component	05	04,5%
ADKPD	04	03,6%
ADKNS	04	03,6%
EC	01	
Cholecystectomy	76	67,8%
Conventional approach	34	30%
Laparoscopic approach	02	
Exploratory		
Delay of reintervention	93, 5days (30 - 387days)	
Surgical procedure at the reintervention	85	76%
IV-V+ lymphadenectomy	18	16%
IV-V+ lymphadenectomy extended to bile duct	10	08,8%
IV-V+ lymphadenectomy to neighborhood viscera (duodenum, omentum, stomach, ...) other than bile duct		
Global residual tumor of series	177/263	67%
Residual tumor of 112 patients	52	46,4%
Tumoral dissemination	25	22,3%
Site of residual tumor		
Node	32	62,7%
Liver	21	41,2%
Peritoneal serous	16	31,4%
Bile	07	13,7%
Various	05	10%
Number of site of residual tumor		
Unic	29	56,9%
Double	09	17,6%
Triple	13	25,5%
Sites of recurrence		
Peritoneal serous (carcinomatosis)	14/32	43,7%
Liver (metastasis)	12/32	37,5%
Bile duct (infiltrative wall)	12/32	37,5%
Various (Node, lung, pancreas, abdominal, wall)	06	

Table 1: Characteristics of patients.

Group	Number	Single residual tumor	Double residual tumor	Triple residual tumor
A	60	00	00	00
B	18	18	00	00
C	19	13	04	02
D	15	00	05	10
Total	112	31	9	12

Table 2: Number of residual tumor according to groups.

* : 3 patients with Mascagni node infiltrated.

7 patients died from another causes – 1patient alive with recurrence.

NB: Profil is not site.

Group	Morbidity	Mortality	Recurrence	5year survival
A	19 (31,6%)	03 (05%)	03 (05%)	40 (66,7%)
B	07 (38,8%)	01 (05%)	07 (38,8%)	06 (33,3%)
C	07 (36,8%)	00 (00%)	07 (36,8%)	06 (31,6%)
D	07 (46,6%)	01 (06,7%)*	13 (86,7%)*	00 (00%)**
	40 (35,7%)	05 (04,5%)	30 (26,8%)	52 (46,4%)

Table 3: Immediate and long terms outcome

*: One patient died on postoperative course and another died from another cause.

**: 23,3 months (03-28months) of mean survival and patients died of their disease.

Figure 2: Number of residual tumoral.

Group D is concerned by double and residual tumor sites compared with other groups.

Group D and C had all 24 cases of disseminated tumor.

Group A and B do not have any disseminated tumor.

Disseminated tumor is represented by peritoneal carcinomatosis in 66,7% of cases.

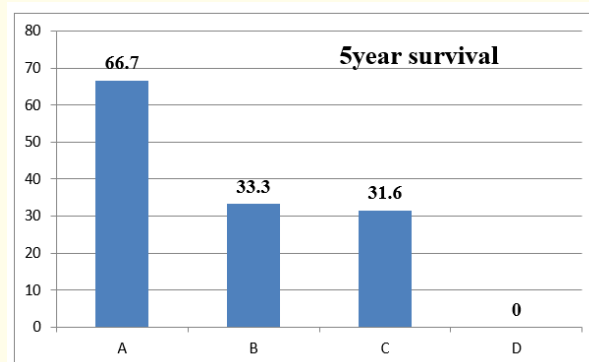


Figure 3: 5year-survival according to each group.

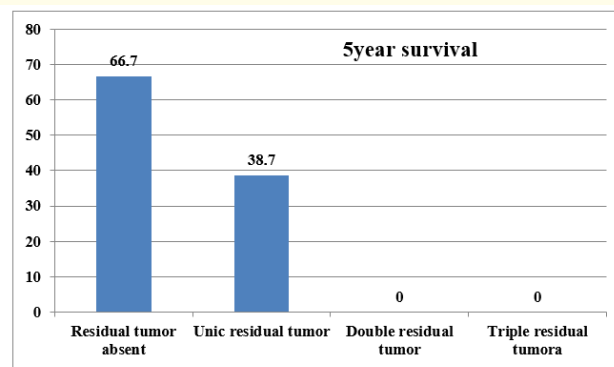


Figure 4: 5 year survival according to number of residual tumor.

time to reoperation [14]. Ausania and all insist and rightly on the fact that the reoperation should not be undertaken before a period of 3 months, at the end of which the residue becomes evident and the morphological exploration will make it possible to make an exact assessment and decide whether or not to reoperation depending on the presence of the tumor residue and its extension [15]. This delay can lead to the discovery of true tumor dissemination, especially in the case of peritoneal carcinoma, hepatic metastases develop rapidly after cholecystectomy. This tumor spread is due to untimely operative maneuvers (forceps traumatizing the tumor, wringing of the vesicle in a trocar opening, etc.), opening of the gallbladder and flow of bile into the operating field. J.H Kim., *et al.* reported in the series a bile flow rate during laparoscopic cholecystectomy of 53.8% [16]. In the present series, this dissemination represented a rate of 20.5%. It is important to note that these histological findings are at the origin of pT1 tumors and especially pT2 and pT3, therefore tumors localized to the gallbladder and that the operative trauma will induce a worsening of the prognosis of the disease via this dissemination of the tumor, specially as peritoneal carcinomatosis and extension to neighboring organs. Our results clearly show that patients free from tumor residue have an excellent prognosis at 5 years with a survival of 66.7% with 76.7% alive until now, whereas patients with a visceral or lymph node residue have a global survival which reaches just the 36%. The most striking fact is zero global survival at 5 years for patients with a double visceral and lymph node residue, regardless of its site. On the other hand, the profile of the residue is decisive since when it is single,

a 5-year survival of 38.7% is achieved while it becomes zero for patients with double and triple tumor foci. At our knowledge, we do not have a similar analysis in the literature. It seems important to us to see things from this angle insofar as the TNM classification is only possible and complete after secondary surgery with its complete intraoperative exploration which will allow to decide whether or not to resect the disease. In this manner, diagnosing double tumor foci or associated visceral and node tumor, can make us relucting or refuse the decision of secondary radical surgery.

Thus, our series shows that preoperative morphological exploration must focus on highlighting the tumor foci (s) which, in the event of a combination of visceral and lymph node tumor residue at a minimum, surgery, even in the event of radical resection, will not bring the patient to a 5-year survival. On the other hand, double or triple tumor residue profile makes radical resection inefficient and 5-year survival null. Elise A., *et al.* reported 562 cases of histological findings (pT1b, pT2 and pT3) of which only 110 (19.6%) were able to have secondary radical resection and the 5-year survival concerned half of them, i.e. survival overall of less than 10% of the whole series [17]. In our experience, 112 patients were able to benefit from a secondary radical resection out of a total of 234 candidates for surgery, i.e. a 47.8% and survival concerned 52/112 (46.4%) and 52/234, i.e. 22.2% of potential candidates. Thus, a large proportion of patients with IGC will not survive 5 years mainly due to a worsening of the tumor stage of their disease after cholecystectomy and one of the goals in this period is to properly select patients not just those who may have radical resection but especially those who can benefit from this resection.

To predict the residual tumor, C.G Ethun., *et al.* and J.M. Creasy and al established a predictive score for tumor residue and prognosis in front of a IGC [18,19]. These 2 scores, established essentially on histological data, make it possible to predict the tumor residue and the prognosis in a simple way.

It is known from the literature that small lesions, whether hepatic or especially peritoneal metastatic foci, are not detected on morphological examinations [20-22] and the use of laparoscopy is a good solution to highlight them [23].

The profile of patients who may benefit from radical resection are those whose exploration has not revealed a tumor residue or a single tumor residue. Beyond that, and as soon as the tumor resi-

due is double (visceral and lymphatic node and/or double or triple visceral) the situation is pejorative. Patients in the latter situation should, if our results are confirmed by oncological community, benefit from a neoadjuvant therapeutic approach [24]. This neoadjuvant approach could be another way to improve the prognosis of the gallbladder cancer. However, our present series has some shortcomings. In the first place, this is a retrospective study which, even if the data were collected prospectively, remains marred by some lack of clinical and biological data. Second, our surgical attitude may have been too aggressive with certain patients in whom we retained the indication for radical surgery when the lesions were too advanced in them. Third, the morphological exploration carried out in our series may have been in some patients, insufficient and missed the tumor lesions discovered intraoperatively. But our results have the advantage of long hindsight and allow us to say:

- Dissemination of the disease is a factor to look for in the course of cholecystectomy because in the overwhelming majority of cases it indicates a poor prognosis even if the lesions are resected.
- The detection of a visceral and lymph node tumor residue is problematic and pejorative situation.
- The detection of double and triple visceral residue (three different sites), in particular with the presence or absence of lymph node infiltration, is also a negative situation.

These 3 situations do not amount to radical surgery even if it is possible.

Demonstration of an absence of tumor residue or the presence of a single tumor residue is the ideal situation to retain an indication for radical surgery. The period between cholecystectomy and radical secondary surgery (Time to surgical revision) must not be short but enough to use all means to highlight the residue and its characteristic (visceral, nodal and its number).

What then is the solution in these patients with a pejorative tumor residue? We believe that in the presence of this situation, it will be necessary to move towards a neoadjuvant therapeutic option and not towards radical surgery, even once again if it is possible (Figure 5).

Figure 5: Algorithm.

Conclusion

In IGC, primary cholecystectomy is responsible for the spread of neoplastic disease in more than 40% of patients. The presence of a visceral and lymph node residue or a number of tumor foci equal to or greater than two is an indicator of a very poor prognosis. In these cases, even radical surgical resection cannot lead to long-term survival. With confirmation of our results by other teams, we believe that only patients with no evidence of a tumor residue on morphological exploration and/or with the presence of a single tumor residue are an indication to secondary radical surgical resection.

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