

Staged Surgery Combined with Chemo
Radiation Improves Outcome after
Incomplete Removal of Gallbladder CancerMarc Daniels^{1*}, Maximilian Brunner¹, Sabine Semrau², Robert Grützmann¹ and
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Abstract

Introduction: Gallbladder carcinoma is the most frequent tumor of the bile system and has a poor prognosis. The main proportion of tumors diagnosed coincidentally after gallbladder removal for various reasons. In these cases, an incomplete removal of the tumors occurs frequently. The adequate treatment of these patients is still under discussion. We present our experience with different procedures.

Patients and Methods: Between 1990 and 2015, we identified 20 patients which were presented at our University Hospital after incomplete removal of gallbladder cancer (R1, R2, RX) as incidental findings after cholecystectomy. The prospectively collected data including surgery, adjuvant treatment, histopathological examinations of the specimens and follow-up data were analyzed retrospectively.

Results: The median age of patients was 72 years (range 47-89 years), 90 % (18/20) were female. The median follow-up period was 10 months (range 0-109 months). The median survival of all patients was 11 months (95 % confidence interval: 5-17 months). The median survival of patients who received staged surgery and chemo radiation after incomplete gallbladder removal was significantly increased (median 32 months; range 4-109 months) vs. patients who received chemo radiation without surgery (median 13 months; range 8-51 months) or chemotherapy alone (median 2.5 months (range 0-40 months)) (p = 0.005).

Discussion: There is no standardized treatment for residual tumor after incomplete gallbladder cancer resection. Our data demonstrate that staged surgery with prior chemo radiation may improve patient's outcome. Surgery can be performed with low morbidity and mortality.

Introduction

Gallbladder carcinoma is the most frequent tumor of the bile system and the sixth most common gastrointestinal malignancy in the United States [1]. In India, Central Europe and in Poland the prevalence is 14/100000, whereas in the United States it is less frequent with 1.5/100000 [2].

Main risk factors for gall bladder cancer are gallstones, female gender, ethnicity, genetic susceptibility and lifestyle factors.

The prognosis of patients with the diagnosis of gallbladder cancer is poor with an overall 5-year survival rate of 10 % and a median survival of 6 months [3]. Surgery with complete removal of the primary tumor and the draining lymph nodes are important prognostic factors. They are essential for long-time survival [3,4]. The value of neoadjuvant or adjuvant treatment is still under discussion [5-19]. The main proportion of tumors are diagnosed coincidentally after gallbladder removal for inflammation or gallbladder stones. Therefore, an incomplete removal of the tumors occurs frequently in these cases, which are not planned as oncological resections. The question how these patients should be treated is still under discussion. There is currently no standardized recommendation for this clinical scenario. The prognosis of incompletely resected gallbladder cancer is poor (Table 1). Adjuvant therapy after R1 resected gallbladder cancer seems to improve the overall survival [7]. Local radiation after R1-resection seems to improve the longtime survival [8,9,16-19]. Kresl et al., [20] showed a higher local control rate for higher adjuvant external beam radiation therapy (100 %) after five years compared to lower doses (63 %). In addition, the study by Takada et al. with subsequent chemotherapy presented survival benefits. The 5-year survival rate was significantly better in the chemotherapy group (26 %) compared to the control group (14.4 %) [21]. Detailed information is shown in Table 1.

Behind these facts this cohort of patients which were treated with several regimens after incomplete gallbladder carcinoma resection was evaluated and the experience is shared.

Table 1: Detailed comparison of literature.

Author	Year	n	CTX	R`T	Chemoradiation	Chemoradiation and Surgery	Follow up; months (range)	Median Survival months	5-year survival rate
Takada et al., [21]	2002	38	38	0	0	0	60	n.a.	8.9 %
Takada et al., [21]	2002	23	0	0	0	0	60	n.a.	0
Kresl et al., [20]	2002	9	0	0	9	0	60 (32-122)	R1: 16 R2: 7	0
Duffy et al., [10]	2008	24	8	0	8 (Chemoradiation + chemotherapy)	0	26.6	23.4 (15.7-47 95% CI)	n.a.
Wang et al., [18]	2011	252	126	0	126	0	n.a.	16	n.a.
Daniels et al.,	2016	20	4		7	3	10 (0-113)	R1: 23 R2: 5	5 %

n.a: not available; CTX: Chemotherapy; RT: Radiotherapy.

Material and Methods

Patients

A comprehensive review of the Tumor Centre at the Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany was performed and identified between 1990 and 2015 twenty patients with R1, R2 and RX resected gallbladder cancer after primary surgery. Inclusion criteria of the study were histopathological validated gallbladder carcinoma and histopathological verified R1, R2 or RX resection to any tumor side. The patients were prospectively documented using defined proformas including general epidemiological data, surgery and adjuvant treatment, histopathological examinations and follow-up data. The median follow-up period was 10 months (range 0-113 months). Furthermore, the anatomic disease extend of the tumors were classified by using the UICC TNM classification 2010. All these gallbladder carcinomas were non-in sano resected incidental findings after cholecystectomy and did not receive any neoadjuvant therapy.

Patients were discussed in an interdisciplinary tumor board and therapy was recommended regarding the general conditions of the patients.

Primary surgery

All twenty gallbladder carcinomas were diagnosed coincidentally after gallbladder removal for inflammation or gallbladder stones. In four cases an open cholecystectomy was performed, in 16 cases laparoscopic surgery was chosen.

Histopathology

The stages were classified according the UICC Classification 2010. Details are listed in Tables 2 and 3. R1-status is defined as microscopically visible tumor residues. R2-status describes macroscopically visible tumor residues. In case of unclear margins because of fragmentation, the classification resulted in Rx. Nodal positivity was diagnosed histologically.

Statistical analyses

Chi-squared test and Fisher’s exact test were used to compare categorical data. The Kaplan-Meier method was applied for univariable analyses of survival rates. For the identification of observed survival, tumor related death was defined as an event. A p-value of less than 0.05 was appreciated to be significant. All analyses were performed using the IBM SPSS Statistics 21.0 software.

Table 2: Patient’s and tumor characteristics.

		n
Sex	Female	18
	Male	2
Age (years)	Median (range)	72 (47-89)
T	1	0
	2	6
	3	11
	4	2
	n.a.	1
N	0	8
	1	8
	n.a.	4
M	0	10
	1	7
	n.a.	3
L	0	7
	1	7
	n.a.	6
V	0	10
	1	4
	n.a.	6
R	1	9
	2	6
	X	5
UICC	II	6
	IIIa	3
	IIIb	2
	IVa	5
	IVb	3
	n.a.	1

n.a: not available.

Table 3: Patients` and tumor characteristics.

Number	Sex	Adjuvanttreatment	Age	UICC	Overall Survival (months)
1	M	Unknown	86	II	40
2	F	Died while primary surgery	64	n.a.	0
3	F	Unknown	65	IVB	0
4	F	No adjuvant treatment	83	IIIA	1
5	F	Adjuvant Chemotherapy	74	IV	5
6	F	Adjuvant Chemotherapy	82	IVA	1
7	F	Adjuvant Radio- and Chemotherapy + Operation	71	IV	109
8	F	No adjuvanttreatment	81	IIIA	0
9	F	Adjuvant Chemotherapy	75	IV	16
10	F	Adjuvant Chemotherapy	47	IVB	8
11	M	Adjuvant Radio- and Chemotherapy	64	IIB	13
12	F	Adjuvant Radio- and Chemotherapy	72	IIIA	11
13	F	Adjuvant Radiotherapy	63	IV	4
14	F	Adjuvant Radio- and Chemotherapy	67	II	30
15	F	Adjuvant Radio- and Chemotherapy + Operation	69	II	32
16	F	Adjuvant Radio- and Chemotherapy	77	IIB	10
17	F	Adjuvant Radio- and Chemotherapy	81	IVB	51
18	F	Adjuvant Radio- and Chemotherapy	72	IIIB	16
19	F	Adjuvant Radio- and Chemotherapy + Operation	47	IIIB	4
20	F	Adjuvant Radio- and Chemotherapy	89	II	8

M: Male; F: Female; n.a.: Not Available.

Results

Patient and tumor characteristics

Between 1990 and 2015 twenty patients were diagnosed with R1 resected gallbladder cancer after primary surgery. The median age of these patients was 72 years (range-89 years). Ninety percent (18/20) of the patients were female. All twenty tumors were adenocarcinomas of the gallbladder. Most carcinomas were T3 tumors 11/20 (55%) and were classified as stage UICC IV 8/20 (40 %). Nodal positivity was diagnosed in 8/20 (40 %) cases. In seven cases, distant metastasis could be detected. Four distant metastases were detected in the liver (2 x R2, 2 x RX), two in the peritoneum (R2 and RX) and one in the transverse colon (R1). Details are listed in Tables 2 and 3. Most tumors were classified as G3 tumors 55 %. Seven tumors were graded as G2 (7/20; 35 %) and one tumor was graded as G1 (1/20; 5%). For one tumor, no grading was available. Patients with R1/R2/RX-resected gallbladder carcinomas presented more advanced tumors (T3 and T4; 60 %) and were mostly classified in stage UICC III and IV (65 %). Six tumors showed a R1-resection at the stump of the cystic duct, four at the liver side, one patient had gastral and peritoneal metastases and another patient presented with an infiltration of the hepatic colonic flexure. Three tumors showed R1-resections without exact local description and five tumors were diagnosed with unclear resection margins.

Adjuvant treatment

In this study group most patients with a R1-resected gallbladder cancer received an adjuvant combined radio- and chemotherapy

(7/20; 35 %) with a total dose of 55.8 Gy and Gemcitabine in combination with Cisplatin. One Patient received Carboplatin instead of Cisplatin. Another patient received an Oxaliplatin and 5-FU based chemotherapy. 4 patients received an adjuvant chemotherapy alone (Gemcitabine/Cisplatin) (4/20; 20 %) and one patient received an adjuvant radiotherapy alone (5 %) (55.8 Gy). Three patients did not receive any adjuvant therapy because of poor general conditions and in 2 cases no data about adjuvant therapy were available.

Staged surgery

In three cases, patients received surgery after chemoradiation. In one case segment resection of the liver segments IVB and V as well as a resection of the peritoneum of the right costal arch and a lymph node dissection of the hepatoduodenal ligament and intraaortocaval were performed (pT3 pN1 cM1, G3, UICC IV). The second patient received an atypical resection of liver segment V combined with a lymph node dissection of the hepatoduodenal ligament and at the hepatic artery (pT2 pNx, pMx L1, G2, UICC II). In the third case resection of the cystic duct, of liver segments IVb and V in combination with lymph node dissection of the hepatoduodenal ligament and intraaortocaval (pT3 pN1 pM0, G3, UICC IIIB) were performed. All Patients are still alive (Mortality 0 %). Residual tumor could be identified in nospecimens after staged surgery and chemoradiation (R0 = 3/3; 100 %).

Survival

The median survival of all patients in this study was 11 months (95 % confidence interval: 5-17 months). The group of patients who

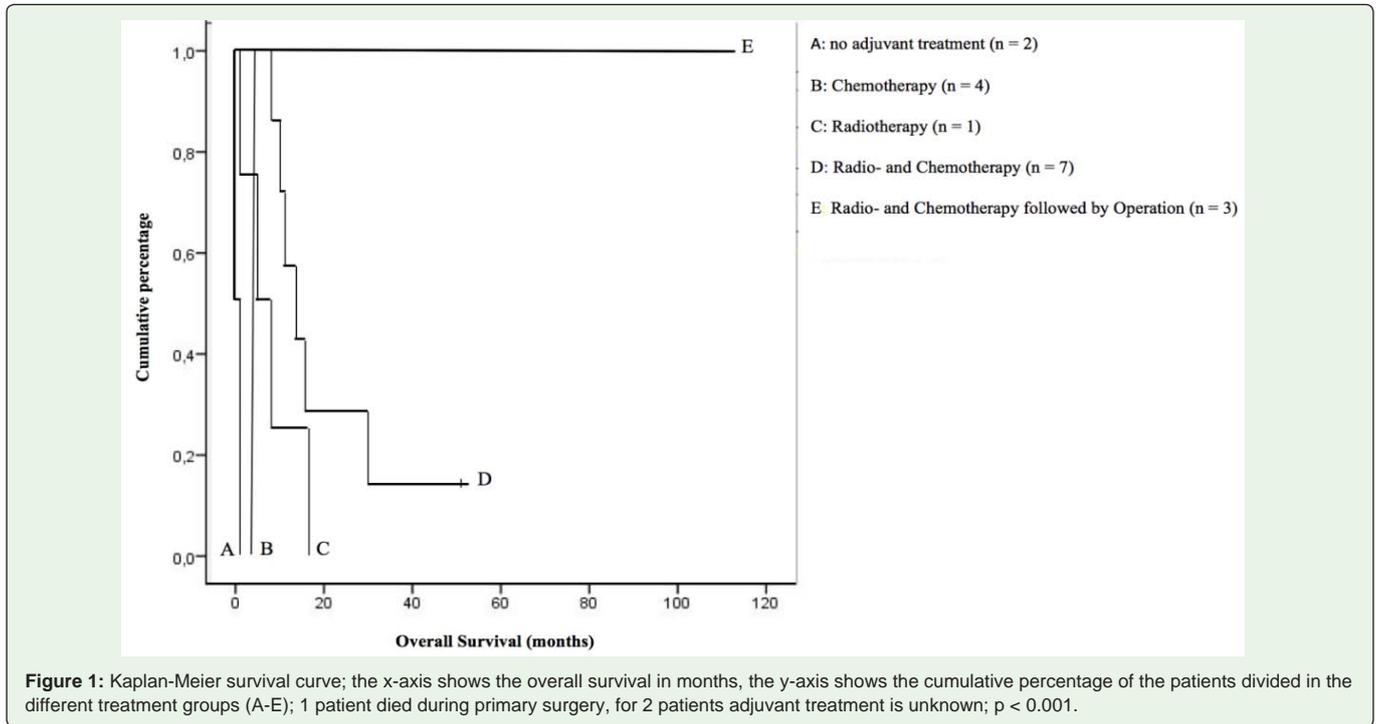


Table 4: Overview of our different treatments and their corresponding median overall survival.

Adjuvant Treatment	Median overall survival (95 %-CI) (months)	p
Chemotherapy (n = 4)	5 (0 – 11.9)	<0.001
Radiotherapy (n = 1)	4 (-)	
Chemoradiation (n = 7)	13 (7.9 – 18.1)	
Chemoradiation + staged surgery (n = 3)	32 (0 – 76.8)	

CI: Confidence Interval.

received surgery after chemoradiation was 32 months (Range 4-109 months). All three patients were still alive after last follow up (Figure 1). Patients who received chemoradiation only without surgery showed a median overall survival of 13 months (range 8-51 months). In comparison the patients without any treatment or chemotherapy only present a median overall survival of 0 months (range 0-40 months) and 5 months (range 0-11.5 months) (Table 4).

Separate consideration of the R-status shows a median survival for R1 tumors of 16 months (range 1-51 months), for R2 tumor of 6.5 months (range 0-109 months) and for RX resected tumors of 4 months (range 0-16 months).

Discussion

The entire current study situation for the subsequent treatment of R1-resected gallbladder cancer is poor. In general, the prognosis of patients with the diagnosis of gallbladder cancer is poor with an overall 5-year survival rate of 10 % and a median survival of 6 months [20]. In this study, the median overall survival was 11 months. This survival benefit compared to the current literature may occur by specific treatment modalities. The group with staged surgery after chemoradiation showed the best survival data. In this group, the median overall survival was 32 months and five times higher than

the median survival described in the literature (6 months) [20]. Therefore, the local radical resection after adjuvant therapy seems to be the most important prognostic factor [3] and is essential for the long-time survival. Staged surgery in these cases must be performed as an extended procedure respecting the localization of the R1 margin after primary surgery. Liver resection and lymph node dissection at least around the hepatoduodenal ligament and in selected cases interaortocaval are mandatory. In cases of positive cystic duct removal of the common bile duct with hepatico jejunostomy are recommended.

Reoperation is recommended in cases of T2 tumors and more advanced stages of disease to achieve R0-Resection. Controversies still exist concerning the need for more radical resection for T1b GBC. During reoperation, it is also unclear what the appropriate extent of hepatic resection is, and whether hepatic resection can prevent liver recurrence. Based on the review of Cavallaro et al. stages starting from T1b should be treated with lymphadenectomy and resection of at least 2-3 cm of liver parenchyma around the liver bed. In cancers with positive margins of the cystic duct, resection of the main bile ducts could be necessary. More extensive liver resection or performance of multiorgan resection can be performed in order to achieve R0 resection [22].

The question remains why patients are not treated immediately

with staged surgery after the diagnosis of R1 resection. There are several reasons for the concept of adjuvant treatment followed by staged surgery: 1. The diagnosis of R1 resection hit patients in a postoperative situation where anatomy is quite vulnerable. Operating in this situation might increase morbidity. 2. During R1 resection in a not planned oncological resection, tumor cell dissemination might have occurred. Chemoradiation could sterilize the disseminated cells prior to staged operations. 3. Treating patient's neoadjuvant after R1 resection might select patients with very aggressive tumors, which develop metastatic disease quite early and did not benefit from staged surgery.

Local radiation after R1-resection seems to improve the longtime survival [18]. Kresl et al., [20] showed a higher local control rate for higher adjuvant external beam radiation therapy (100 %) after five years compared to lower doses (63 %). In addition, the study by Takada et al., [21] with subsequent chemotherapy presented survival benefits. The 5-year survival rate was significantly better in the chemotherapy group (26 %) compared to the control group (14.4 %) [9,21]. Similar results with survival benefits for adjuvant treatment with chemotherapy or chemoradiation were reported by Murakami et al., Gold et al., and Wang et al., [12,17,19]. In addition, Horgan et al., [13] could show that adjuvant treatment shows clear improvement especially for the overall survival of R1 resected tumors.

By contrast Duffy et al., [10] and Glazer et al., [11] could not observe a survival benefit for those who received adjuvant therapy.

Conclusion

In this cohort, the best results for overall survival were achieved with chemoradiation followed by radical staged surgery. Furthermore, exclusively adjuvant radio- and chemotherapy showed better results for overall survival (13 months) adverse all other treatments (2.5 months).

Certainly, there are differences between R1, R2 and RX- resected tumors. Whereas R1-resected tumors present a median overall survival of 16 months, R2- an RX-resected tumors show median overall survivals of 6.5 and 4 months. Notably the R2-resected tumor which received adjuvant chemoradiation and surgery shows a clearly higher overall survival with 109 months. Worth mentioning is that the patients treated with adjuvant chemoradiation and surgery in the R1-resected tumor group are all still alive, therefore these overall survival rates represent current states only.

Obviously, this is just a small retrospectively evaluated study group with 20 patients but it shows nevertheless a tendency to treat non in sano resected gallbladder cancers with an adjuvant radio- and chemotherapy with subsequent post operation. In future, it is important that there will be studies with greater collectives of patients.

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