

# Adequate extent in radical re-resection of incidental gallbladder carcinoma: analysis of the German Registry

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## Abstract

**Background** Complete surgical resection is the only potentially curative treatment of gallbladder cancer. Gallbladder carcinoma is suspected preoperatively in 30% of patients, and 70% are incidentally discovered by the pathologist (incidental gallbladder carcinoma, IGBC). If IGBC is detected postoperatively, a re-resection, including liver resection and lymph node dissection, in T2 tumor cases and more advanced stages is recommended. It remains unclear whether the prognosis of wedge resection (2–3-cm margin) of the gallbladder bed is the same as that of resection of segments IVb/V.

**Methods** The German Registry, founded in 1997, aims to prospectively record all IGBC cases in Germany. In this study patients with a radical re-resection were treated according to the S3 Guidelines in Germany. The aim of this study was to clarify whether different techniques of liver re-resection show comparable results or if they differ depending on the tumor stage in IGBC patients ( $n = 624$ ).

**Results** A significant survival advantage in patients who have an early re-resection was observed. There was a trend of better survival in T1 tumor stage patients who undergo the less radical re-resection, especially the wedge-resection technique of 3 cm in the gallbladder bed. In T2 tumor stage patients there is a tendency for better survival with the IVb/V-resection technique compared to the 3-cm wedge resection in the gallbladder bed, and a significant survival benefit for these two techniques compared to less radical resection was evident. T3 tumor cases showed better survival with the more radical resection techniques.

**Conclusions** The wedge-resection technique combined with lymph node dissection may be the surgical strategy of choice in T1 tumor cases. For T2 tumors, IVb/V resection combined with lymph node dissection of the hepatoduodenal ligament appears to be the minimum volume of resection required. More radical procedures are needed for tumors infiltrating the serosa or beyond.

**Keywords** Pancreatobilio · Cholecystectomy · Gallbladder carcinoma · Surgical · Technical

## Introduction

Gallbladder carcinoma is the fifth most common neoplasm of the digestive tract, with an incidence of 2.5 per 100,000 in the United States [1, 2]. The outcome of gallbladder carcinoma is poor, with a 5-year survival rate of less than 5% [1–3]. There is no effective therapy for gallbladder cancer except surgical resection [4], and complete surgical resection is the only potentially curative treatment of this cancer [5]. However, the overall 5-year survival rate is 5–13%, even after radical resection [6–8]. The aggressive surgical approach to gallbladder carcinoma practiced in Japanese centers has yielded encouraging results [9–15].

Gallbladder carcinoma is suspected preoperatively in only 30% of all patients [1, 2], while the other 70% of cases are discovered incidentally by the pathologist (incidental or occult gallbladder carcinoma or IGBC) [16, 17]. Gallbladder carcinoma is found in 0.2–3% of all cholecystectomies [18, 19], and if it is suspected preoperatively, an open cholecystectomy must be performed to enable complete evaluation of disease progression and to perform radical resection if necessary. Gallbladder carcinoma patients undergoing laparoscopic resection have a poorer

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clinical outcome than those with open surgery [20–23]. However, German Registry data and recent retrospective analyses showed that laparoscopic cholecystectomy has no such adverse effect [24, 25]. No differences in long-term survival after curative resection were detected between patients treated with either one and those treated with a second radical re-resection [26]. Extended resection with regional lymph node dissection for T2 carcinomas and for more advanced carcinomas has been suggested [11, 26–29]. If IGBC is detected postoperatively by the pathologist after simple cholecystectomy, radical re-resection in cases of T2 tumors and more advanced stages is recommended [30].

According to the effective guidelines in Germany [30], radical cholecystectomy includes a liver resection as a wedge resection of the gallbladder bed with a margin of 3 cm in the liver or an anatomic resection of liver segments IVb/V. In addition, locoregional lymph node dissection of the hepatoduodenal ligament should be performed. It remains unclear whether a wedge resection with a margin of 2 cm [6] to 3 cm [30] has the same prognosis as an anatomic resection of segments IVb/V. Micrometastases [31] and direct extension of the tumor through the gallbladder wall into the liver [29, 32] are reasons for these two kinds of liver resection techniques.

Nevertheless, a large variety of recommendations for resection margins ranging from 1 to 5 cm have been proposed for the liver [33, 34] to extended right hepatic lobectomy, but none were based on rigorously collected data. Lymph node dissection should be performed to make the resection more radical and to obtain a definite diagnosis of the lymph node status.

In the present study, we evaluated the efficacy of the wedge-resection technique and the bisegmentectomy of IVb/V combined with standardized lymph node dissection of the hepatoduodenal ligament based on the criteria of the S3 Guidelines [30] and other hepatic resection techniques combined with, for example, extrahepatic bile duct resection or en bloc resection with adjacent organs to make the procedure more radical. We analyzed 624 cases of IGBC with the aim of clarifying whether different techniques of liver resection have comparable results or if they differ depending on the tumor stage.

## Methods

This investigation was based on the central register of “incidental gallbladder carcinoma” of the German Society of Surgery (German Registry). The German Registry was founded in 1997 [35] by the surgical association of endoscopy (CAES) and is also supported by the surgical association of minimal invasive surgeons (CAMIC); both

are institutions of the German Society of Surgery (DGCH). This registry aims to prospectively record all cases of incidental gallbladder carcinoma in Germany.

In this study, all patients who had a radical re-resection were treated according to the S3 Guidelines in Germany [30]. Patients had a liver resection either as a wedge resection of the gallbladder bed with a 3-cm margin in the liver or as an anatomic resection of liver segments IVb/V combined with a locoregional lymph node dissection of the hepatoduodenal ligament. These patients were divided into four groups. Group 1 underwent a standardized wedge resection and group 2 had a IVb/V resection. Group 3 patients underwent another resection technique (e.g., en bloc resection with adjacent organs or a right hemihepatectomy). Group 4 included patients for whom the resection technique used was unknown. The early re-resection is a resection performed in the first 45 days after the initial “cholecystectomy” to make it more radical.

A standardized questionnaire was sent to all German surgical clinics. This questionnaire included questions about the OP indication (because all of the carcinomas were incidentally discovered), preoperative diagnostics, the operative (OP) method, any intraoperative and/or postoperative complications, location of the tumor (fundus, body, neck), histology, TNM stage, and information about further therapy such as early re-resection, chemotherapy, or radiation. Clinical and histopathological staging was based on the 6th edition of the UICC/AJCC classification of 2002 [10].

Statistical analysis was performed using SPSS v11.5 (SPSS Inc., Chicago, IL, USA). Survival was calculated according to the Kaplan–Meier method and comparison between groups was performed using the log-rank test. A  $p < 0.05$  was considered statistically significant.

## Results

A total of 624 cases of gallbladder cancer were in the German Registry, including 473 (75.8%) females (Table 1). The distribution of operations was 348 laparoscopies, 160 open surgeries, and 114 cases that started as a laparoscopy but was then converted to open surgery for nononcological reasons. Table 2 gives patient population classified according to tumor (T) stage.

Figures 1 and 2 show the survival rates for all patients ( $n = 624$ ) in the registry. An early radical re-resection was performed in only 231 of the 624 patients with IGBC and these patients showed a significant survival advantage (log rank,  $p < 0.005$ ) (Table 3).

An early radical re-resection was performed in 28.0% ( $n = 33$ ) of the 118 T1 tumor patients (Fig. 3). The median survival time for T1 tumor cases was 1692 days and the

**Table 1** Age and sex of patients who underwent one of the three operation methods ( $n = 624$ )

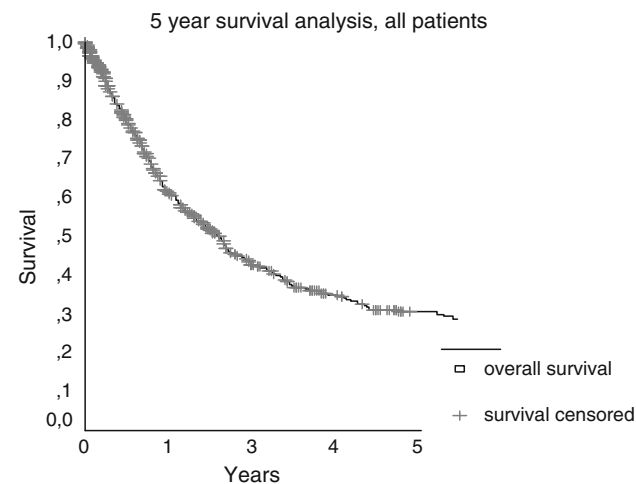
	Laparoscopy ( $n = 348$ )	Open ( $n = 160$ )	Conversion ( $n = 114$ )	Method unknown ( $n = 2$ )
Age [mean (SD)]	68.2 (10.6)	72.7 (11.1)	70.6 (11.3)	85.5
Sex [ $n$ (%) female]	267 (76.7)	113 (70.6)	92 (80.7)	1 (50)

**Table 2** Patients categorized according to T stage ( $n = 624$ )

	Laparoscopy ( $n = 348$ )	Open ( $n = 160$ )	Conversion ( $n = 114$ )	Method unknown ( $n = 2$ )
pTis	18	3	1	0
pT1	70	31	17	0
pT2	200	62	38	0
pT3	51	40	51	1
pT4	5	19	6	0
pTx	4	5	1	1

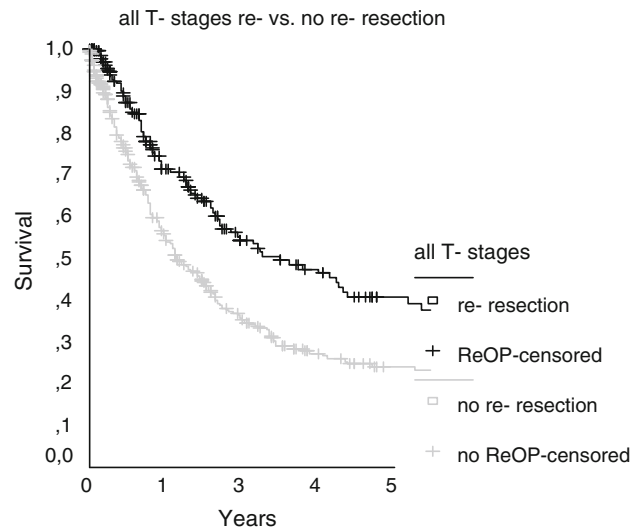
**Table 3** Five-year survival rate and mean and median survival times (days) of all patients in the German Registry ( $n = 624$ )

	All patients ( $n = 624$ )	No re-resection ( $n = 393$ )	Re-resection ( $n = 231$ )
Mean	2028	1322	3219
Median	792	567	1245
Five-year survival rate (%)	32	25	41

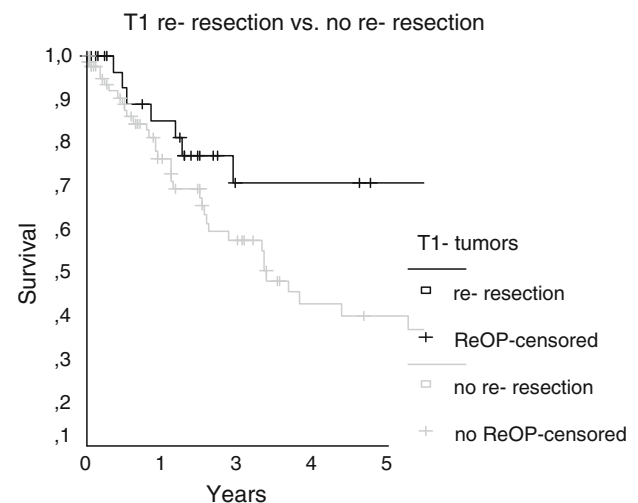


**Fig. 1** Five-year survival rate for all patients ( $n = 624$ ) in the German Registry

5-year survival rate was 49% (Table 4). According to the Kaplan–Meier curves, extended re-resection increased the 5-year survival rate from 40 to 71% for patients with T1



**Fig. 2** Five-year survival rate for all patients with re-resection ( $n = 231$ ) versus without re-resection ( $n = 393$ )



**Fig. 3** T1 carcinomas with re-resection ( $n = 33$ ) versus without re-resection ( $n = 85$ )

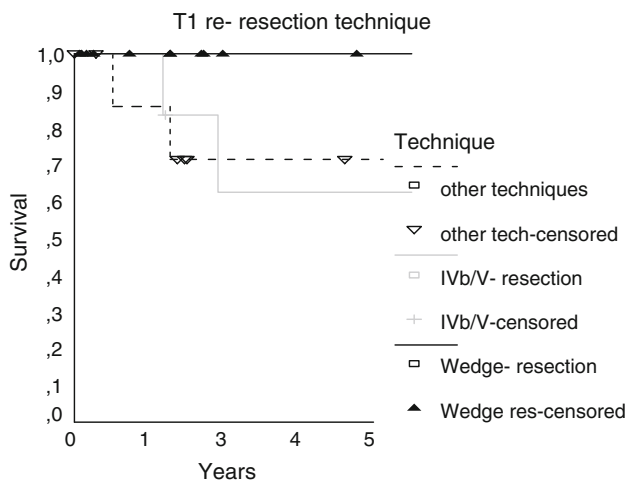
tumors. Patients with early re-resection showed a significant survival advantage (log rank,  $p = 0.04$ ).

In the 33 T1 tumor patients who had a re-resection, 45.5% ( $n = 15$ ) had a wedge resection of 3 cm in the liver bed, 18.2% ( $n = 6$ ) had a IVb/V segment resection, and in 9 cases other resection techniques were performed (group 3), including local ( $n = 2$ ), liver ( $n = 2$ ), cystic duct

**Table 4** Five-year survival rate and mean and median survival times (days) for different re-resection techniques for T1 tumors ( $n = 118$ )

	No re-resection ( $n = 85$ )	Re-resection ( $n = 33$ )	Wedge resection ( $n = 15$ ) (Group 1)	IVb/V resection ( $n = 6$ ) (Group 2)	Other techniques ( $n = 9$ ) (Group 3)
Mean	1799	2195	— <sup>a</sup>	1857	1605
Median	1192	—	— <sup>a</sup>	—	—
Five-year survival rate (%)	40	71	100	62	71

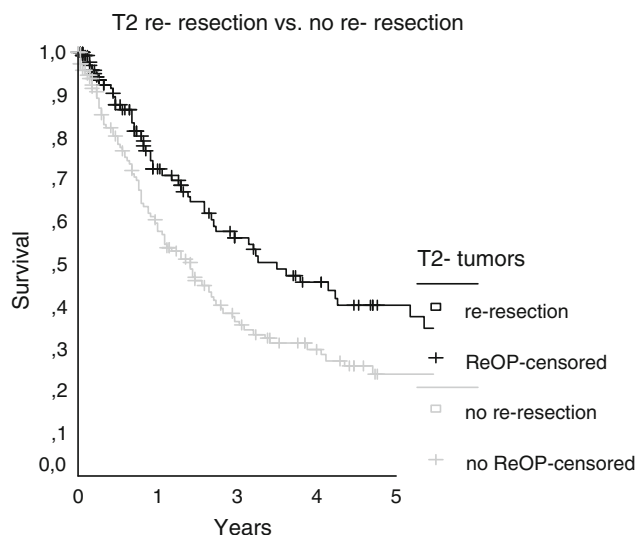
<sup>a</sup> Survival estimates cannot be calculated since all observations were censored

**Fig. 4** Different re-resection techniques in T1 carcinomas

( $n = 3$ ), and bile duct ( $n = 1$ ) resections and one right hemihepatectomy. All group 3 resections were combined with lymph node dissection of the hepatoduodenal ligament. Group 4 ( $n = 3$ ) included patients for whom there was no information about the resection technique used.

Figure 4 shows that 100% of the T1 tumors treated with a wedge resection of 3 cm in the liver bed had a 100% 5-year survival rate, whereas T1 tumor patients who had a resection of segment IVb/V had a 5-year survival rate of 62%. Patients who underwent other techniques (group 3) had a 5-year survival rate of 71%. Group 3 of the T1 tumor patients underwent mostly less radical resection techniques. There was a trend for better survival in T1 tumor patients with the less radical re-resection techniques ( $p > 0.05$ ).

Figure 5 shows the survival rates for the T2 tumors ( $n = 300$ ). An early radical re-resection was performed in 46.3% ( $n = 139/300$ ) of the patients with T2 tumors, and their median survival time was 841 days and 5-year survival rate was 31% (Table 5). According to the Kaplan–Meier curves, extended re-resection increased the 5-year survival rate from 25 to 41% for patients with T2 tumors. T2 patients had a significant survival advantage with early re-resection (log rank,  $p = 0.0061$ ). Wedge resection of 3 cm in the liver bed was performed in 48.2% ( $n = 67/139$ )

**Fig. 5** T2 carcinomas with re-resection ( $n = 139$ ) versus without re-resection ( $n = 161$ )

of the T2 tumor patients, whereas 22.3% ( $n = 31$ ) had a IVb/V segment resection (Table 6). In 23 cases other resection techniques were performed (group 3), including 3 local, 9 liver, 6 cystic duct, and 3 bile duct resections, 1 right hemihepatectomy, and 1 resection of segment 2,3,4b,5. All group three resections were combined with lymph node dissection of the hepatoduodenal ligament. Group 4 consisted of 16 patients for whom there was no information about the resection technique used.

The 5-year survival rate of the T2 tumor patients who had a wedge resection of 3 cm in the liver bed was 46%, whereas for those who had a resection of segment IVb/V it was 54% (Fig. 6). Patients who underwent other techniques (group 3) had a 5-year survival rate of only 15% and a significant survival disadvantage (log rank,  $p < 0.05$ ) compared to that of the wedge- and the IVb/V-resection techniques. Group 3 of T2 tumor patients underwent mostly less radical resection techniques. There was a trend for better survival in T2 tumor stage patients with the IVb/V-resection technique compared to those with the wedge-resection technique ( $p > 0.05$ ), and a significant survival benefit for groups 1 and 2 compared to group 3 ( $p < 0.05$ ) (Table 5).

**Table 5** Five-year survival rate and mean and median survival times (days) for different re-resection techniques for T2 tumors ( $n = 300$ )

	No re-resection ( $n = 161$ )	Re-resection ( $n = 139$ )	Wedge resection ( $n = 67$ ) (Group 1)	IVb/V resection ( $n = 31$ ) (Group 2)	Other techniques ( $n = 23$ ) (Group 3)
Mean	1471	3029	3624	1799	820
Median	703	1245	1579	2090	795
5-year survival rate (%)	25	41	46	54	15

**Table 6** Re-resection techniques and the corresponding T stages

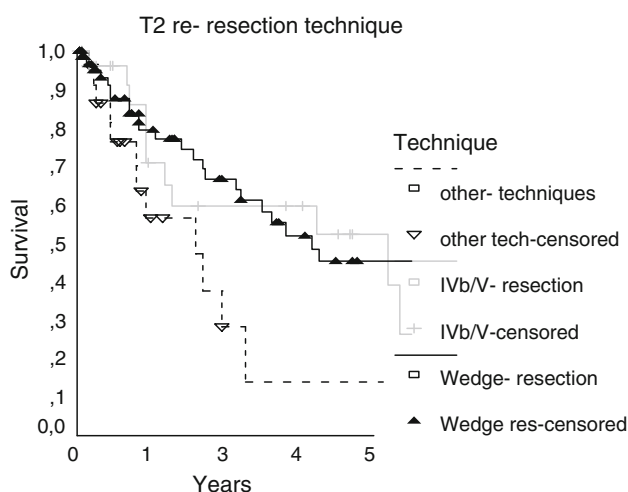
T stage	Wedge resection	IVb/V resection	Other techniques	Unknown technique	Not calculated by statistics
T1 ( $n = 33$ )	15	6	9	3	0
T2 ( $n = 139$ )	67	31	23	16	2
T3 ( $n = 46$ )	19	6	8	11	2
T4 ( $n = 4$ )	1	0	2	1	0

An early radical re-resection was performed in 32.4% ( $n = 46/142$ ) of the patients with T3 tumors (Fig. 7). The median survival time for T3 tumor patients was 349 days and the 5-year survival rate was 10% (Table 7). According to the Kaplan–Meier curves, an extended re-resection increased the 5-year survival rate from 8 to 17% for patients with T3 tumors. There is a significant survival advantage for patients who underwent an early re-resection (log rank,  $p = 0.0075$ ). Of the T3 tumor patients who had a re-resection ( $n = 46$ ), 41.3% ( $n = 19$ ) had a wedge resection of 3 cm in the liver bed while 13.0% ( $n = 6$ ) had a IVb/V segment resection (Table 6). In 8 cases other resection techniques were performed (group 3), including 5 local advanced resections, 1 liver resection, and 2 right hemihepatectomies. All resections in group 3 were combined with a lymph node dissection of the hepatoduodenal

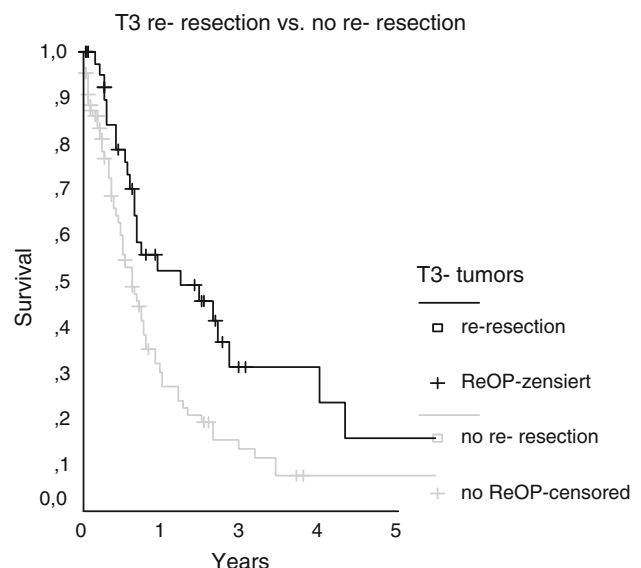
ligament. Group 4 ( $n = 11$ ) included patients for whom there was no information about the resection technique used.

None of the T3 tumor patients who underwent a wedge resection of 3 cm in the liver bed or a resection of segment IVb/V survived 3 years, whereas the patients who underwent another technique (group 3) survived 4 years 4 months (Fig. 8). Group 3 of the T3 tumor patients underwent more radical resection techniques such as a right hemihepatectomy. There was a trend of better survival for the more radical resection techniques in T3 tumor stage patients.

Tables 8, 9, 10 give the age and sex of the patients who had one of the three different re-resection techniques.



**Fig. 6** Different re-resection techniques in T2 carcinomas



**Fig. 7** T3 carcinomas with re-resection ( $n = 46$ ) versus without re-resection ( $n = 96$ )

**Table 7** Five-year survival rate and mean and median survival times (days) for different re-resection techniques for T3 tumors ( $n = 142$ )

	No re-resection ( $n = 96$ )	Re-resection ( $n = 46$ )	Wedge resection ( $n = 19$ ) (Group 1)	IVb/V resection ( $n = 6$ ) (Group 2)	Other techniques ( $n = 8$ ) (Group 3)
Mean	608	979	514	583	1140
Median	311	617	368	342	933
5-year survival rate (%)	8	17	0	0	0

## Discussion

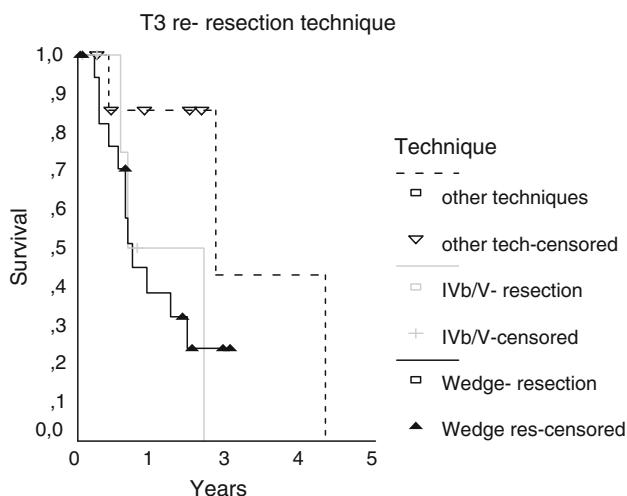
In spite of current reports showing improvements in the outcome of radical resection techniques, including various hepatectomy techniques and regional lymph node dissection techniques, no consensus regarding the appropriate extent of resection has been established. A rational approach that recommends wedge resection of the liver involving the gallbladder bed as well as a regional lymph node dissection of the hepatoduodenal ligament was proposed in 1954 [36], and regional lymph node dissection was recommended in 1963 [37]. Lymphatic and venous infiltrations were reported to be present in 33.3% of T1b cancers [38], and lymph node metastasis and lymphatic infiltration was shown in 15.7 and 18.4% of T1b cancers, respectively [39]. Another study found no lymph node metastasis or lymphatic or perineural infiltration in the T1a tumors [40]. The incidence of lymph node metastasis was reported to be 46% in T2 gallbladder cancer [41]. The poor 5-year survival rates are due to the aggressive nature of gallbladder carcinoma, and if it is not resected, prognosis is poor [5].

A role for chemo- and radiation therapy in the management of gallbladder cancer remains undefined [5]. However, effectiveness of radical re-resection for incidental gallbladder carcinomas at the T2 or more advanced stages has

been reported [27]. The effectiveness of a radical surgical approach for gallbladder cancer has been the subject of a number of reports [42–45] from centers in Japan [46–48] and the United States. Therefore, there seems to be a need of more radical treatment of gallbladder carcinoma. The extent of surgery necessary to treat gallbladder cancer varies widely and seems to depend on the depth of tumor penetration. For tumors confined to the mucosa (T1a), simple cholecystectomy is enough [12]. For T2 cancers, simple cholecystectomy is associated with a 5-year survival rate of 24–40%, whereas a simple cholecystectomy combined with other liver resection techniques and regional lymph node dissection is associated with a 5-year survival rate of up to 80% [12, 41]. In cases up to T2 tumors, a liver resection should be performed because of the possibility of micro-metastasis in the gallbladder bed [31] and because the perimuscular (subserosal) connective tissue, the layer infiltrated by T2 carcinomas, is dissected by the surgeon at the time of cholecystectomy. In cases more advanced than the T2 stage, tumor cells directly infiltrate the gallbladder bed so an extended resection is the only way to achieve negative margins. Direct extension of the tumor through the gallbladder wall into the adjacent liver is common. In 34–89% of patients with gallbladder carcinoma, such an invasion into the liver has been suggested [29, 32]. Most micrometastases were seen in an area of 15–27 mm [31]. T3 and T4 tumors are more invasive and therefore require more extensive resections; however, this does not result in improved long-term survival [49, 50].

According to the German Registry data and current literature, radical re-resection of T1b and more advanced tumors offers a survival benefit for patients compared to those who do not have radical re-resection [51, 52]. In general, there is a consensus among hepatobiliary surgeons that T1b tumors require an extended procedure [53]. However, there is still no consensus regarding the appropriate extent of the resection or re-resection for the different T stages of gallbladder cancer.

There is a significant survival advantage for re-resected T1 tumor patients ( $n = 33$ ) in the German Registry. The wedge-resection technique combined with lymph node dissection of the hepatoduodenal ligament seems to be the surgical strategy of choice for treating T1 tumors over the more radical re-resection techniques.

**Fig. 8** Different re-resection techniques in T3 carcinomas

**Table 8** Age (median/minimum–maximum) and sex of patients with T1 tumors who underwent one of the three different re-resection techniques (re-resection  $n = 33$ )

	Wedge resection ( $n = 15$ ) (Group 1)	IVb/V resection ( $n = 6$ ) (Group 2)	Other techniques ( $n = 9$ ) (Group 3)
Sex [ $n$ (%) female]:	10 (66.7)	4 (66.7)	5 (55.6)
Age [median (range)]	66.0 (51–83)	72.5 (64–77)	71.0 (46–84)

**Table 9** Age (median/minimum–maximum) and sex of patients with T2 tumors who underwent one of the three different re-resection techniques (re-resection  $n = 139$ )

	Wedge resection ( $n = 67$ ) (Group 1)	IVb/V resection ( $n = 31$ ) (Group 2)	Other techniques ( $n = 23$ ) (Group 3)
Sex [ $n$ (%) female]	49 (73.1)	29 (93.5)	15 (65.2)
Age [median (range)]	67.5 (45–83)	68.0 (52–82)	70.5 (44–87)

**Table 10** Age (median/minimum - maximum) and sex of patients with T3 tumors who underwent one of the three different re-resection techniques (re-resection  $n = 46$ )

	Wedge resection ( $n = 19$ ) (Group 1)	IVb/V resection ( $n = 6$ ) (Group 2)	Other techniques ( $n = 8$ ) (Group 3)
Sex [ $n$ (%) female]	15 (78.9)	6 (100)	6 (75.0)
Age [median (range)]	64.0 (48–84)	62.0 (56–72)	60.0 (41–68)

There is also a significant survival advantage for re-resected T2 tumor patients ( $n = 139$ ) in the German Registry. The resection of segment IVb/V combined with lymph node dissection of the hepatoduodenal ligament yields the best 5-year survival rates. Less radical re-resection techniques show a survival disadvantage in T2 carcinomas compared with the survival rate for the IVb/V resection. A better survival for T2 tumor patients who undergo IVb/V resection or more radical resection techniques compared to the wedge-resection technique has been reported [54].

None of the patients with T3 tumors in the German Registry who underwent a IVb/V or a wedge resection combined with the standardized lymph node dissection survived more than 3 years. Those T3 tumor patients who survived more than 3 years had more aggressive surgery, e.g., local advanced resections or a right hemihepatectomy. However, the power of this group (T3 tumors group 3) is still too low to make definite recommendations. However, resection of the IVb/V segment may not be adequate for T3 and T4 cancers [55].

Of the T4 tumor patients in the German Registry, classified according to the AJCC/UICC staging system of 2002 and therefore deemed to have unresectable tumors, only four patients received a radical re-resection. None of the patients who had a radical re-resection survived 3 years. Again, the power of this group is too small to make any kind of recommendation.

In conclusion, the wedge-resection technique with a margin of 3 cm in the gallbladder bed combined with dissection of the lymph nodes of the hepatoduodenal ligament seems to be the surgical strategy of choice in cases of T1 tumors. For T2 tumors resection of liver segments IVb/V combined with the dissection of the lymph nodes of the hepatoduodenal ligament seems to be the minimum volume of resection required. More radical procedures are needed for tumors infiltrating the serosa or beyond.

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