

Long-term follow-up of surgically treated gallbladder cancer patients

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Aims: Palliative attempts have traditionally led treatment of gallbladder cancer but resection offers the only chance for long-term survival. This study investigates the impact of surgery with curative intent in gallbladder cancer treatment and evaluates prognostic factors for survival.

Methods: Two hundred and sixty-seven patients were admitted for surgical therapy. Sixty received resection with curative intent and form the basis of this analysis.

Results: R0 resection ($n = 45$) was a highly significant independent survival predictor ($P < 0.001$). All 5-year survivors ($n = 10$) had tumour-free resection margins. Early T stage ($P = 0.017$) and highly differentiated cancer ($P = 0.008$) had a significant better outcome. Nodal spreading increased by local tumour extension and lymphatic involvement decreased patient survival ($P = 0.018$). Patients' age (>75 years) was without influence on long-term survival.

Conclusions: Long-term survival is possible both in elderly patients and in advanced cancer.

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Key words: gallbladder cancer; surgical resection; long-term follow-up.

INTRODUCTION

The Viennese Maximilian Stoll first described gallbladder cancer in 1777.¹ Since then different treatment options have been advocated, mainly due to the fact that unresected gallbladder cancer is a rapidly fatal disease. When diagnosed the tumour has often extended to other organs^{2–5} and patients are beyond the 6th decade of life. In this aged patient-group perioperative mortality was high, therefore conservative treatment was the therapy of choice in previous days.⁶ Nowadays major improvements of surgical techniques and refinements of anaesthetic and intensive care unit facilities have improved postoperative outcome in elderly patients suffering from gallbladder cancer. Therefore many authors recommend radical tumour resection whenever feasible, because surgical treatment offers the only chance of long-term survival.^{7–19} However, the operative procedure in early

tumour stages is controversial discussed.^{2,24,25} Some patients are discovered to have gallbladder cancer during operative therapy for presumed gallstone disease. The influence of the time of diagnosis on patient survival is still poorly taken into account.¹⁴ This retrospective study investigates the impact of surgery with curative intent in a Caucasian gallbladder cancer patient group and evaluates prognostic factors for survival. Time of diagnosis and the value of an extended resection to prolong survival are analysed separately.

PATIENTS AND METHODS

From 1984 to 1999, 267 consecutive patients were admitted to the surgical department of either one University hospital or one district hospital with the diagnosis of gallbladder cancer. Sixty patients were resected with curative intent and form the basis of this study. Data were recruited from patient records of the two hospitals and the operations were performed under supervision of the two leading surgeons. No evidence of malignancy at the resection margin was defined as R0, histological detection of malignant cells at the surgical

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Table 1 Operative procedure related to resection margin and T, N stage

	T1a N0	T1b N0	T2 N0	T2 N1	T3 N0	T3 N1	T3 N2	T4 N0	T4 N1	Total
<i>Tumour free resection margin (R0)</i>										
Cholecystectomy	3	5	13	1				1		23
Wedge liver resection		1	1	2	1					5
Resection segment 4			1			1		4	1	7
Right hepatectomy					2			1		3
Right trisectionectomy						1	1		2	4
Right anterior sectionectomy			1		2					3
Total	3	6	16	3	5	2	1	6	3	45
<i>Tumour positive resection margin (R1/R2)</i>										
Cholecystectomy			3	1		2	1		1	8
Wedge liver resection						2		1	1	4
Resection segment 4										0
Right hepatectomy						1				1
Right trisectionectomy						1		1		2
Right anterior sectionectomy										0
Total			3	1	0	6	1	2	2	15

margin was defined as R1 and macroscopically visible tumour at the margin was defined as R2.

Laparoscopic cholecystectomy risks tumour dissemination,^{20,21} therefore we excluded laparoscopic operations ($n = 17$). The benefit of adjuvant chemotherapy on survival in resected patients is uncertain,^{22,23} therefore we excluded 10 resected patients receiving adjuvant chemotherapy. Metastatic disease ($n = 15$), palliative operation ($n = 163$) and patients suffering from an additional malignant disease ($n = 2$) were also excluded from this analysis. Eleven patients were male and 49 were female. The mean age was 69.3 years (SD \pm 10.6). The median follow up time was 67.3 months (range 0.3–170).

The diagnostic work-up for the 39 patients who were resected prior to 1991 included an ultrasound in 30 patients (76.9%), computertomography in three (7.8%), endoscopic retrograde cholangiopancreatography (ERCP) in two (5.12%), one magnetic resonance imaging (MRI) and a cholangiography in five patients (12.8%). Seven of these 39 patients (17.9%) had more than one of these examinations and nine had none of them. In the period from 1991 to 1999, 21 of the included patients were operated. During the preoperative imaging work-up 19 patients received an ultrasound (90.5%), 13 a computertomography (61.9%), seven ERCP (33.3%), four MRI (19.4%) and one cholangiography (4.8%). Fifteen patients (71.4%) had more than one of these examinations.

Gallbladder stones were present in 51 patients (85%). Ten patients (16.7%) were referred to our centre after diagnosis of gallbladder cancer was established during a non-curative operation or an explorative laparotomy: these operations consisted of eight cholecystectomies (CHE; 1 R0, 3 R1, 4 R2) and two explorative laparotomies. After a median time of 20.5 days (range 2–197) definitive operation was performed. In 19 patients

Table 2 Classification of the modified Nevin staging

Modified Nevin staging	
Stage I	<i>In situ</i> carcinoma
Stage II	Involvement of mucosa or muscularis
Stage III	Transmural direct liver invasion
Stage IV	Lymph node metastasis
Stage V	Distant metastasis

(31.7%) gallbladder cancer was diagnosed preoperatively, whereas in 15 patients (25%) diagnosis was made during an operation for symptomatic cholecystitis and a curative resection was intended at the same time. In 16 patients (26.7%) gallbladder cancer was found during histological examination following operation for symptomatic gallstones.

The operative procedure and the T, N, R stage are summarized in Table 1. Tumour stage was classified according to the TNM system²⁴ and the modified Nevin system^{25–27} (Table 2).

Personal patient contact, their relatives or the general physician evaluated survival status; at last follow up 47 patients had died.

Dichotomous variables were compared by Fisher's exact test and categorical by χ^2 test. The patient survival rate was calculated from the date of operation and determined using the Kaplan–Meier method, and the log-rank test was used to assess survival differences. Patients who died during the postoperative course (30 days) were excluded from survival estimations. Survival was declared in terms of median. Cox Regression Model was used for multivariate survival analysis.

The analysis was performed using SPSS 9.0 for Windows (Statistical Package for Social Science, Chicago, IL, USA).

RESULTS

Operative procedure

Eight of the T1 tumours were treated with simple CHE and in one T1 cancer wedge resection and lymphadenectomy was performed after diagnosis during prior operation. Median survival after simple CHE in T1 tumours was 153.7 months; three patients are alive 5.5, 33.9 and 119.9 months postoperatively. The patient receiving wedge resection is alive 1 month postoperatively. Out of 23 patients with T2 tumour 18 had a CHE and survived 15.4 months whereas five patients had a liver resection including hilar lymphadenectomy and survived 35.8 months, $P = 0.237$. In 26 out of 28 patients with advanced cancer (T3, T4) an extended resection including five confluence resections of the hepatic duct, six bowel resections, two partial duodenopancreatectomies and four lymphadenectomies and a median survival of 9.1 months was achieved. A simple CHE for patients with advanced cancer led to a survival of 1.8 and 2.4 months (Table 1).

Morbidity and mortality

Postoperative 30 day morbidity differed according to the extent of resection: in patients after CHE ($n = 28$) one pneumonia and one pneumothorax treated by thoracic drainage were encountered (7.1%); after liver resection ($n = 29$) or three extended resections (one partial duodenopancreatectomy, one distal gastric resection including hemicolectomy, one hepatic duct confluens resection including hepaticojejunostomy) two intra-abdominal retentions, one wound infection and one anastomotic leakage treated by surgery, two bile duct fistulas and one pancreatic fistula treated conservatively were noted, leading to a morbidity of 21.9% ($P = 0.111$).

Mortality after CHE was 10.7% (one sepsis, two cardiac failure) and 6.3% following liver resection or other extended resections (one pulmonary embolus, one liver failure). The overall postoperative mortality rate was 8.3% ($n = 5$). Thirty-day mortality was excluded from further survival estimation. The median survival of all remaining patients was 15.4 months.

Long-term survival

Ten out of 55 patients (18.2%) survived 5 years and all of them had tumour-free resection margins (24.3% of R0). Three out of T1a (66.7%), two out of T1b (40%), four out of T2 (19%), one out of T3 (7.1%) and one out of T4 (8.3%) survived more than 60 months, $P = 0.082$. Eight patients in Nevin Stage II (30.8%), one in Stage III (9.1%) and one in Stage IV (5.6%) survived more than 5 years, $P = 0.070$.

Seven out of 14 (50%) G1 (well differentiated cancer), one out of 31 (3.2%) G2 (moderate differentiated cancer) and two out of eight (25%) G3 (poor differentiated

cancer) patients survived beyond 5 years, $P = 0.001$ (Table 3).

Resection margin

R0-resection was possible in 45 patients. In this group a median survival of 22.8 months was calculated. R1 ($n = 14$) resected patients survived 4.3 months and one patient with macroscopic positive resection margin (R2) survived 2.7 months ($P < 0.001$) (Fig. 1).

Operative procedures and their relation to TN Stage and resection margin are shown in Table 1.

TN staging

T1a ($n = 3$) tumour patients survived 9.0, 88.4 and 118.9 months; a survival of 153.7 months was calculated for patients with a T1b tumour ($n = 6$) and in none of T1 cancer patients tumour related death was documented. T2 ($n = 23$) patients survived a median of 22.8 months, T3 ($n = 15$) patients survived 9.1 months and T4 ($n = 13$) patients 7.9 months; this was statistically different, $P = 0.017$. Tumour related death was documented in eight

Table 3 Tumour classification of long-term survivors regarding T, N stage, grading, UICC staging and the modified Nevin staging

n	T	N	G	UICC stage	Mod. Nevin
2	Ia	0	I	I	2
1	Ib	0	I	I	2
1	Ib	0	2	I	2
3	2	0	1	II	2
1	2	0	3	II	2
1	3	0	1	III	3
1	4	1	3	IVA	4

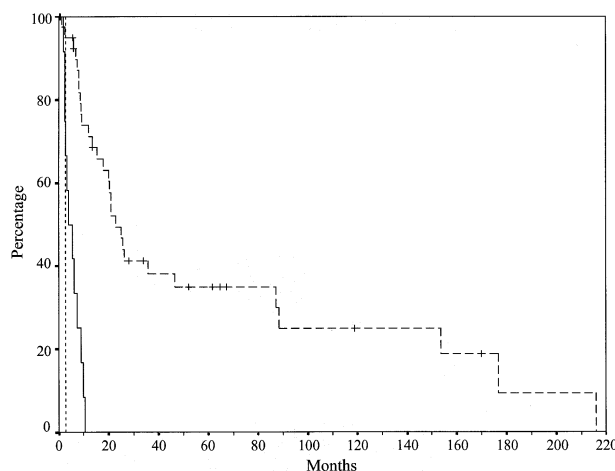


Figure 1 Survival related to resection margins. R0: ---, R1: —, R2: R0 showed a significant better patient survival ($P < 0.001$).

out of 18 deaths (44.4%) in T2, in five out of 14 deaths (35.7%) in T3 and in seven out of 10 deaths (70%) in T4.

Positive regional lymph nodes were found in 4/23 T2 tumours (17.4%), in 10/15 T3 (66.7%) and in 5/13 T4 tumours (38.5%); none of the nine T1 tumour patients had any evidence of involved lymph nodes, $P=0.004$. Lymph node tumour seeding was detected in 10 patients by lymphadenectomy and in nine by a lymph node biopsy.

Median survival time of patients with positive regional lymph nodes ($n=19$) was significantly worse compared to patients without involved nodes ($n=41$; 9.1 vs 20.4 months, $P=0.018$).

Modified Nevin staging

Patients who were classified stage II ($n=28$) reached a median survival of 46.6 months. Stage III patients ($n=13$) survived 8.6 months and stage IV ($n=19$) survived 9.1 months, $P=0.012$.

UICC

Patients in tumour-stage I ($n=9$) survived 153.7 months, stage II patients ($n=19$) survived 20.4 months, stage III ($n=17$) 10.5 months, stage IVA patients ($n=13$) 7.9 months and in stage IVB patients ($n=2$) survived 7.3 and 26.3 months, $P=0.026$.

Grading

G1 gallbladder cancer patients ($n=14$) survived 87.2 months, patients with a G2 ($n=36$) differentiated tumour survived 9.1 months and G3 ($n=10$) differentiated cancer patients survived 8.6 months ($P=0.008$). Poorly differentiated cancer was significantly linked to advanced T stages ($P=0.038$). Grading did not influence lymph node involvement ($P=0.272$). The relation of differentiation and T, N Stage is demonstrated in Table 4.

Time of diagnosis

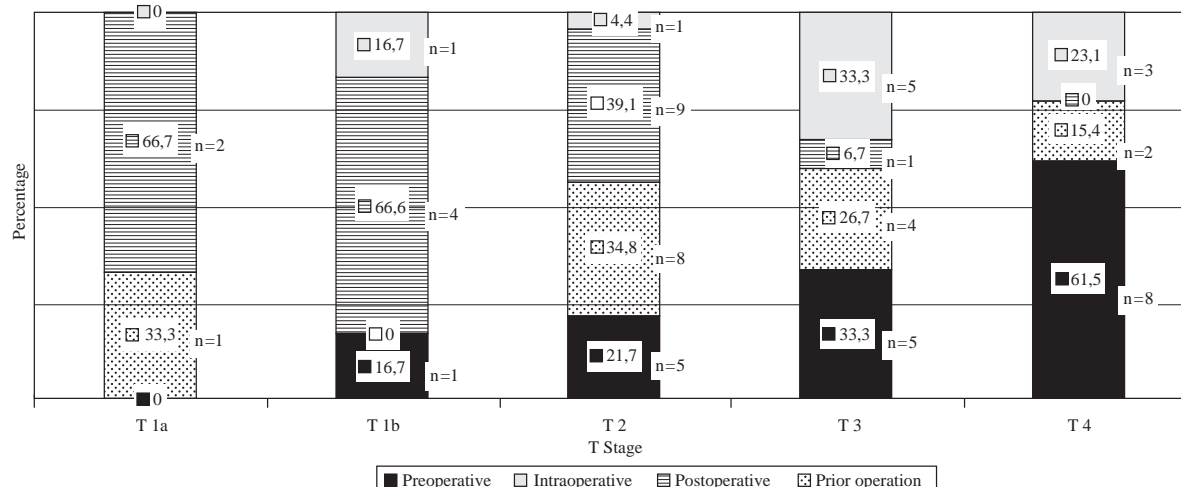
In T1 gallbladder cancer ($n=9$) diagnosis was made in 11.1% ($n=1$) during prior surgical exploration, in 11.1% ($n=1$, CHE (R0)) preoperatively and in 77.8% ($n=7$) of the patients during definitive operation or postoperatively by histological examination of the specimen. In case of advanced (T4) tumour gallbladder cancer was found in 84.6% ($n=11$) preoperatively or during prior surgical exploration (two explorative laparotomies, one CHE (R2)) and in 15.4% ($n=2$) of the patients intra- or postoperatively. The number of preoperatively suspected gallbladder cancers increased in advanced tumour stages. ($P=0.030$) (Table 5).

Before 1991 diagnosis of gallbladder cancer was suspected preoperatively in 11 patients (28.2%), detected during definitive operation in 10 (25.6%), diagnosed postoperatively in 11 (28.2%) and during prior operation

Table 4 T, N stage related to tumour cell differentiation (all patients included)

	T1a N0	T1b N0	T2 N0	T2 N1	T3 N0	T3 N1	T3 N2	T4 N0	T4 N1
G1 ($n=14$)	2	2	5		3	1	1		
G2 ($n=36$)	1	4	12	3	2	7		4	3
G3 ($n=10$)			2	1			1	4	2

Table 5 Relationship of distribution of the time of diagnosis to T stage



in seven patients (17.9%). In the period after 1991 malignancy of the gallbladder was suspected in eight patients (38.1%) preoperatively, diagnosed intraoperatively in five (23.8%), postoperatively in five (23.8%) and during prior operation in three (14.9%) patients.

The time of diagnosis did not influence patients survival (during prior operation and following definitive resection ($n = 10$) median survival 9.9 months, preoperative diagnosis ($n = 19$) median survival 9.1 months, intraoperative diagnosis ($n = 15$) median survival 20.1 months, postoperative diagnosis ($n = 16$) median survival 17.8 months, $P = 0.720$).

Age

Patients below 75 years of age ($n = 40$) at the time of operation reached a median survival of 20.1 months (95% CI: [8.4; 31.8]), older patients ($n = 20$) survived a median of 12.2 months (95% CI: [6.2; 18.2]), $P = 0.344$.

Jaundice

Data of preoperative bilirubin levels was available in 55 patients. Normal preoperative total serum bilirubin level ($n = 38$) led to a median survival of 20.1 months and none of them received preoperative stenting or drainage. Out of 17 preoperatively jaundiced patients two received papillotomy by ERCP and another two a drainage by percutaneous transhepatic cholangiography. Jaundiced patients survived 13.5 months, $P = 0.771$.

Multivariate analysis

Out of all investigated prognostic parameters tumour-free resection margin ($P < 0.001$) and tumour grading ($P = 0.051$) remained statistically significant (Table 6).

DISCUSSION

Most patients with gallbladder cancer are diagnosed in an advanced tumour stage due to the lack of suitable diagnostic methods and the non-specific nature of early

signs and symptoms. Curative resection is only possible in around 25% of all patients and remains the only treatment modality with a potential for cure.⁷⁻¹⁹ The diagnostic modalities and numbers of the preoperative investigations changed over the years, therefore diagnosis of gallbladder cancer was made prior to surgery more often in recent years.

Our patients were operated with curative intent and analysis showed a significant survival advantage depending on T stage, which is in accordance with other reports.^{14,18} Multivariate analysis of our data demonstrated that tumour free resection margin is the most important predictor of survival. If R0 resection is feasible, extended resection is warranted.

A major limitation to long-term survival in gallbladder cancer patients is the high percentage of lymphatic dissemination even in an early tumour stage.^{14,17,28-30} Recent data^{17,18,29} suggest that hilar and hepato-duodenal ligament lymph node dissection can be omitted in T1 tumour patients. These findings have certain implications in the area of laparoscopic cholecystectomy. Our current policy is a conservative approach in patients with the diagnosis of T1 gallbladder cancer on histology after cholecystectomy as long as the gallbladder was removed entirely without spillage.

A total of 44.4% of our T1 tumour patients survived to 5 years and none of them died of tumour related causes. Other authors reported even 87% 10 years survival for T1b tumours.²⁹ The published morbidity and mortality rates associated with extended resection^{2,13} do not justify its use in T1 tumours.^{14,18,19,29} In our series the higher mortality rate after CHE compared to extended resections was related to an increased co-morbidity (cardiovascular disease) in the CHE group. Extended resection is certainly warranted and recommended in patients with T2 tumour^{14,16-19,30} and was mainly done during recent years of this analysis. Long-term survival is possible even in T3/T4 tumours following extended resection^{9,13,16,19} and interestingly a 5-year survival of up to 28% has been reported.¹⁴ A simple cholecystectomy for these advanced tumour stages is of no benefit and results in a significantly impaired patient survival (1.8 and 2.4 months in our data). Applying an extended operative procedure we were able to achieve a 9.2% 5-year survival in this patient group. Our data demonstrate that the incidence of positive lymph nodes increased significantly with advanced T stages ($P = 0.004$), which was also reported by Kondo *et al.*³¹ A staging lymphadenectomy is recommended in patients with \geq T2 tumour, which is of specific interest in early tumour stages, where a significant survival benefit for patients undergoing lymphadenectomy has been demonstrated.³⁰ However, many authors report a poor outcome after surgery if cancer has already spread to the lymph nodes.¹⁴⁻¹⁹

The modified Nevin system²⁵⁻²⁷ emphasizes that lymph node involvement leads to a worse outcome compared

Table 6 Multivariate survival analysis of univariate significant variables

Variable	BETA	SE	Significance	HR
T stage	0.047	0.372	0.890	1.048
N stage	-0.534	0.463	0.249	0.587
Grading	0.507	0.259	0.051	1.660
Resection margin	2.001	0.456	<0.001	7.393
Modified Nevin	0.345	0.247	0.162	1.412
UICC	-0.009	0.015	0.569	0.991

to direct liver involvement. The presence of nodal metastases may indicate a more aggressive biology compared to a tumour, which locally invades the liver.¹⁹ A patient with direct tumour invasion of the liver is more likely to be cured by radical resection than a patient with nodal metastases.¹⁴

Tumour grading significantly influences the outcome of the disease. In the multivariate analysis tumour grading was a borderline significant predictor of survival. A significant higher rate of poorly differentiated tumour cells was found with advanced tumour stages ($P = 0.038$), which was also described by Schauer *et al.*¹⁷ and Ouchi *et al.*¹²

A total of 28.3% of our patients were preoperatively jaundiced, which did not influence patient survival. Fong *et al.* reported that 23% of their resected patients had jaundice, and they had a similar survival compared to patients without preoperative jaundice.¹⁴ As long as operative treatment is not delayed jaundiced patients can be resected without higher perioperative risk.

Published data report a higher perioperative risk in patients over 70 years of age.^{2,28} Our patients over 75 years of age had similar risk of perioperative complications compared to the younger age group. The multi-centre analysis by Cubertafond *et al.*² included patients who were operated on in small hospitals with certain limitations in the perioperative management. In our study three out of 20 patients (15%) older than 75 years of age and seven out of 40 younger patients (17.5%) survived more than 5 years. It is therefore recommended that a radical operative approach in patients with gallbladder cancer should not be limited to any age. If gallbladder cancer is suspected, patients should be referred to a specialised centre for further management, an approach that is emphasised by Fong's data demonstrating a survival benefit in patients transferred after primary non-curative operation.¹⁴

The benefit of adjuvant chemotherapy on patient's survival following curative resection is still uncertain.^{22,23} No improvement of survival was detected after using adjuvant radiation for R0 resected patients.¹⁸ These therapies may be considered if curative treatment is impossible. Therefore some promising reports using radiation and chemotherapy have recently been published.^{18,23,32}

CONCLUSION

Tumour resection is the only chance of cure and even in aged patients a curative operation can safely be performed. For T1 tumour stage our data are limited due to lack of sufficient 5 years follow-up in some patients, but the remaining data do support current ideas of omitting extended surgery in T1 tumour. For other T stages liver resection including lymphadenectomy is mandatory.

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