

# Surgical Treatment of 724 Carcinomas of the Gallbladder

## Results of the French Surgical Association Survey

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### Objective

The objective of this study was to evaluate the benefit of an aggressive approach to gallbladder carcinoma on long-term survival.

### Summary Background Data

Recent studies have shown that an aggressive surgical treatment of bile duct carcinoma can be associated with a surprising long-term survival. However, recent data on gallbladder carcinoma are not available.

### Methods

Data were obtained from a questionnaire sent to 73 institutions in France, Europe, and overseas, and they were analyzed retrospectively. The review included an analysis of patient sex and age, associated hepatobiliary diseases, symptoms and signs, diagnostic tests, operative management, pathology reports, and survival.

### Results

Seventy-eight per cent of the patients were woman, and 22% were men ( $p < 0.001$ ). Gallstones were present in 86% of the cases. Four per cent of the patients had Tis stage lesions, 11% had T1 to T2 stage lesions, and 85% had T3 to T4 stage lesions ( $p < 0.001$ ). Pain was the most frequent symptom (77%). Twenty-three per cent of the patients underwent curative operations, and 77% had a palliative treatment (25% of the patients underwent exploratory laparotomy). Exploratory laparotomy was followed by the highest mortality rate (66%), and older patients ( $> 70$  years) had a higher operative risk ( $p < 0.04$ ). The overall median survival was 3 months, and long-term survival correlated with the cancer stage (Tis,  $> 60$  months; T1 to T2,  $> 22$  months, and T3 to T4, 2 to 8 months). No differences were observed among the different surgical procedures adopted.

### Conclusions

No progress has been made in the last 10 years in the treatment of gallbladder malignancies.

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Carcinoma of the extrahepatic biliary tract has always been associated with a dismal prognosis. This is essentially the result of the slow and asymptomatic growth of the neoplasm that infiltrates the surrounding structures, such as the portal vein and hepatic artery, making a curative surgical treatment almost impossible.

However, in the last decade, we have observed improvements in surgical, anesthetic, and intensive care techniques that have allowed us to ameliorate both the pre- and postoperative general condition of these patients<sup>1,2</sup> and offer a wider range of surgical options. Several authors recently showed that an aggressive surgical

treatment of bile duct carcinoma can be associated with a surprising long-term survival.<sup>3,4</sup> To evaluate the benefit of an aggressive approach to gallbladder carcinoma, the French Surgical Association organized a survey of patients diagnosed with gallbladder cancer who were treated between 1980 and 1989 in several French, European, and overseas institutions.

## METHODS

We reviewed data obtained from a questionnaire sent to 73 different institutions. The questionnaire consisted of several aspects of the clinical history of patients hospitalized between 1980 and 1989 with histologically proved gallbladder carcinoma. The review included an

analysis of patient sex and age, associated hepatobiliary diseases, symptoms and signs, diagnostic tests, operative management, and macroscopic and microscopic pathologic findings. The microscopic pathologic results were reviewed independently. The cancers were classified by using the staging criteria of the American Joint Committee on Cancer.<sup>5</sup> (Tis, carcinoma *in situ*; T1, tumor invades the mucosa; T2, tumor invades perimuscular connective tissue, with no extension beyond the serosa or into the liver; T3, tumor invades beyond the serosa or into one adjacent organ or both; T4, tumor extends more than 2 cm into the liver and or into 2 or more adjacent organs).

Follow-up data were obtained from patients' records. All patients included in the study were regularly monitored at the different institutions.

Statistical analysis for continuous variables was performed using Student's t test for unpaired data, and the chi square test was used for categoric variables. The differences between sample means are presented along with the 95% confidence interval values.<sup>6</sup> Survival curves were constructed according to the Kaplan-Meier method, and the differences were compared using the log-rank test.

## RESULTS

Seven hundred twenty-four patients underwent surgery for gallbladder malignancies between January 1980 and December 1989. Most patients (684, 85%) were hospitalized in France, with 75 patients (10%) either in Switzerland, Italy, Germany, or Belgium and 37 patients (5%) either in Lebanon, Turkey, Haiti, Hungary, or Hong Kong. It was impossible to collect the data regarding all the variables originally considered in the study for all 724 patients, and the number of patients analyzed with regard to each variable varied.

Among the 724 patients studied, 563 were women (78%), and 161 were men (22%,  $p < 0.001$ ). The mean age was  $69 \pm 18$  years (range, 25 to 101 years) among women and  $67 \pm 15$  years (range, 37 to 101 years) among men. Most patients were older than 60 years of age (76%), and the disease incidence peaked after 60 years of age among men and after 70 years among women (Fig. 1).

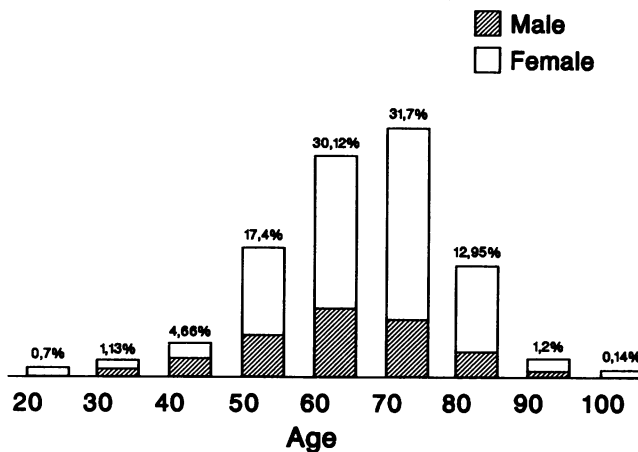
Data on associated hepatobiliary diseases were available for 504 patients. Gallstones were present in 443 (85%) patients, 18 were hepatitis B surface antigen positive, and 13 had other malignancies. With regard to pathologic findings, data on tumor localization and extension were available on 724 patients. The lesions were localized to the entire gallbladder in 407 patients (57%). In a significantly lower number of patients, the neoplasm was localized to the fundus (99 cases, 13%), the corpus

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This work was a multicenter collaborative study involving the following surgeons and members of the French Surgical Association (the country is France unless otherwise noted): M. Adloff (Strasbourg), S. Agboku (Sainte-Claude, Guadeloupe), J. C. Balique (Sainte-Étienne), J. Barbier (Poitiers), J. C. Baste (Bordeaux), H. Baumel (Nîmes), R. Benabadi (Alger, Algeria), P. Blondel (Mantes-la-Jolie), F. Boileau (Neufchâteau), P. Boissel (Nancy), C. Bonhomme (Nevers), O. Bonnard (Sainte-Étienne), M. Boumghar (Lausanne, Switzerland), B. Bouiadjra (Lille), R. Bouly (Bondy), P. Boutelier (Bondy), M. Chabert (Sainte-Étienne), G. Champault (Bondy), G. Chapuis (Lausanne, Switzerland), P. Chastan (Lormont), O. Cunci (Le Havre), R. Decoud (Santa Fe, Argentina), M. Degardin (Montdidier), B. Deixonne (Nîmes), O. Delassus (Marmande), J. P. Descottes (Lyon), T. Dodart (Le Havre), C. Dubost (Paris), F. Dumeige (Saint-Mandé), B. Ferrand (Limoges), G. Fillaudeau (Belfort), M. Firouz Abadi (Confolens), F. Fournier (Moulins), L. Gaillard (Clermont-Ferrand), J. F. Gigot (Brussels, Belgium), D. Gossot (Paris), J. L. Gouzi (Toulouse), J. Grosdidier (Nancy), M. Guntz (Angers), E. Guthy (Weiden, Germany), L. Hervouet (Chalans), S. Houry (Paris), M. Huguier (Paris), P. J. Kestens (Brussels, Belgium), A. Labazbidi (Nogent-le-Rotrou), J. Lacaze (Arcachon), P. E. Labour (Luçon), L. Lagriffoul (Rouen), J. Leborgne (Nantes), P. Le Douarec (Dieppe), P. Le Meur (Sainte-Étienne), J. Loup (Marmande), C. F. Madsen (Petion-Ville, Haiti), J. N. Maillard (Colombes), M. Malafosse (Paris), O. H. Mammoni (Buenos Aires, Argentina), J. M. Marcon (Chalons-sur-Marne), P. Manara (Bastia), S. Mestri (Tunis, Tunisia), G. Michotey (Marseille), P. Monteggia (Milan, Italy), W. Montorsi (Milan, Italy), J. N. Nuss (Ingwiller), J. B. Otte (Brussels, Belgium), J. L. Paillet (Paris), C. Partensky (Lyon), J. L. Peix (Lyon), M. Pelon (Villefranche-de-Rouergue), F. Pernot (Saintes), A. Pissas (Bagnols-sur-Cèze), R. C. Praderi (Montevideo, Uruguay), C. Proye (Lille), P. Quandalle (Lille), P. Revelin (Roanne), P. Rivalan (Ploermel), Y. A. Salembier (Lille), B. Sastre (Marseille), A. Secchi (Buenos Aires, Argentina), S. Serkal (Rabic, Lebanon), E. Steiner (Ussel), A. Sezeur (Paris), G. Spay (Lyon), R. Steinsleger (Santa Fe, Argentina), F. Teboul (Lyon), P. Teniere (Rouen), J. P. Triboulet (Lille), A. Uras (Istanbul, Turkey), J. P. Van Damme (Sijsele Damme, Belgium), M. Vankemmel (Lille), A. Vidrequier (Nancy), and A. Wurtz (Lille).

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Accepted for publication September 23, 1993.



**Figure 1.** Incidence of gallbladder cancer according to age and sex (n = 724).

(123 cases, 17%), and the neck (95 cases, 13%) of the gallbladder ( $p < 0.001$ ). Histologic data were available in 619 patients; adenocarcinoma constituted 87% of the cases and undifferentiated carcinoma, 13% ( $p < 0.001$ ). The classification according to the tumor-node-metastasis (TNM) stage is shown in Table 1. T3 and T4 stage lesions were statistically more frequent than were Tis, T1, and T2 lesions ( $p < 0.001$ ). Patients with Tis disease were younger than were patients with more extended lesions ( $59 \pm 7$  vs.  $68.5 \pm 6$  years,  $p < 0.05$ ). With regard to local spread, 81% of the patients had nodal involvement ( $p < 0.001$ ), 21% had hepatic metastasis, and in 16%, the disease had spread to the entire hepatobiliary system.

Symptoms related to gallbladder cancer were available for 641 patients. They are listed in Table 2. Pain (77%) was significantly more frequent than fever (9%), weight loss (11%), and right upper quadrant palpable mass (3%,  $p < 0.001$ ). Preoperative diagnostic investigations consisted of abdominal ultrasonography in 481 patients

**Table 1. PATIENT CLASSIFICATION BY STAGE**

Lesion	N	Percent	Confidence Interval
T1s	23	4	3-4.4
T1	20	3	0.6-2
T2	58	8	4-12
T3	233	32	24-36
T4	390	53	52-62
Total	724		

Patient classification according to the criteria of the American Joint Commission on Cancer. T3 and T4 lesions were significantly more frequent than T1s, T1, and T2 lesions ( $p < 0.001$ ).

**Table 2. SYMPTOMS**

Symptom	N	Percent	Confidence Interval
Pain	493	77	73-81
Fever	56	9	2-15
Weight loss	71	11	4-18
Palpable mass	21	3	0-10
Total	641		

Symptoms related to gallbladder cancer. Pain was the most frequent symptom ( $p < 0.001$ ).

(64%; sensitivity, 0.95), abdominal computed tomography in 66 (9%; sensitivity, 0.95), cholangiography in 69 (9%; sensitivity, 0.95). The sensitivity of tumor markers (alpha-fetoprotein and CA 19-9) appeared to be lower (0.79). The correct preoperative diagnosis was made only in 53% of the patients. After a complete preoperative screening, 69% of the patients seemed to have a localized lesion, and in 21% of the cases, a radical surgical procedure was thought to be possible.

A surgical or drainage procedure was withheld in 15

**Table 3. SURGICAL PROCEDURES ACCORDING TO AGE**

	<70 Years		>70 Years	
	No.	Percent	No.	Percent
Curative surgery				
Cholecystectomy	57	16	44	14
Cholecystectomy + resection of adjacent organs	2	1	0	—
Cholecystectomy + resection of hepatic bed	15	5	20	6
Cholecystectomy + segmentectomy (IV-V)	8	2	4	1
Cholecystectomy + right epatectomy + IV	5	1	0	—
Total	87	25	75	21
Palliative surgery				
Exploratory laparotomy	99	26	93	24
Cholecystectomy	92	21	84	20
Biliary-entero anastomosis	54	14	53	15
Transluminal stenting	38	10	53	15
Kron prosthesis	5	1	4	1
External biliary drainage	3	1	3	1
Gastro-entero anastomosis	6	1.5	4	1
Cholecystectomy + hepatico-duodenostomy	1	0.25	0	—
Cholecystectomy + ileo-transverse anastomosis	1	0.25	0	—
Total	272	75	275	79

**Table 4. SURGICAL PROCEDURES ACCORDING TO CANCER STAGE PERFORMED IN 709 PATIENTS**

	Tis	Percent	T1	Percent	T2	Percent	T3	Percent	T4	Percent
Cholecystectomy	23	100	20	100	52	88	94	41	78	20
Biliary drainage	0	—	0	—	4	8	103	45	102*	27
Hepatic resection	0	—	0	—	0	—	13	6	39	10
Exploratory laparotomy	0	—	0	—	1	2	18	8	167	43
Total	23		20		57		228		381	

\* Seven patients had the procedure performed percutaneously (n = 3) or endoscopically (n = 4). In 15 patients, no procedure was performed because of general poor conditions.

patients because of their general poor conditions (3%). Of the remaining 709 patients, 688 (97%) underwent surgery, and 21 patients (2%) had a combined surgical and drainage procedure. Seven patients (1%) had only percutaneous (three cases) or endoscopic (four cases) biliary drainage. Age and TNM classification are shown in Tables 3 and 4, respectively.

The overall 30-day mortality rate was 22%, and it was related to the histologic type (Table 5) and surgical procedure (Table 6). The mortality rate was significantly higher in older patients (> 70 years old, 27%; < 70 years old, 15%;  $p < 0.04$ ). The mortality rate was significantly higher in stages T3 to T4 (24%) than in the Tis and T2 stages (5%,  $p < 0.0001$ ). The high mortality rate observed in patients with T1 stage disease (20%), which was significantly higher than that in stages Tis and T2 ( $p < 0.0001$ ), was probably caused by the small number of reported T1 stage tumors. Exploratory laparotomy was followed by a significantly high mortality rate (66%,  $p < 0.0001$ ) compared with other surgical procedures. The mortality rate after cholecystectomy (12%) was significantly lower than after biliary-enteric anastomosis (15%) and transtumor stenting (25%,  $p < 0.04$ ).

The overall median survival time was 3 months (range, 1 to 24 months). The overall survival rates at 1 and 5 years were 14% and 5%, respectively (Fig. 2), and

these were related to histologic type (Table 7). The average survival time for patients with Tis tumors was longer than 60 months; for stages T1 and T2, it was longer than 22 months. The presence of locally extended lesions (stages T3 and T4) worsened the prognosis, with an average survival of 2 to 8 months (Table 7) and a mortality rate of 75% at 1 year. The survival rates after cholecystectomy in stages Tis, T1, and T2 are shown in Figure 3; 93% of the patients with stage Tis disease were alive at 5 years compared with 28% and 20% of those with stage T1 and T2 disease, respectively ( $p < 0.001$ ). No patient with stage T3 or T4 disease survived more than 36 months, and 90% of these patients died at 12 months after extended cholecystectomy. Thirty-five patients with stage T3 to T4 disease underwent an atypical liver resection.<sup>7</sup> The postoperative mortality rate was 20%, and the median survival times were 13 and 5 months for stages T3 and T4, respectively. Twelve patients with stage T4 disease underwent liver segmentectomy (IV and V lobe). The mortality was 20%, and the median survival was 7 months. Five patients with stage T4 disease underwent right hepatectomy plus lobe IV resection. The

**Table 6. MORTALITY RATE ACCORDING TO SURGICAL PROCEDURE**

	Mortality (%)	Confidence Interval
Cholecystectomy	12	9-13*
Biliary-enteric anastomosis	15	17-21*
Transtumoral stenting	25	15-40*
Atypical hepatic resection	25	11-39
Liver segmentectomy (IV + V)	20	0-42
Right hepatectomy + segmentectomy (IV)	0	—
Exploratory laparotomy	66	60-72†

\* The mortality rate after cholecystectomy was significantly lower than after biliary-enteric anastomosis and transtumoral stenting ( $p < 0.04$ ).

† Exploratory laparotomy was followed by a significantly higher mortality rate when compared to other surgical procedures ( $p < 0.0001$ ).

**Table 5. 30-DAY OPERATIVE MORTALITY RATE ACCORDING TO CANCER STAGE**

Stage	No.	Deaths	Percent	Confidence Interval
Tis	26	1	4	2.8-3.8
T1	21	1	5	17-23
T2	60	1	2	2-5
T3	241	31	13	16-22
T4	398	94	24	24-28

The mortality rate was significantly higher in T1, T3, and T4 stage ( $p < 0.0001$ ).

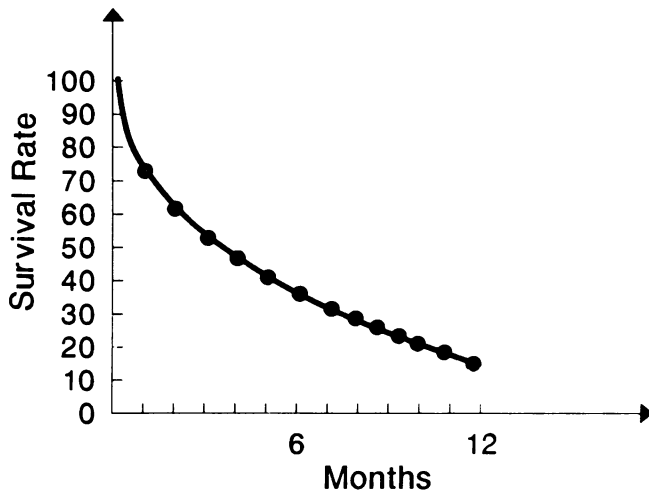


Figure 2. Overall survival rate curves at 12 months (n = 724).

postoperative mortality rate was 0%, and the median survival was 6 months.

**DISCUSSION**

Cancer of the gallbladder has always been associated with an unfavorable prognosis.<sup>8-10</sup> Recent improvements in diagnostic imaging modalities,<sup>11,12</sup> a better knowledge of the natural history of gallbladder cancer<sup>13-16</sup> and its mode of spread,<sup>17,18</sup> and reports of long-term survival after resection of bile duct carcinoma<sup>1,2</sup> have induced several authors to advocate radical surgical treatment of gallbladder cancer in an attempt to prolong survival.<sup>19</sup>

This report, based on a large population of patients treated aggressively, showed no differences in patient survival compared with older reports.<sup>20-22</sup> Gallbladder malignancies are still diagnosed too late. In 27% of the patients, no surgical treatment was possible, and 77% of the patients had lesions beyond the possibility of any curative treatment. This finding is not surprising when we consider that improved diagnostic imaging techniques cannot be applied until late in the disease course in le-

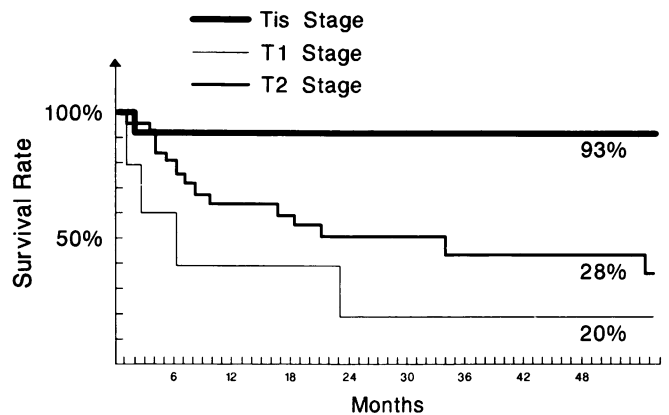


Figure 3. Survival curves at 5 years for patients with stages Tis, T1, and T2 disease. The difference between the stage Tis and T1 and T2 curves was significant (p < 0.001).

sions that have an almost asymptomatic evolution, such as gallbladder neoplasms. Moreover, a correct preoperative diagnosis was made only in 53% of the patients.

There was a good correlation among the preoperative evaluation of the neoplasm, its local extension, and the operative findings. The lesion appeared to be localized in 69% of the patients on the basis of the preoperative examinations and in 73% of the patients at the time of laparotomy. However, the preoperative tests generally used in this study were not sensitive enough to evaluate the actual resectability of the lesions because only 35% of the patients underwent operations with a curative intent or a palliative resection, and 26% underwent exploratory laparotomy. This observation has clinical relevance because the mortality rate after exploratory laparotomy in this series was high (66%), and this emphasizes the need for more sensitive preoperative examinations. Two decades ago, laparoscopy was frequently used to assess the nature and extent of gastrointestinal malignancies. The availability of ultrasonography and computed tomographic scan has replaced the need for laparoscopy in many cases. However, the minimally invasive nature of laparoscopy offers significant advantages over exploratory laparotomy in regard to postoperative mortality and morbidity rates, particularly in compromised patients, such as those with gallbladder carcinoma. Laparoscopy permits direct visualization of gallbladder lesions and an evaluation for a possible local or extended resection.<sup>23,24</sup> Wider use of diagnostic laparoscopy could prevent unnecessary exploratory laparotomies, and patients could undergo external biliary drainage with lower mortality and morbidity rates.

The current study confirmed that only patients with stage Tis disease have a real chance of cure after cholecystectomy<sup>17,25,26</sup> and that prognosis worsens rapidly in stages T1 and T2. No differences were seen among the

**Table 7. SURVIVAL RATE ACCORDING TO CANCER STAGE**

Stage	Average (mos)	Median (mos)
Tis	>60	—
T1	23	24
T2	26	24
T3	8	6
T4	2	3

different procedures performed in stages T3 and T4. The mortality rate and median survival were similar after either radical cholecystectomy or right hepatectomy or liver bisegmentectomy. The failure of radical resection to improve the median survival contradicts previous reports in which patients with stages T3 and T4 disease had 5-year survival rates ranging from 15% to 29%.<sup>9,27,28</sup> Thus, it does not seem that more than an extended cholecystectomy should be performed in stage T3 and T4 disease.<sup>10,29</sup> The role of radical cholecystectomy in less advanced lesions, such as stages T1 and T2, was not elucidated in this survey. Despite a theoretic advantage and a few reports<sup>18,26,27,28,30</sup> of improved survival after extended cholecystectomy (between 22% and 100% 5-year survival rates) for gallbladder cancers not involving the serosa, the lack of prospective studies and recent cautious reports<sup>9,10</sup> show the need of prospective trials to demonstrate a real benefit of radical cholecystectomy in stage T1 and T2 disease.

In conclusion, The French Surgical Association survey confirmed that no progress has been made during the last 10 years in the treatment of gallbladder malignancies. Because of the almost asymptomatic evolution of this disease, the only area where there could be an improvement in its management is in prophylactic surgery<sup>8</sup> or liver transplantation.

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