Surg Endosc (2013) 27:2821–2828
DOI 10.1007/s00464-013-2819-5

Prognosis of incidental gallbladder carcinoma is not influenced by the primary access technique: analysis of 837 incidental gallbladder carcinomas in the German Registry

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Received: 11 October 2012 / Accepted: 28 December 2012 / Published online: 13 February 2013

Abstract
Background The use of the laparoscopic approach (LC) for gallbladder carcinoma and incidental gallbladder carcinomas (IGBC) remains controversial. However, recent studies suggest that LC has no adverse effects relative to the open approach. A definitive conclusion regarding the safety of LC that is based on data from a large patient cohort is needed.
Methods To draw a definite conclusion about the safety of LC in IGBC, data from the 837 patients with IGBC [registered in the German Registry (GR)] were analyzed.
Results Of the 837 patients, 492 underwent LC, 200 underwent open surgery (OC), and 142 initially underwent LC, but the approach was converted to OC. The 5-year survival rates of the three groups indicated that LC was associated with significantly better survival. LC was not associated with a poorer prognosis in patients with T1, T2, or T3 stage disease or in patients who underwent immediate radical re-resection (IRR; $n = 330$). LC was associated with a significant survival benefit in the 490 patients who did not undergo IRR. LC was comparable with OC in terms of overall recurrence rates and the rate of accidental intraoperative perforation.
Conclusions The GR data, which relate to a large homogenous patient cohort, showed that when other potential influencing factors, e.g., IRR were eliminated, the primary access technique had no effect on prognosis. Stage-adjusted therapy should always be performed irrespective of the primary access technique.

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Keywords Gallbladder carcinoma · Laparoscopic cholecystectomy · German-Registry · Tumor cell dissemination · Access technique · Hepatobiliary surgery

The use of the laparoscopic approach for treating gallbladder carcinoma (GBC) remains controversial. When GBC is suspected preoperatively, the laparoscopic approach is contraindicated for several reasons, including an increased risk of not removing the carcinoma completely, organ perforation, bile spillage, and port-site recurrence [1–4]. Consequently, when GBC is suspected preoperatively an open approach is recommended for performing a radical cholecystectomy if needed. However, because laparoscopic cholecystectomy is now performed more frequently, postoperative GBC (particularly early stage GBC) is detected more often [5, 6]. Such postoperatively detected GBCs are termed "incidental" or "occult" GBCs (IGBC). Depending on the tumor stage, a second operation for radical re-resection is recommended for IGBCs [6–8].

Whereas GBC is detected in 0.2–3 % of laparoscopic cholecystectomies [9, 10], only about one-third are detected preoperatively and undergo surgery for malignant gallbladder disease [11–14]. In most cases, gallbladder malignancy is first diagnosed by the pathologist after a routine cholecystectomy in patients with benign disease. Several early reports and studies suggest that in IGBC, laparoscopy is associated with a greater risk of tumor cell seeding and a worse prognosis compared with open cholecystectomy [15–17]. However, other studies did not detect differences between the two methods in terms of prognosis [5, 18–20]; indeed in the more recent literature there is evidence that the laparoscopy has no adverse effects on GBC surgery and it is recommended for preoperatively known GBCs without liver invasion or in

incidentally discovered carcinomas during laparoscopy [21–24]. Despite this body of evidence, doubts about laparoscopic cholecystectomy remain.

A study with a large cohort of patients is needed to draw a more definitive conclusion regarding the safety of the laparoscopic approach for IGBC. An excellent source of such a cohort is the German Registry, which contains more than 800 IGBC cases and, as such, is the largest collection of GBC cases in Europe. These data were analyzed in the present study to determine the influence of the access technique on IGBC prognosis. In addition, the discrepancies and inconsistencies between the conclusions of older and more recent studies regarding the access technique are described.

Materials and methods

The German Registry (GR) of IGBC cases was founded in 1997 [25]. It also is known as the CAES/CAMIC Central Registry of Incidental Gallbladder Carcinoma, because it is supported by the Surgical Association of Endoscopy and Ultrasound (CAES; which was once called the Surgical Association of Endoscopy) and the Surgical Association of Minimally Invasive Surgery (CAMIC). Both associations belong to the German Society of Surgery (DGCH). Cases of IGBC in Germany, Switzerland, and Austria are registered in the German Registry. All cases in the registry were used for data analysis. To secure comparable groups without mixing or slicing the data, patients were matched into patients with immediate radical re-resection and separately opposed to patients without immediate radical re-resection for obtaining comparable homogenous groups and correct data.

To obtain the registry data, a standardized form is sent periodically to all surgical hospitals in Germany. This form contains questions about the preoperative diagnosis, the surgical approach, the intra- and/or postoperative complications, the tumor location (fundus, body, or neck of the bladder), the histology, and the TNM stage. The form also collects information about further therapy, such as re-resection and chemo- or radiotherapy. In addition, there are questions regarding the indications for cholecystectomy, because all of the registered carcinomas are IGBCs. In all cases, nononcological reasons motivated the selection of the open access technique or the intraoperative conversion of the laparoscopic technique to the open method. These reasons included severe inflammation of the organ or confusing anatomy. Staging was based on the sixth edition of the UICC/AJCC classification of 2002 [26].

SPSS version 11.5 (SPSS Inc., Chicago, IL) was used for statistical analysis. Five-year survival rates were calculated using the Kaplan–Meier method. The patient groups were compared using log-rank and Chi squared tests. $P < 0.05$ was considered statistically significant.

Results

In total, 837 patients with IGBC were registered in the German Registry. All cases were included in the analysis. Of these, 492 underwent laparoscopy, 200 underwent open surgery, and 142 underwent conversion of laparoscopy to open surgery. The primary access technique used for the remaining three patients was unknown. This entire patient population was stratified according to the postoperative tumor (T) stage and the three access techniques (Table 1). As shown in Fig. 1, the 5-year survival rates for the laparoscopic cholecystectomy, primary open approach, and intraoperative conversion groups were 37, 25, and 29 %, respectively, and differ significantly (log-rank test, $P < 0.05$).

Figures 2, 3, and 4, show the 5-year survival rates of the T1, T2, and T3 patients, respectively, after stratification according to the access technique. With regard to the T1 patients (Fig. 2), laparoscopic cholecystectomy, the primary open approach, and intraoperative conversion were associated with 5-year survival rates of 52, 57, and 59 %, respectively (log-rank test, $P > 0.05$). For the T2 patients (Fig. 3), the rates were 33, 25, and 31 %, respectively (log-rank test, $P = 0.002$). For the T3 patients (Fig. 4), the rates were 24, 6, and 11 %, respectively (log-rank test, $P = 0.001$). Thus, laparoscopy was as safe as the open technique regardless of T stage.

In another analysis, all but 17 of the patients were grouped according to whether they did or did not undergo immediate radical re-resection (Figs. 5, 6, 7, 8, 9). The 17 patients were excluded because it was not clear whether they underwent radical re-resection. Five-year survival rates without the influence of radical re-resection on the outcome are shown in Figs. 7, 8, 9.

The patients were then stratified according to access technique (Figs. 5, 6). Laparoscopic cholecystectomy ($n = 251$), a primary open approach ($n = 35$), and intraoperative

Table 1 Number of patients (of 837) with different T stages who underwent laparoscopy, the primary open technique, or open conversion

	Laparoscopy ($n = 492$)	Open ($n = 200$)	Conversion ($n = 142$)	Method unknown ($n = 3$)
pTis	22	5	1	0
pT1	95	34	20	0
pT2	282	81	52	1
pT3	81	59	58	1
pT4	7	19	10	0
pTx	5	2	1	1

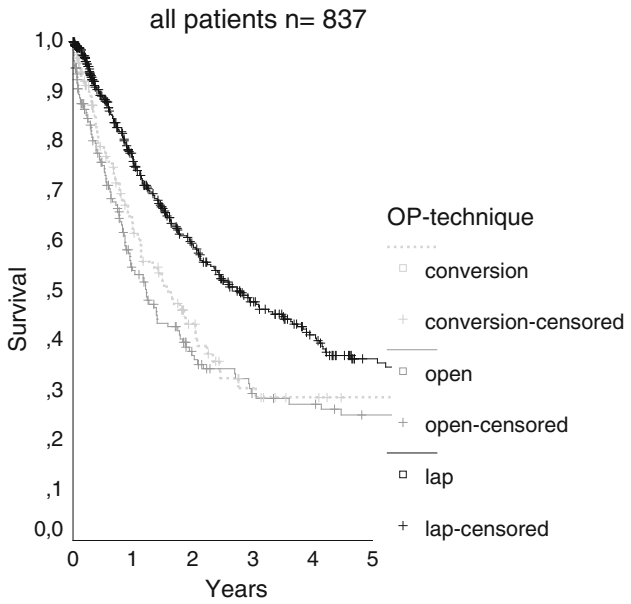

Fig. 1 Five-year survival of all patients ($n = 837$) in the registry after stratification according to the primary surgical approach: laparoscopy ($n = 492$), primary open access technique ($n = 200$), and intraoperative conversion from the laparoscopic to the open technique ($n = 142$). In the remaining three patients, the primary surgical approach was not specified. The survival curves for the three access technique-related groups differed significantly ($P < 0.05$)

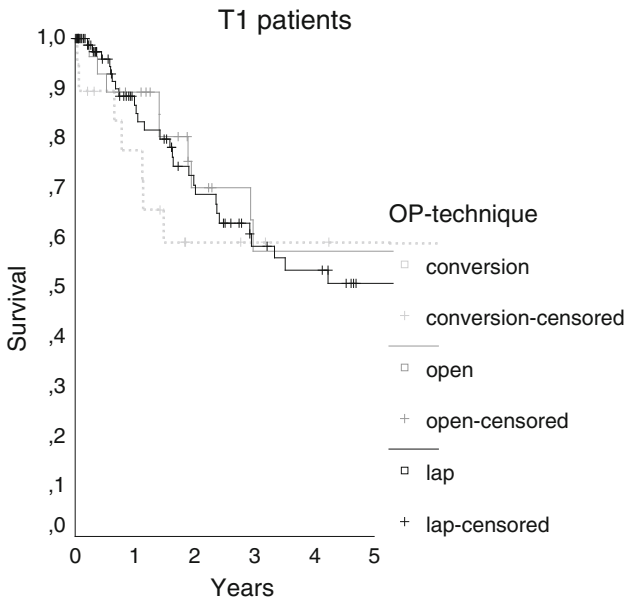

Fig. 2 Five-year survival of all T1 patients ($n = 149$) after stratification according to the primary surgical approach: laparoscopy ($n = 95$), primary open access technique ($n = 34$), and intraoperative conversions ($n = 20$). The survival curves for the three access technique-related groups did not differ significantly ($P > 0.05$)

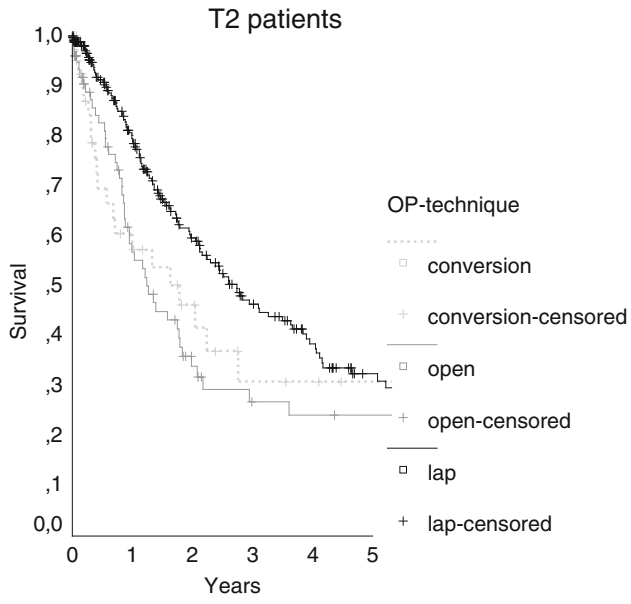

Fig. 3 Five-year survival of all T2 patients ($n = 416$) stratified according to the primary surgical approach: laparoscopy ($n = 282$), primary open access technique ($n = 81$), and intraoperative conversion ($n = 52$). The primary surgical approach used for one patient was not specified. The survival curves for the three access technique-related groups differed significantly ($P = 0.002$)

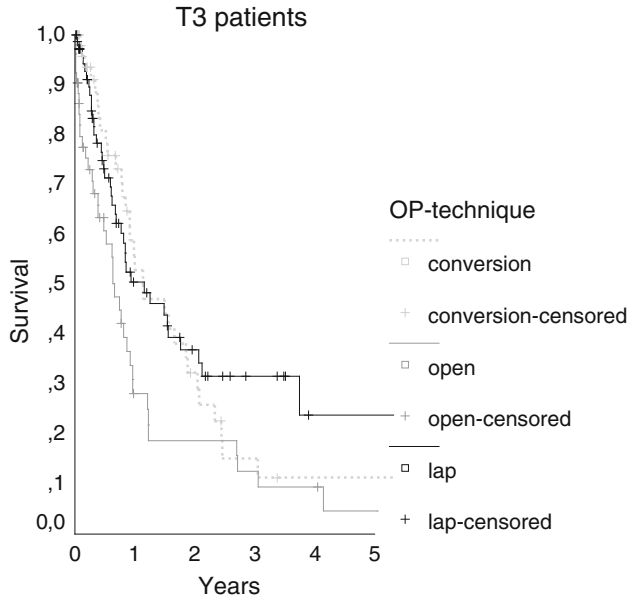

Fig. 4 Five-year survival of all T3 patients ($n = 199$) after stratification according to the primary surgical approach: laparoscopy ($n = 81$), primary access open technique ($n = 59$), and intraoperative conversion ($n = 58$). The primary surgical approach used for one patient was not specified. The survival curves for the three access technique-related groups differed significantly ($P = 0.01$)

conversion ($n = 44$) were associated with 5-year survival rates of 40, 34, and 35 %, respectively ($P > 0.05$), in 330 patients who underwent immediate radical re-resection (Fig. 5). The corresponding separation according to the different T stages in patients with radical re-resection shows similar results regarding 5-year survival and the access

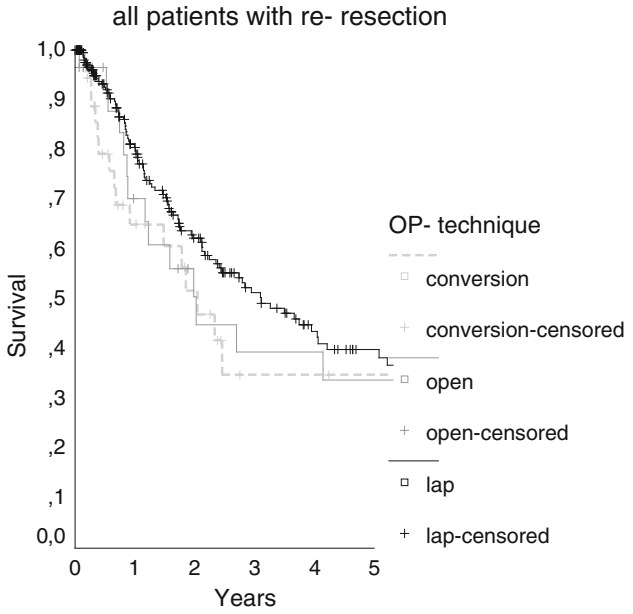

Fig. 5 Five-year survival of all registry patients who underwent re-resection ($n = 330$) after stratification according to the primary surgical approach: laparoscopy ($n = 251$), primary open access technique ($n = 35$), and intraoperative conversion ($n = 44$). The survival curves for the three access technique-related groups did not differ significantly ($P > 0.05$)

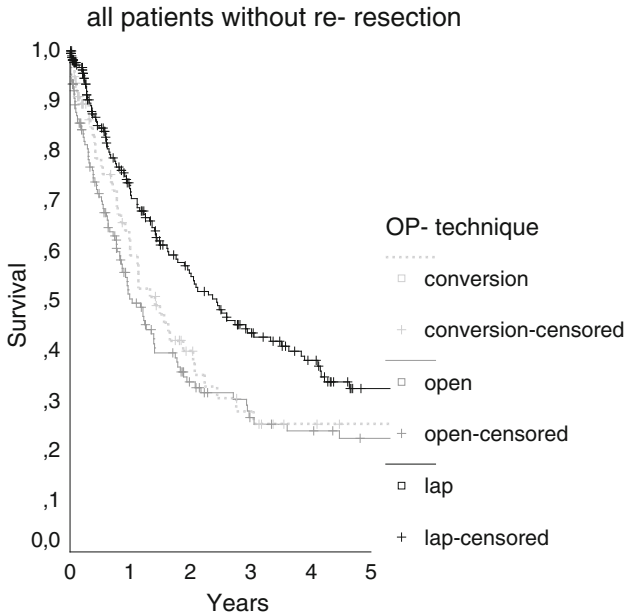

Fig. 6 Five-year survival of all registry patients who did not undergo re-resection ($n = 490$) after stratification according to the primary surgical approach: laparoscopy ($n = 236$), primary open access technique ($n = 163$), and intraoperative conversion ($n = 91$). For 17 cases, it was not known whether the patient underwent re-resection. The survival curves for the three access technique-related groups differed significantly ($P < 0.0001$)

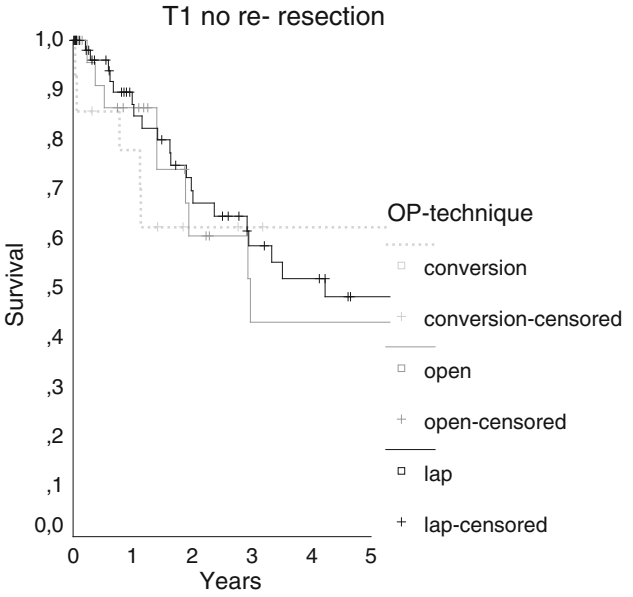

Fig. 7 Five-year survival of all T1 registry patients who did not undergo re-resection ($n = 103$) after stratification according to the primary surgical approach: laparoscopy ($n = 61$), primary open access technique ($n = 27$) and intraoperative conversion ($n = 15$). The survival curves of the three access technique-related groups did not differ significantly ($P > 0.05$)

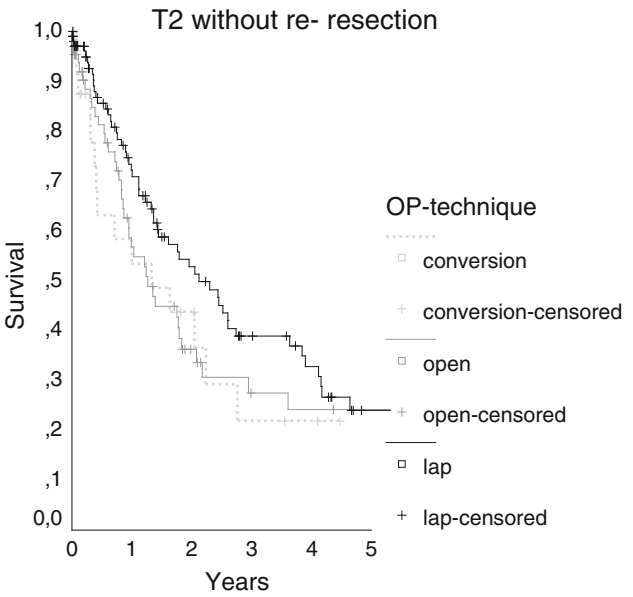

Fig. 8 Five-year survival of all T2 registry patients who did not undergo re-resection ($n = 209$) after stratification according to the primary surgical approach: laparoscopy ($n = 113$), primary open access technique ($n = 66$), and intraoperative conversion ($n = 30$). The survival curves for the three access technique-related groups differed significantly ($P < 0.0001$)

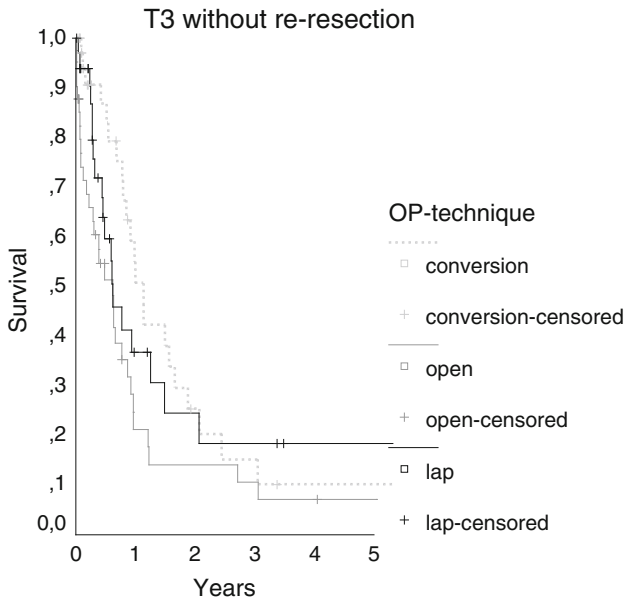

Fig. 9 Five-year survival of all T3 registry patients who did not undergo re-resection ($n = 124$) after stratification according to the primary surgical approach: laparoscopy ($n = 37$), primary open access technique ($n = 48$), and intraoperative conversion ($n = 39$). The survival curves for the three access technique-related groups did not differ significantly ($P > 0.05$)

technique. Thus, laparoscopy did not differ from the open technique in terms of prognosis for patients who underwent immediate radical re-resection.

By contrast, laparoscopy ($n = 236$), the primary open approach ($n = 163$), and intraoperative conversion ($n = 91$) were associated with 5-year survival rates of 33, 23, and 25 %, respectively, in the 490 patients who did not undergo immediate re-resection (Fig. 6). These differences were statistically significant ($P < 0.0001$).

The patients who did not undergo re-resection were then stratified according to whether they had T1, T2, or T3 stage disease (Figs. 7, 8, 9, respectively). Regarding the 103 T1 patients without re-resection (Fig. 7): laparoscopy ($n = 61$), the primary open approach ($n = 27$), and intraoperative conversion ($n = 15$) were associated with 5-year survival rates of 48, 43, and 62 %, respectively ($P > 0.05$). Regarding the 209 T2 registry patients without re-resection (Fig. 8), laparoscopy ($n = 113$), the primary open approach ($n = 66$), and intraoperative conversion ($n = 30$) were associated with 5-year survival rates of 25, 25, and 0 %, respectively ($P < 0.0001$). Regarding the 124 T3 patients without re-resection (Fig. 9), laparoscopy ($n = 37$), the primary open approach ($n = 48$), and intraoperative conversion ($n = 39$) were associated with 5-year survival rates of 19, 8, and 10 %, respectively ($P > 0.05$).

Table 2 shows how the access technique associated with different kinds of recurrence. Laparoscopy, the primary open approach, and intraoperative conversion were associated with overall recurrence rates of 30, 36, and 30 %, respectively ($P > 0.05$). There was no correlation between access technique and recurrence rate (Spearman correlation-coefficient = 0.025).

Table 2 Number of patients who underwent laparoscopy, the open technique, or conversion and the different types of recurrence

	Port-site or wound metastasis*	Peritoneal carcinosis	Local recurrence	Another location
Laparoscopy ($n = 492$)	30	75	71	94
Open ($n = 200$)	7	26	32	44
Conversion ($n = 142$)	4	23	20	28

* The recurrence rates after laparoscopy, open surgery, and conversion were 30, 36, and 30 %, respectively. The three groups did not differ significantly in terms of recurrence rate ($P > 0.05$)

Of the registry patients, 24 % had intraoperative macroscopic perforation of the organ. This occurred in 23 % of the laparoscopic cholecystectomies, 21 % of the primary open access surgeries, and 35 % of intraoperative conversions ($P = 0.006$).

Discussion

Some studies suggest that laparoscopy for IGBC is associated with a greater risk of tumor cell seeding and a worse prognosis than open cholecystectomy [15–17]; however, these conclusions are based on small sample sizes and inhomogeneous patient groups. Also, some studies are old and do not reflect current medical practice. These prior studies, which are still often cited today when arguing against the laparoscopic approach, are described below.

In 1998, Z′graggen et al. [27] reported that laparoscopic cholecystectomy was associated with a port-site metastasis incidence of 9 % when the organ was not injured; this incidence increased to 40 % in cases of macroscopic perforation of the gallbladder. However, this report was based on a prospective study conducted by the Swiss Association of Laparoscopic and Thoracoscopic Surgery (10,925 patients) and only 37 patients had GBC; of these, only five had port-site metastasis. Despite this extremely small sample number, the report was cited in a 2011 review that opposed the use of laparoscopy in IGBC [28].

In the present study of GR data, laparoscopy was associated with a rate of port-site metastasis of 6.1 %, which was almost double the wound metastasis rate associated with the primary open access technique (3.5 %). However, the overall recurrence rates for the two access techniques were comparable (30 vs. 36 %). The GR data also showed

that the two techniques had comparable rates of intraoperative accidental perforation of the gallbladder (23 vs. 21 %). However, intraoperative conversion group was associated with a significantly higher rate of gallbladder perforation (35 %, $P = 0.006$); this higher rate of perforation may have been the main reason for the conversion.

Many current reports suggest that laparoscopic cholecystectomy is more risky than open techniques; however, these reports refer to older literature suffering from the disadvantage of small sample sizes. These include Case Reports published in 1991, 1996, and 1999 by Drouard et al. [29], Cotlar et al. [30], and Lane et al. [31], respectively. Copher et al. [32] and Jeon et al. [33] published additional case reports and reviews of the literature in 1995 and 1999, respectively. However, the total number of cases analyzed in these reports was very small.

By contrast, two later reports (in 2002 and 2003, respectively) by Ouchi et al. [34] and Toyonaga et al. [10] comprised multicenter studies with larger sample sizes ($n = 498$ and 73, respectively). These studies showed that the primary approach does not significantly influence the prognosis of IGBC. Moreover, in 2006, Chan et al. [35] and Shimizu et al. [36] showed that laparoscopic cholecystectomy is not associated with a prognostic disadvantage if stage-adjusted treatment is performed.

However, in the same year, Meriggi [37], while providing a good overview of GBC, suggested (on the basis of the above-described 1998 report by Z′graggen et al. [27]) that the laparoscopic approach is associated with a poor prognosis. To support this notion, Meriggi also cited the 2004 paper by De Aretxabala et al. [38]. However, a close analysis of the latter study, which was based on 64 patients, revealed that the laparoscopic approach was not associated with poorer outcomes than the open approach. Thus, the arguments against the laparoscopic approach are based on reports from another medical era (which involved very small sample sizes), or on the misinterpretation of other studies.

Three studies published in 2007 by Shih et al. [22] ($n = 107$), Kang et al. [23] ($n = 57$), and Pawlik et al. [24] (a multicenter study; n= 115) did not conclude that the laparoscopic approach is associated with poorer outcomes. Moreover, in 2008, a review by Miller and Jarnagin [39] stated that laparoscopy is not associated with negative effects if stage-adjusted therapy is performed. A year later, the same journal published a review by Charles Pilgrim et al. [40], which showed that the survival graphs of patients who underwent laparoscopy did not support the notion that this technique had a worse outcome than the conventional open technique. In addition, a third review in 2009 by Hueman et al. [41] did not find that laparoscopic cholecystectomy in GBC is less safe than the open procedure. Finally, interim results of a 2010 study [21] on the safety and efficacy of the laparoscopic approach for suspected early-stage GBCs show that this approach is feasible in a carefully selected group of patients.

The present study of 837 patients showed that laparoscopy associated significantly with an overall survival advantage. When the patients were stratified according to T stage and access technique (Figs. 1, 2, 3, 4), the open access technique tended to be associated with a slightly better 5-year survival rate in patients with T1 stage disease than the laparoscopic approach (57 vs. 52 %), although this difference did not achieve statistical significance ($P > 0.05$; Fig. 2). However, for the whole patient population (Fig. 1) and patients with T2 and T3 stage disease (Figs. 3, 4), laparoscopy was associated with a significant survival benefit ($P = 0.002$, 0.01, and <0.05, respectively).

Our analysis of the patients after stratification according to whether they underwent re-resection revealed some interesting findings. In patients who did not undergo immediate re-resection, laparoscopy was significantly better than the open technique in terms of prognosis ($P < 0.0001$; Fig. 6). By subtracting the influence of re-resection on the Kaplan–Meier graphs as a prognostic factor, the German-registry is still able to present relatively large but homogenous subgroups that are not influenced by other factors than the access technique and tumor prognosis (Figs. 6, 7, 9). There is no prognostic disadvantage for the laparoscopic approach in these adjusted subgroups.

Recent reports [35, 36, 39] suggest that laparoscopy has no negative effects if stage-adjusted therapy is performed. This suggests that maybe an immediate radical re-resection can, or even should, compensate for the negative effects of laparoscopy. According to the knowledge of the authors, the present study is the first to show that laparoscopy did not have a negative effect relative to the open approach in an adjusted subgroup of 490 patients who did not undergo immediate re-resection. Furthermore, we have already shown the prognostic effects of liver resection [42] and lymph node dissection [43] on the course of immediate radical re-resection in registry patients.

In conclusion, the GR data analyzed in the present study show that the primary access technique (laparoscopy vs. the primary open technique) did not affect prognosis. However, stage-adjusted therapy [42, 43] should always be performed irrespective of the primary access technique.

Acknowledgments The authors thank CAMIC (surgical working group of minimally invasive surgeons) and CAES (surgical working group of endoscopy) of the German Society of Surgery as well as the clinics and colleagues supporting the Registry, as listed under www.ketteler-krankenhaus.de/register.

Disclosures Thorsten Oliver Goetze and Vittorio Paolucci have no conflict of interest or financial ties to disclose.

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