THE TIME OF DIAGNOSIS IMPACTS SURGICAL MANAGEMENT BUT NOT THE OUTCOME OF PATIENTS WITH GALLBLADDER CARCINOMA

F. Löhle1,2, G. Meimarakis1, C. Schauer3, M. Angele1, K. W. Jauch1, R. J. Schauer1,3

1Surgical Department, Klinikum Grosshadern, Ludwig-Maximilians University of Munich, Germany,
2Surgical Department, Academic Hospital Klinikum Landshut, Germany,
3Surgical Department, Academic Hospital Klinikum Traunstein, Germany

Abstract
Background: Only 50% of gallbladder cancers (GBC) are recognized before operation and the remaining tumors are diagnosed during surgery or afterwards by the pathologist. These situations may demand substantial modifications of the proceeding during surgery as well as the need for reoperation in some cases. Therefore, the time of diagnosis may strongly influence the surgical management of GBC and the prognosis of the patients.

Methods: Records and follow-up of 152 patients with gallbladder carcinoma who underwent surgery between 1980 and 2004 were examined according to the time of diagnosis, TNM staging system, surgical procedures, morbidity and predictors of survival. There were 76 patients with preoperative diagnosis of GBC (50%; group 1), 44 patients with intraoperative diagnosis (29%; group 2) and 32 patients (21%; group 3) with postoperatively incidental finding of GBC. In all cases radical resection of the GBC was intended, except in 5 patients from group 1. Surgical procedures comprised from simple cholecystectomy to multivisceral resections.

Results: Overall 5-year survival rate was 7% with a significantly better median survival in group 3 (53.2 month), when compared to only 6.1 month (group 2) and 5.4 month (group 1), respectively. Findings at operation forced significant modifications of the surgical strategy in 85%. Complete resection of GBC was achieved in 38% of the patients. Stage-dependent survival was comparable between the groups following R0 resection. Tumor stage, in particular the nodal status and radicality of the procedure, but not the time of diagnosis were the most powerful predictors of outcome.

Conclusions: Complete tumor resection may provide long-term survival even in locally advanced GBC. Although the time of diagnosis of GBC causes significant changes of the intended procedures during and after surgery, it has no influence on the prognosis provided that radical (R0) resection was accomplished.

Key words: Gallbladder cancer, Surgery, Follow up, Prognosis

Abbreviations: GBC, Gallbladder Carcinoma

INTRODUCTION

Gallbladder carcinoma has a poor prognosis. Five-year survival ranges between 5% and 13% with a median survival of less than 6 month [1, 2]. Because tumor growth is often locally advanced at the time of surgery, no marked improvement of patients outcome was achieved during the last decade [4]. Therefore, once GBC is diagnosed, curative resection can be expected only in 20-40% of patients [3, 4]. Recent studies suggest the efficacy of a radical approach to enhance survival even in patients with advanced tumor stages [5-7]. However, these reports need careful evaluation because the prognosis strongly depends on the chance to achieve complete tumor resection (R0) [8, 9].

It is specific for GBC that only about 50% of the tumors are recognized before an operation [10]. Then, most of the cancers are unresectable due to local or distant tumor growth. Although some studies advocated radical resection in advanced-stage disease, there is no consensus as to the selection of patients considered for surgery [10]. In contrast, intra- or postoperative findings of GBC were usually associated with smaller tumors and a better prognosis, even though recent literature could demonstrate that preoperative diagnostic workup may fail to predict GBC also in tumor stages T3 and T4 [11, 12]. Particularly with regard to incidental GBC findings by the pathologist, the debate continues about the adequate stage-dependent tumor therapy, when the patients age, morbidity of secondary procedures and 5-year survival rates are taken into account. Therefore, the commonness of incidental GBC, either as an intra- or postoperative finding lies in the need for a substantial switch of the operative strategy during surgery, i.e. from simple cholecystectomy to extended liver resection, or in the need for stratifying patients after removal of the gallbladder to more aggressive, secondary procedures [13-16].

The rarity of GBC limits the ability to perform prospective, randomized studies of therapy. However, there is good evidence from numerous retrospective surveys that tumor stage and radical surgery (R0) are the strongest predictors of survival [17-19]. The purpose of this study is to provide data, how the time of diagnosis of GBC may influence surgical procedures.
as well as the outcome of patients, in particular following radical resection.

**PATIENTS AND METHODS**

Between 1980 and 2004, 196 consecutive patients with GBC were seen at the Surgical Department of the University of Munich. Of these, 165 patients underwent surgery, but only 152 patients were eligible for follow up until July 2006 (Fig. 1). In another 31 patients (16%), metastatic disease of GBC was confirmed by biopsies at presentation, yielding a total of 152 patients for data analysis. Mean age was 66.3 years (38-92 years) and there were 93 woman and 59 men in this study (Table 1). Data was collected from chart review and a telephone questionnaire, including patient demographics, laboratory data, operative management, surgical morbidity, pathologic findings, and length of hospital stay. Histologic examination revealed adenocarcinoma in 141 patients (93%), adenosquamous tumors in 7, and squamous carcinoma in 4 patients.

Demographic data as well as the comorbidity of patients were comparable between the groups. The majority of patients showed ASA 1/2 score (72%) and liver cirrhosis was absent in most cases (93%). Data about malignant tumors in the history of some patients included breast cancer (3), prostate cancer (3), and colonic cancer (1) and at the time of admission to our institution, there was no evidence for local or metastatic recurrence of these cancers. GBC was staged according to the TNM classification (UICC; Table 1) [20].

Only 26 patients (17%) had tumors limited to the gallbladder wall (T1a, n = 5; T1b, n = 9; T2, n = 12) and all of these were recognized only by the pathologist. The remaining patients (n = 126) had locally advanced or metastatic cancer.

The most common symptom at presentation was pain (87%; no difference between the groups). In contrast, mild jaundice (64%) and weight loss (31%) were predominantly present in group 1 (p<0.05 vs. groups 2 and 3). Ninety-four percent of tumors were associated with gallstones. Therefore, routine laboratory tests prior to the operation did not markedly help to identify GBC (Table 2).

The surgical procedure in patients with presumed benign disease was simple cholecystectomy (SCE), either as an open or laparoscopic operation. Early stages of GBC were treated by an "extended cholecystectomy" (ECE) which consisted of an en-bloc removal of the gallbladder with hepatic wedge resection of segments IVb/V, and lymphnode dissection of the ligament. Locally advanced cancers with infiltration of the liver underwent extended liver resection (ELR) and lymphnode dissection of the ligament. In case of involvement by the GBC, bile duct resection (BDR), lymphnode dissection and hepatico-jejunostomy was performed. In some patients multivisceral resections (MVR) were done to achieve radicality. Only laparotomy or palliative surgery was performed when unresectability was suspected. Survival was calculated by the Kaplan-Meier method. Cox univariate and multivariate analysis was performed to determine prognostic factors for survival.

**Table 1. TNM (UICC) staging of GBC by time of diagnosis.**

|       | UICC I | UICC II | UICC III | UICC IVb | UICC IVb |
|-------|--------|---------|----------|----------|----------|
| Group 1 (n=76) | 0       | 0       | 15       | 8        | 53       |
| Group 2 (n=44)  | 0       | 0       | 10       | 14       | 20       |
| Group 3 (n=32)  | 14      | 12      | 6        | 0        | 0        |
| Total (n=152)   | 14      | 12      | 31       | 22       | 73       |

**Note:** In UICC stages I and II GBC is limited to the gallbladder wall (I: T1a/b; II: T2), in UICC stage III lymphnodes are positive (T1-3), in UICC IVa the tumor is locally destructive (T4), and in UICC stage IVb local or distant metastases are present.
RESULTS

INDICATIONS AND PROCEDURES

Seventy-six patients out of 152 (50%) were admitted to our institution because of a presumed benign disease. Most of these had gallbladder stones (n = 71) and others had concomitant acute (n = 13) or chronic cholecystitis (n = 21). Diagnostic procedures comprised ultrasound in all patients of this group whereas CT or MRI scans were considered necessary prior to the operation only in 16 patients (21%). All 76 patients were subjected to simple cholecystectomy (27 laparoscopic and 49 open procedures).

The pathologist recognized GBC postoperatively in 32 patients (group 3) whilst the surgeons did not praise any of these gallbladders suspicious for cancer (Table 3). Fourteen patients had stage I- tumors (T1a, n = 5; T1b, n = 9) and 12 patients were classified as stage II- tumors. Three patients had positive lymphnodes at the cystic duct (stage III) while the carcinoma was limited to the gallbladder wall (T2) and 3 more patients had T3 cancers (one R1 resection). Although the indication for a second procedure was defined as T-stage ≥T1b, or positive resection margins after SCE, only 12 patients (48%) underwent definitive cancer surgery.

In 44 patients (group 2) GBC was found incidentally at operation and all of them had advanced tumors (Table 1). Twenty patients were considered unresectable due to bulky lymphnodes in

Table 2. Laboratory data at admission to our institution.

|         | GGT (U/l) | AP (U/l) | Bilirubin (mg/dl) | Leucocytes (E3/ml) | CRP (mg/dl) |
|---------|-----------|----------|-------------------|-------------------|-------------|
| Group 1 (n=76) | 104±78   | 148±64   | 1.9±3.2           | 8.6±7.4           | 4.9±6.2     |
| Group 2 (n=44) | 86±54    | 126±61   | 1.3±2.4           | 9.5±6.9           | 9.2±5.9     |
| Group 3 (n=76) | 68±42    | 97±54    | 1.0±1.2           | 8.2±5.6           | 3.6±4.8     |
| Total (n=152) | 87±43    | 127±47   | 1.5±2.0           | 8.9±5.1           | 5.4±4.9     |
| p         | 0.04*    | 0.7      | 0.02**            | 0.8               | 0.2         |

Note: * group 3 vs. group 1; ** group 1 vs. groups 2 and 3.

Table 3. Intended and performed operations (first procedure) by time of diagnosis.

| Indication | Intended procedure | n | Performed procedure | n | Change of procedure | Radical (R0) resection |
|------------|--------------------|---|---------------------|---|--------------------|-----------------------|
| Group 1 (n=76) |                   |   |                     |   |                    |                       |
| Suspected  | SCE                | 0 | 0                   | 0 | 0                  | -                     |
| GBC       | ECE                | 5 | 2                   | 60% | 1/50%              |                       |
|           | ELR                | 26| 14                  | 46% | 8/57%              |                       |
|           | BDR                | 19| 4                   | 79% | 2/50%              |                       |
|           | MVR                | 21| 8                   | 62% | 2/25%              |                       |
|           | PALL               | 5 | 5                   | 0%  | 0%                 |                       |
|           | LAP                | 0 | 43                  | 100% | 0%                 |                       |
| Group 2 (n=44) |                   |   |                     |   |                    |                       |
| Stones    | SCE                | 30| 0                   | 100% | -                  |                       |
| Acute Chol.| SCE                | 4 | 0                   | 100% | -                  |                       |
|           | SCE                | 10| 0                   | 100% | -                  |                       |
|           | ECE                | 6 | 0                   | 100% | -                  |                       |
|           | ELR                | 6 | 0                   | 100% | -                  |                       |
|           | BDR                | 10| 0                   | 100% | -                  |                       |
|           | MVR                | 2 | 0                   | 100% | -                  |                       |
|           | PALL               | 3 | 0                   | 100% | -                  |                       |
|           | LAP                | 17| 0                   | 0%   | -                  |                       |
| Group 3 (n=32) |                   |   |                     |   |                    |                       |
| Stones    | SCE                | 12| 12                  | 0%  | 12/100%            |                       |
| Acute Chol.| SCE                | 9 | 9                   | 0%  | 9/100%             |                       |
|           | SCE                | 11| 11                  | 0%  | 10/91%             |                       |
| Total (n=152) |                 | 152 | 152               | 85% | 58/38%             |                       |

Note: SCE, simple cholecystectomy; ECE, extended cholecystectomy; ELR, extended liver resection; BDR, bile duct resection; MVR, multivisceral resection; PALL, palliative procedures; LAP, only laparotomy; Chol., Cholecystitis.
the ligament (n = 8), liver metastasis (n = 6), and peritoneal implants of the GBC (n = 6). In the remaining patients, the surgical strategy was changed immediately at operation and radical resection of the tumor was attempted. The procedures performed, included all options of resective surgery as demonstrated in Table 3.

The remaining patients (n = 76) presented prior to surgery pathological findings which were in accordance with GBC disease (group 1). Five patients had intestinal obstruction as the main symptom and thus required palliative surgery (Table 3). In contrast, CT- and MRI findings of the remaining patients with suspected GBC were evaluated as suitable for a radical approach. However, in 44 patients of group 1 (58%) the tumor size and infiltration pattern as well as the intraoperative detection of distant metastasis (liver, n = 21; peritoneum, n = 14; liver and peritoneum, n = 9) did not allow curation from GBC, and obliged the surgeon to terminate the operation as a diagnostic procedure. The remaining patients (n = 32) underwent radical surgery which was strongly dependent on differential types of local tumor growth (Table 3).

The R-status, as indicated in Table 3 describes radi- cality at first operation. Twenty-five patients of group 3 had tumor stages which required re-operation but only 12 of them were referred to additional surgery. In that collective, complete tumor resection (R0) was achieved in all cases (ECE, n = 9; ELR, n = 3). However, patients with suspected GBC (group 1) had a significantly (p<0.05) higher risk for incomplete tumor control after surgery (83%) when compared to patients with GBC detected at operation (69%) or as an incidental finding by the pathologist (3%).

**PERIOPERATIVE PARAMETERS**

There was no mortality in the study population, although it is sometimes a challenge for the surgical team as well as the anaesthesiologist to cope with a radical change of the surgical procedure at operation [3, 10]. However, as Table 4 indicates there were no marked differences seen when perioperative data of groups 1 and 2 are compared. Blood loss as well as the operating time and complication rates were similar in both groups, indicating no additional risk for patients with incidental GBC finding at operation. In all patients of group 2, a definitive procedure was aimed at the first operation so that secondary interventions were avoided. Mean hospital stay was 12.2 days in group 1 (7-31 days), 11.8 days in group 2 (6-24), and 4.8 days (2-8) in group 3.

**SURVIVAL**

The overall 1-, 3-, and 5-year survival rates of the 152 patients were dismal with 43%, 24%, and 7%, respectively. This is the result of a highly metastatic potential of GBC which resulted in lymphnode involvement in 71% and systemic tumor spread in 49% of the analyzed patients. These advanced tumors did not allow a cumulative R0 resection rate beyond 38%. As demonstrated in Table 3, we found a significant correlation between the time of diagnosis and the radicality (R status), indicating a poorer chance of complete tumor resection with respect to the procedures performed. Figure 2 illustrates the dependency of survival from the groups. It is clearly demonstrated that in univariate analysis the time of recognizing GBC has a highly significant impact on the probability for survival as shown by median survival times of 53.2 month (group 3), 6.1 month (group 2), and 5.4 month (group 1).

The median survival for the 94 patients with unresectable tumors (R1/R2) was 5.1 month with only 1 patient alive beyond 2 years (26 month). For those resected, the 1-, 3-, and 5-year survival was 79%, 47%, and 26%, respectively. Interestingly, when the patients of groups 1 - 3 who underwent radical tumor resection (R0) are compared, we found no differences with regard to the prognosis when GBC was an incidental finding (Table 5). In contrast, patients with incomplete tumor resection (R1/2) showed median survival times of only 4.8 month (R1 resection) and 3.2 month (R2 resection).

As demonstrated in Table 5, the time of diagnosis has no effect on the outcome of patients once complete tumor resection was possible. This finding was confirmed in multivariate analysis which showed the UICC stage (p<0.001) and radicality of the procedure (p<0.001) as the only independent predictors of survival. In contrast, the parameter “time of diagnosis” did not have the power as a prognostic factor of survival (p = 0.4; Cox regression analysis).
DISCUSSION

Gallbladder carcinoma carries a poor prognosis, and the only chance for cure lies in early detection and complete resection. However, the extent of surgical procedures remains controversial, particularly after incidental findings or in advanced stages of disease [13, 21, 22]. Some reasons for this are the lack of a uniform classification of staging systems in previous reports [23-25] and a different use of terms like “extended cholecystectomy” and “extended resection” which included various surgical procedures in some studies [7, 23, 26]. The 5-year survival rate following surgery for GBC is reported to be 5–13% in the recent literature [1, 2, 27] except as a study of a small number of cases [2]. The aim of our retrospective study was to highlight the perioperative situation, the surgeon is confronted with: (1) ad hoc decision at incidental findings of GBC during operation about the extent of further procedure, and (2) stratification of patients with postoperatively found GBC to a second operation. In particular, it was of interest if the time of diagnosis may influence radicality of surgical procedures and the prognosis of patients.

The diagnosis of GBC is difficult because of the lack of reliable diagnostic methods [11, 12, 28] and the unspecific symptoms of patients who, to a considerable extent presented in this study with gallbladder stones (94%) or cholecystitis (22%). Furthermore, in 16 out of 92 patients (17%) who underwent CT or MR imaging prior to the operation GBC was not detected even though T3 and T4 tumors were present. Laboratory data usually are of limited significance as reported earlier and shown in Table 2 [29]. Consequently, it seems specific that GBC is just partly recognized at diagnostic work up before surgery and that the remaining carcinomas are detected not until as by the surgeon at operation or by the pathologist thereafter. In this study, GBC was suspected in 50% of the patients preoperatively, which is in line with recent literature [10, 30]. In all other cases, diagnosis was made at the time of surgery (29%) or postoperatively (21%).

Table 5. Survival of patients with complete resection (R0) of GBC.

| Group 1 (76) | n  | N+ | M+ | Survival (month) | Survival (5 years) |
|-------------|----|----|----|------------------|--------------------|
| T3          | 9  | 6  | 2  | 21.9             | 19.9               |
| T4          | 4  | 3  | 1  | 17.2             | 12.2               |

| Group 2 (44) | T3 | 7 | 5 | 2 | 23.8 | 21.1 |
|--------------|----|----|----|----|------|------|
| T4          | 7  | 5  | 4  | 18.9| 11.8 |

| Group 3 (32) | T1 | 14 | 0  | 0  | 67.8 | 79.3 |
|--------------|----|----|----|----|------|------|
| T2          | 15 | 3  | 0  | 58.3| 68.9 |
| T3          | 3  | 1  | 1  | 23.4| 26.0 |

Note: Given are median survival times.

![Fig 2. Survival by time of diagnosis of GBC.](image)

Note: p<0.001 (group 3 vs. groups 1/2) and p<0.05 (group 2 vs. group 1).
survival [17-19, 31]. That requires special considera-
tion as to the indication to extended surgery, in par-
ticular when GBC is an incidental finding. We could
demontrate that the time of diagnosis of GBC has a
strong influence on tumor stages: significantly more
patients with stage III and IV disease were observed in
groups 1 (suspected GBC) and 2 (incidental finding at
operation). Ninety-three percent and 72% had lymph
node involvement in groups 1 and 2, respectively,
whereas only 3% were affected in group 3. Local or
distant metastasis was present in 70% of patients in
group 1, 45% (Group 2), and 3% (group 3).

Therefore, it is obvious that the tumor stage directly
imparts the chance for radical cure of the disease.
Consequently, the rates of complete tumor resections
(R0) varied significantly between the groups, showing
the best result in group 3 (R0;100%) and disappoint-
ing results in group 2 (R0;32%), and group 1 (R0;17%)
which is for the most part consistent with earlier work
[28, 32]. The indication to secondary procedures after
SCE was based on data which demonstrated venous,
lymphatic, or perineural tumor invasion also in T1b
stages, although lymph node involvement is rare in T1
stage [33] and some authors refuse additional surgery
[23, 33, 34]. In our series, only 5 patients had T1a dis-
ease and 9 were staged as T1b. All of them were
staged as node- negative. Five patients with T1b stage
underwent a second procedure and no residual tumor
was found. Five- year survival of patients with T1 dis-
ease was 79%. In contrast, we found a 48% risk of
positive nodes as well as a 21% risk of tumor spread
in T2 cases which clearly demands a more radical ap-
proach than SCE [30].

In the present study, only 15% of the operations
were accomplished as intended, the rest of the pa-
tients underwent either a dramatic change of the pro-
cedure or a second intervention. All the more, careful
evaluation of the tumor stage at operation, the age
and prognosis of the diseased patients and the addi-
tional risk of extended resections should be in mind
of the surgeon [27]. Although we had no mortality in
our patients, some indications for extended tumor re-
sections seemed too optimistic with regard to R0 rates
of only 31% in group 2 and 17% in group 1. More-
ever, we and others could demonstrate that not only
the tumor stage, but also the pattern of tumor growth,
and consequently the kind of surgical procedure has a
strong impact on radicality [6]. Infiltration or local tu-
mor spread to the liver usually required ELR whereas
the involvement of the common bile duct demanded
resection and hepatico-jejunostomy. In our series, we
achieved complete resection after ELR in 13 out of 20
cases (65%) compared to only 36% (5/14) following
BDR. From similar findings, Miyazaki et al. developed
a stratification system for patients with significantly
different prognoses due to tumor localization and the
involvement of adjacent organs [32]. Some authors
suggest extended lymphnode resection for radical
treatment of GBC in these cases [6, 8, 23]. However,
and others [34] precluded patients with proven in-
volvement of coeliac, superior mesenteric and para-
aortic lymph nodes from radical resection because the
prognosis seems similar to metastatic disease [7]. Ex-
tended resections were performed in our series with a
low morbidity which is in line with recent reports,
demonstrating low mortality and complication rates
after major liver resections even in the older popula-
tion [35]. Complete macroscopic and microscopic resec-
tion of the gallbladder including adjacent tissue of various
extent is a prerequisite for long- term survival, partic-
ularly in advanced tumor stages [17, 27]. Our findings
support this contention, demonstrating gross tumor
remnants (R2) as well as microscopically positive tu-
mor margins (R1) as significantly negative predictors
of survival. As we could show that the time of diag-
nosis of GBC strongly influences surgical procedures
and radicality, it was of special interest if survival was
dependent on the time of diagnosis when complete
tumor resection was accomplished. Interestingly, we
observed comparable median and five- year survival
rates, regarding T3 and T4- staged GBC of groups 1
and 2. Patients with T3 cancer had a median survival
time of about 22 month whereas in cases with T4
stage, the prognosis was decreased to approximately
18 month. Taking the median survival of patients
with unresected GBC into account, the survival bene-
fit of those undergoing radical surgery (R0) is almost
about 20 month. Therefore, it seems justified to sub-
ject patients with initial findings of advanced
GBC to aggressive surgery at the same operation [3],
in particular because of the low morbidity as demon-
strated in this series. We had only 3 patients with T3-
staged GBC in the postoperative findings, one had
positive lymphnodes and another had a single liver
metastasis next to the gallbladder bed. Reoperation
resulted in complete tumor control, but median sur-
vival was also disappointing with 23.4 month. Al-
though there is no group in this study undergoing ob-
servation alone for comparison, it is certain that resid-
ual disease would lead to recurrence and death within
6 month [23].

In conclusion, the present study confirms earlier
reports which demonstrated a significant impact of
the tumor stage and a radical resection of GBC on
survival [27]. This analysis additionally proved that the
time of diagnosis has no influence on the prognosis
of patients after radical resection. However, substan-
tial decisions concerning the indication, the framing
of the approach to resection, the expected morbidity
and survival time are requested by the surgeon. Spe-
cial attention has to be drawn in the future on a care-
ful imaging before surgery to avoid R1/R2- resec-
tions.

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Address for correspondence:
Rolf J. Schauer, M.D.
Surgical Department
Klinikum Traunstein
Cuno-Niggel-Str. 3
83278 Traunstein
Germany
Fax: 0861-705-1470
Phone: 0861-705-1201
Email: rolf.schauer@klinikum-traunstein.de