Laparoscopic surgery for colon cancer

A systematic review with special focus on real-world data

Worldwide, laparoscopic surgery is becoming the new standard for curative resection of colon cancer. In recent decades, many studies were performed to analyze its advantages and disadvantages and, above all, its oncologic safety compared to the open technique.

Today, there exists quite extensive but also very heterogeneous evidence on laparoscopic colorectal tumor surgery. Many publications are dedicated exclusively to postoperative endpoints such as duration of surgery, resection margins, or short-term mortality. Others report long-term outcomes including overall survival or recurrence rates. The study designs range from small case studies to large randomized controlled trials (RCTs), which are regarded as the gold standard in medical research. However, due to strict in- and exclusion criteria, RCTs often reflect the situation in a selected patient collective only; therefore, it might not be sufficient to rely exclusively on the findings of RCTs. In contrast to this, large population-based retrospective multicenter or registry-based studies use “real-world data”, offering insight into the efficiency in daily clinical practice. This renders them an indispensable part of the clinical evaluation process. To account for the lack of randomization, such studies employ adequate statistical methods like multivariable regression analysis, which needs to be considered when interpreting the corresponding outcomes. This paper is the first systematic review on the topic providing a synthesis of the most important RCTs and relevant retrospective trials, drawing a holistic picture of laparoscopic surgery in colon cancer patients.

Materials and methods

To identify relevant literature on the topic, PubMed and Cochrane Central were searched [1, 2]. For this purpose, three fields of interest were defined:

- Colorectal cancer: the corresponding MeSH term is “Colorectal Neoplasms”. Moreover, a free-text search with the following (truncated) terms was performed: “colorectal cancer*”, “colorectal carcinoma*”, “colorectal tumor*”, “colorectal tumour*”, and “colorectal neoplasm*”. Local differences in spelling (e.g., “tumour” instead of “tumor”) were considered.

- Laparoscopy: the corresponding MeSH term is “Laparoscopy”. In addition, a free-text search with the truncated term “laparoscop*” in all available fields provided by PubMed was performed, leading to identification of 102,255 relevant publications.

- Open surgery: the corresponding MeSH term is “Laparotomy”. To also identify relevant literature not tagged by this MeSH term, a free-text search with the truncated terms “laparotom*”, “celiotom*”, and “coeliotom*” in all fields was performed. Thus, 424,689 publications were identified.

In total more than 1800 relevant publications address all three aspects simultaneously, of which more than 1600 were written in English or German (Fig. 1). To identify representative high-quality retrospective studies, a selection process based on the widely accepted Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)-criteria [3] was performed. Special focus was placed on the following aspects:

- Study design: How was data acquisition performed? How many patients were included? What were the exact in- and exclusion criteria? Is the whole exclusion process transparent for the reader? Is the study collective representative for the population/setting it was gathered from?

- Study variables: Is the set of predictor and outcome variables meaningful?
Are the variable definitions clear and transparent? Methods: Were adequate statistical methods applied to account for the lack of randomization? Are all analyses clearly described?

Finally, 14 retrospective studies met the standards for inclusion in the present literature review. A similar workflow was applied to identify 9 relevant RCTs on the topic. Table 1 and 2 give an overview of the included literature.

Endpoints in the focus of the current review were intraoperative blood loss and duration of surgery, lymphadenectomy and resection margins, postoperative morbidity and mortality, long-term overall survival, and tumor recurrence.

Results

Laparoscopy rate

According to the Arbeitsgemeinschaft Deutscher Tumorzentren (ADT; Working Group of German Tumor Centers), the share of laparoscopic resection procedures in Germany has increased from 3.4% in 2000 to 31.0% in 2018 (Fig. 2). These figures are based on reports from 30 clinical cancer registries representing approximately one quarter of all colon carcinoma cases in Germany based on data presented at the National Quality Conference of the German Cancer Congress 2020 [4].

Intraoperative blood loss and duration of surgery

In all included RCTs, the mean intraoperative blood loss was significantly lower after laparoscopic surgery. The reported mean values range between 46 and 105 ml compared to 127 to 193 ml after open surgery [5–7]. Similar results can be observed in the population-based trial of McKay et al. from Australia [8], which reports a significantly lower average need for intraoperative blood transfusions of 0.4 vs. 0.7 per patient in favor of the laparoscopic procedure.

Lymphadenectomy and resection margins

A sufficient number of removed and histologically evaluated lymph nodes is regarded as a positive quality indicator of successful tumor removal. For example, the German treatment guideline on colorectal carcinoma recommends a minimum count of 12 nodes, although there is no international consensus concerning the exact number [11]. Moreover, there exists no generally recognized standard for the pathological examination of lymph nodes, which has to be considered when comparing and analyzing results of different studies. A systematic review from Kuhry et al. [12] published by the Cochrane Collaboration in 2008 pools the results of five RCTs reporting on lymphadenectomy [5, 7, 13–15]. Compared to the open approach, the number of harvested lymph nodes after laparoscopic procedures is smaller by 1 lymph node (confidence interval, CI: [–1.65 to 0.35]). The results of the retrospective trials on this endpoint are comparable (Kolfschoten et al. [16]: more than 10 harvested lymph nodes: odds ratio, OR: 0.87, CI: 0.76–1.00, reference: open; McKay et al. [5]: mean count of harvested lymph nodes per patient: laparoscopic intention-to-treat, itt: 17.4 vs. open: 18.2, p = 0.38; Völkel et al. [17]:
more than 12 harvested lymph nodes: laparoscopic itt: 88.9% vs. open: 92.2%,
$p = 0.028$).

Tumor-free resection margins are the primary goal of each tumor resection. In 2005, the randomized CLASICC trial reported a higher share of tumor-positive margins after laparoscopic procedures [9]. This outcome misses the significance level considerably ($p = 0.45$), but caused an extensive discussion on the topic anyway. Therefore, the real-world data publications are even more interesting. A population-based survey from the US by Zheng et al. [18] observed a significantly lower share of tumor-positive resection margins after laparoscopic procedures (laparoscopic 3.4% vs. open 5.5%; $p < 0.001$), although this advantage is mitigated after risk adjustment and propensity matching. In the study of Kolfschoten et al. [16] the advantage for the laparoscopic procedure remains constant even after risk adjustment (OR: 0.68, CI: 0.48–0.98, reference: open). According to a registry-based trial from southern Germany published in 2018, positive resection margins are less frequently associated with laparoscopic procedures [17]; however, due to a low absolute count of postoperatively tumor-positive patients, significance testing was not possible. Contrary to this, the Australian registry study of McKay et al. [8] reports a (non-significantly) smaller mean distance between tumor border and resection margin in laparoscopic patients.

Postoperative morbidity and mortality

Various trials have shown that laparoscopic patients suffer less from postoperative pain and wound infection, leading to faster convalescence and a shorter hospital stay [16, 19–23]. This was confirmed by a meta-analysis from Schwenk et al. [24] and a systematic review from Otani et al. [25]. There are different outcome measures to quantify postoperative mortality: depending on the trial, in-hospital-, 30-day, or 90-day mortality were evaluated. According to the randomized CLASICC trial, there is no significant difference between laparoscopy and laparotomy: 88.9% vs. open: 92.2%.

Abstract · Zusammenfassung

Laparoscopic surgery for colon cancer. A systematic review with special focus on real-world data

Abstract

Background. To evaluate a new procedure in daily clinical practice, it might not be sufficient to rely exclusively on the findings of randomized clinical trials (RCTs). This is the first systematic review providing a synthesis of the most important RCTs and relevant retrospective cohort studies on short- and long-term outcomes of laparoscopic surgery in colon cancer patients.

Materials and methods. In a literature search, more than 1800 relevant publications on the topic were identified. Relevant RCTs and representative high-quality retrospective studies were selected based on the widely accepted Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria. Finally, 9 RCTs and 14 retrospective cohort studies were included.

Results. Laparoscopic surgery for colon cancer is associated with a slightly longer duration of surgery, but a variety of studies show an association with a lower rate of postoperative complications and a shorter duration of hospital stay. Particularly in older patients with more frequent comorbidities, laparoscopy seems to contribute to decreasing postoperative mortality. Concerning long-term oncologic outcomes, the laparoscopic and open techniques were shown to be at least equivalent.

Conclusion. The findings of the existing relevant RCTs on laparoscopic surgery for colon cancer are mostly confirmed by representative retrospective cohort studies based on real-world data; therefore, its further implementation into clinical practice can be recommended.

Keywords

Minimally invasive surgical procedures · Registries · Cohort studies · Randomized controlled trial · Evidence-based medicine

Laparoskopische Chirurgie beim Kolonkarzinom. Eine systematische Übersichtsarbe it mit speziel lem Fokus auf „real world data“

Zusammenfassung

Hintergrund. Um die Eignung eines neuen Behandlungsverfahrens im klinischen Alltag zu überprüfen, sollte man sich nicht ausschließlich auf die Ergebnisse randomisierter Studien (RCTs) verlassen. Dies ist die erste Übersichtsarbeit zum Thema laparoskopische Tumorresektion beim Kolonkarzinom, welche neben RCTs repräsentative retrospektive Kohortenstudien zu Kurz- und Langzeitergebnissen berücksichtigt.

Methoden. In einer Literaturrecherche wurden über 1800 relevante Publikationen identifiziert. Eine Selektion der relevanten pro- und retrospektiven Studien zum Thema Laparoskopie beim Kolonkarzinom fand auf Grundlage der STROBE-Kriterien statt. Schließlich wurden 9 RCTs und 14 retrospektive Studien eingeschlossen.

Ergebnisse. Laparoskopische Chirurgie beim Kolonkarzinom ist zwar mit einer etwas längeren Operationsdauer, jedoch auch mit einer niedrigeren postoperativen Komplikationsrate und einer kürzeren Krankenhausverweildauer assoziiert. Vor allem ältere Patienten mit mehr Komorbiditäten scheinen von einer niedrigeren postoperativen Mortalität zu profitieren. Was das onkologische Langzeitergebnis betrifft, ist das laparoskopische die offenen Verfahren mindestens ebensicher.

Schlussfolgerung. Die Ergebnisse der existierenden relevanten RCTs zur Laparoskopie beim Kolonkarzinom werden größtenteils von repräsentativen retrospektiven Kohortenstudien aus dem Klinikalltag bestätigt. Daher kann die weitere Implementierung der Laparoskopie in den Klinikalltag empfohlen werden.

Schlüsselwörter

Minimal-invasive Chirurgie · Register · Kohortenstudien · Randomisierte kontrollierte Studie · Evidenzbasierte Medizin
Table 1  Randomized clinical trials on laparoscopic and open surgery for colon cancer

| Period of recruitment | Data source | Patients, N | Follow-up |
|-----------------------|-------------|-------------|-----------|
| Curet [29] 1993–1995  | 1 US center | Laparoscopic: 25 Open: 18 | 59 months |
| Kaiser [13] 1995–2001 | 1 US center | Laparoscopic: 28 Open: 28 | 35 months |
| Leung [14] 1993–2002 | 2 Chinese centers | Laparoscopic: 203 Open: 200 | 51 months |
| Liang [15] 2000–2004 | 1 Taiwanese center | Laparoscopic: 135 Open: 134 | 40 months |
| Lacy [7] 1993–1998 | 1 Spanish center | Laparoscopic: 111 Open: 108 | 95 months |
| COST [10, 28] 1994–2001 | 48 US centers | Laparoscopic: 435 Open: 437 | 84 months |
| COLOR [6, 30, 31] 1997–2003 | 29 centers in 8 European countries | Laparoscopic: 627 Open: 621 | 53 months |
| CLASICC [9] 1996–2002 | 27 GB centers | Laparoscopic: 273 Open: 140 | 56 months |
| Braga [5] 2000–2004 | 1 Italian center | Laparoscopic: 134 Open: 134 | 73 months |

Table 2  Representative retrospective cohort studies (RETRO) on laparoscopic and open surgery for colon cancer

| Period of recruitment | Data source | Patients, N | Follow-up |
|-----------------------|-------------|-------------|-----------|
| Benz [33] 2003–2011 | Germany, ADT dataset using data from 30 regional cancer registries | ~37,000 colectomies, laparoscopy rate: 10.7% | Maximum follow-up: 5 years |
| Bilimoria [34] 1998–2002 | USA, National Cancer Database, ~63% of all US cancer diagnoses | 231,381, laparoscopy rate: 4.6% | 5 years |
| Fox [23] 2008–2009 | USA, Nationwide Inpatient Sample Databases, documenting ~70% of all US cancer diagnoses | ~6800 colectomies, laparoscopy rate: 50% | Only short-term |
| Kolfschoten [16] 2010 | Netherlands, Dutch Surgical Colorectal Audit, featuring data from 90 hospitals/93% of all colectomies in the country | ~5000 colectomies, laparoscopy rate: 41% | Only short-term |
| Kube [22] 2000–2003 | Germany, Bundesweite Qualitätssicherungsstude Kolon-/Rektumkarzinome (Primärtumor) database with voluntarily contributed data from 340 hospitals | ~13,000 colectomies, laparoscopy rate: 4.4% | Maximum follow-up: 5 Jahre |
| McKay [8] 2001–2008 | 6 Australian centers | Laparoscopic: 434, open: 742 | Only short-term |
| Panis [26] 2006–2008 | All French cases (registered by programme de médicalisation des systèmes d’information, PMSI) | 84,524, laparoscopy rate: 26% | Only short-term |
| Sammour [21] 2003–2009 | 3 Australian centers | ~58,100 colectomies, laparoscopy rate: 51% | Maximum follow-up: 5 years |
| Steele [20] 2003–2004 | USA, Nationwide Inpatient Sample Databases, documenting ~70% of all US cancer diagnoses | ~98,900 colectomies, laparoscopy rate: 3% | Only short-term |
| Stormark [32] 2007–2010 | Norway, National Cancer Registry | ~8700 colectomies, laparoscopy rate: 27% | Maximum follow-up: 5 years |
| Taylor [19] 2006–2008 | Great Britain, National Cancer Data Repository, a representative national cancer registry | ~58,100 colectomies, laparoscopy rate: 41% | Maximum follow-up: 1 year |
| Völkel [17, 27, 35] 2004–2013 | Representative cancer registry from southern Germany with 1.1 million inhabitants | ~2700 colectomies, laparoscopy rate: 16% | Maximum follow-up: 5 years |
| 2005–2014 | Germany, ADT dataset using data from 30 regional cancer registries | ~1500 patients aged 80+, laparoscopy rate: 17.1% | Maximum follow-up: 5 years |
| Zheng [18] 2010–2011 | USA, National Cancer Database, documenting ~70% of all US cancer diagnoses | ~55,400 colectomies, laparoscopy rate: 41% | Only short-term |
laparotomy concerning in-hospital mortality (Table 3), but most registry-based studies show a lower risk of postoperative mortality in laparoscopic patients (OR after multivariable risk adjustment ranges between 0.49 and 0.63, Table 3; [5, 13–20]).

The trials of Panis et al. [26] and Vökel et al. [27] point towards an age- and partial comorbidity-dependent gradient: older patients and patients with a somewhat higher level of comorbidity benefit more from the laparoscopic approach in terms of postoperative mortality. Based on US registry data, Fox et al. [23] showed a significant association between a higher laparoscopy rate in a hospital and a shorter duration of stay and lower postoperative morbidity. However, postoperative mortality seems to be independent of this. However, it must be acknowledged that in all the studies it was adjusted for many but not all important confounders. Items such as intraabdominal adhesions or lipodistribution are often poorly documented and, thus, usually cannot be included in the statistical analyses.

In summary, it seems safe to postulate a positive influence of laparoscopy on postoperative morbidity. An association with lower postoperative mortality is also very likely, particularly in old and comorbid patients. Other aspects of perioperative management including establishment of an ostomy, limited resection, and failure-to-rescue situations supposedly play an even more important role in this context.

**Long-term overall survival**

“Mortality turned out to be equal in patients who had undergone laparoscopic surgery as compared to patients who underwent open surgery” (OR: 0.82, CI: 0.62–1.09, reference: open). This is the conclusion of the systematic Cochrane review by Kuhry et al. [12], which incorporated four RCTs in the corresponding meta-analysis on long-term survival after laparoscopic and open colon carcinoma resection [7, 13, 28, 29]. Concordantly, the renowned randomized COLOR trial reports almost identical 5-year survival rates after laparoscopic (73.8%; standard deviation, sd: 69.7–77.9%) and open (74.2%, sd: 70.1–78.2%) resection [30]. After a very long observation time of 10 years, the situation has not changed much: “Laparoscopic surgery for non–metastatic colon cancer is associated with similar rates of disease-free survival, overall survival and recurrences as open surgery” [31].

High-quality retrospective studies on long-term survival are scarce. Based on Norwegian cancer registry data, Stor- mark et al. did not find significant differences between the two surgical techniques concerning overall survival in Union for International Cancer Control (UICC) stage I–III patients (relative survival after 5 years: laparoscopic 77.7% vs. open: 80.6%, p = 0.54) [32]. Sammou et al. used Australian registry data and observed superior 5-year survival rates after laparoscopic resection (laparoscopic itt: 75.9% vs. open: 69.2%, p = 0.015), although the significance level was no longer reached after risk adjustment [21]. Kube et al. analyzed

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**Table 3 Postoperative mortality**

|                          | Laparoscopic | Open | Significance | Type of study |
|--------------------------|--------------|------|--------------|---------------|
| **In-hospital mortality**|              |      |              |               |
| CLASICC                  | 5%           | 4%   | n.s.         | RCT           |
| Fox                      |              |      |              | RETRO         |
| Descriptive              | 0.7%         | 1.2% | s.           |               |
| Risk adjusted            |              |      |              |               |
| Kube                     |              |      |              | RETRO         |
| Descriptive              | 0.7%         | 2.7% | s.           |               |
| McKay                    |              |      |              | RETRO         |
| Descriptive              | 0.9%         | 1.6% | n.s.         |               |
| Steele                   |              |      |              | RETRO         |
| Descriptive              | 0.6%         | 1.4% | s.           |               |
| **30-day postoperative mortality**|              |      |              |               |
| Benz                     |              |      |              | RETRO         |
| Descriptive              | 3.3%         | 0.9% | s.           |               |
| Risk adjusted            |              |      |              |               |
| Kolfschoten              |              |      |              | RETRO         |
| Descriptive              | 2.4%         | 4.9% | s.           |               |
| Risk adjusted            |              |      |              |               |
| Panis                    |              |      |              | RETRO         |
| Descriptive              | 2.0%         | 6.0% | s.           |               |
| Risk adjusted            |              |      |              |               |
| Sammour                  |              |      |              | RETRO         |
| Descriptive              | 0.7%         | 1.6% | n.s.         |               |
| Taylor                   |              |      |              | RETRO         |
| Risk adjusted            |              |      |              |               |
| Zheng                    |              |      |              | RETRO         |
| Descriptive              | 1.3%         | 2.3% | s.           |               |
| Risk adjusted            |              |      |              |               |
| **90-day postoperative mortality**|              |      |              |               |
| Vökel                    |              |      |              | RETRO         |
| Descriptive              | 2.3%         | 6.0% | n.s.         |               |
| Risk adjusted            |              |      |              |               |

s. significant (p < 0.05), n.s. not significant, OR odds ratio, RCT randomized controlled trial, RETRO representative retrospective cohort study.
Table 4  Long-term survival

| Study | Laparoscopic | Open | Significance | Type of study |
|-------|--------------|------|--------------|---------------|
| Overall mortality risk for the whole long-term observation period |
| Benz  | HR right 0.67; left 0.7 | Reference | Right/left p < 0.001 | RETRO |
| Bilimoria | HR 0.91 | Reference | s. | RETRO |
| UICC I–III | HR 0.97 | Reference | n.s. | RETRO |
| Curet | HR: 0.3 | Reference | n.s. | RCT |
| Kaiser | HR: 2.3 | Reference | n.s. | RCT |
| Kuhry (Cochrane review) | HR: 0.84 | Reference | n.s. | Meta-analysis |
| Lacy | HR: 0.6 | Reference | n.s. | RCT |
| 5-year overall survival |
| Braga | 72.0% | 64.0% | n.s. | RCT |
| CLASICC | 55.7% | 62.7% | n.s. | RCT |
| COLOR | 73.8% | 74.2% | n.s. | RCT |
| COST | 76.4% | 74.6% | n.s. | RCT |
| Völkel | Descriptive | 82.8% Conversions: 68.7% | 66.9% | s |
| Sammour | Descriptive | 75.9% | 69.2% | s |
| Risk adjusted | No significant difference between laparoscopy and laparotomy concerning overall survival |
| Völkel | Overall (perioperative deaths not excluded) | 80.2% | 69.0% | s |
| T1–3N0 | 86.5% | 78.8% | s |
| T4/N1–2 | 72.5% | 65.3% | n.s. |
| Risk adjusted | T1–3N0 | HR: 0.65 | Reference | s |
| T4/N1–2 | HR: 0.98 | Reference | n.s. |
| Relative 5-year overall survival |
| Stormark | Descriptive | 77.7% | 80.6% | n.s. |

s. significant (p < 0.05), n.s. not significant, HR hazard ratio, RCT randomized controlled trial, RETRO representative retrospective cohort study, UICC Union for International Cancer Control

Data of the An-Institut Magdeburg and also saw a significant advantage for the laparoscopic procedure (5-year overall survival: laparoscopic as treated: 82.8% vs. open: 66.9%, p = 0.005), although it must be noted that participation in this retrospective cohort study performed 15 years ago in Germany was voluntary [22].

A more recent study of Benz et al. [33] analyzes cancer registry data from the Arbeitsgemeinschaft Deutscher Tumorzentren (ADT; Working Group of German Tumor Centers), which gathers patient-, diagnosis-, and treatment-related medical records in approximately 30% of German tumor patients on a legal basis. It stratified the patients into four groups: “laparoscopic left”, “laparoscopic right”, “open left”, and “open right”. According to this study, tumor location does not serve as an effect modifier for the surgical approach. In both the Kaplan–Meier and the multivariable analyses, there was a significant survival benefit for the laparoscopic technique, regardless of tumor location and UICC stage (only stages I–III were included in the analysis).

These findings are in contrast to an earlier analysis of the National Cancer Database (NCDB) registry by Bilimoria et al. [34], who did not observe a positive influence of the laparoscopic approach on overall survival. In the study of Völkel et al., the advantage for the laparoscopic approach was also restricted to low-risk situations (T1–3, N0), while high-risk patients (T4 or N1) did not benefit significantly from the minimally invasive technique [35].

Taking all of the presented evidence (Table 4) into account, the laparoscopic and the open approach seem to be equivalent in terms of overall survival. There might perhaps be a slight advantage for the laparoscopic approach. Future studies on this topic should focus on the standardization of certain surgical standards such as the extent of lymphadenectomy, since this has been neglected by virtually all existing pro- and retrospective trials.

Tumor recurrence

Colorectal tumor resection aims to maximize tumor-free survival. According to the Cochrane meta-analysis by Kuhry et al., laparoscopy and laparotomy do not differ significantly in terms of local and distant metastasis rates [12].

Since local recurrence events are not common in colon cancer patients, most studies simply report disease-free survival. For example, the COLOR study reports a disease-free survival rate of 66.5% (sd 62.2–70.7) in patients with laparoscopic and 67.9% (sd 63.6–72.2) in patients with open resection [30]. Despite the randomized study design, it was decided to additionally perform multivariable Cox regression to adjust for age, sex, and UICC stage, resulting in a hazard ratio (HR) of 0.92 (CI 0.74–1.15, reference: open) in favor of the laparoscopic approach. This figure is almost perfectly matched by the cancer registry study of Völkel et al.: HR 0.94 (CI 0.74–1.19, ref-
Laparoscopic surgery for colon carcinoma is associated with a slightly longer duration of surgery, but a variety of studies show that it is also associated with a lower rate of postoperative complications and a shorter duration of hospital stay. Particularly in older patients with more comorbidities, laparoscopy seems to contribute to decreasing postoperative mortality. Concerning long-term oncologic outcomes, the laparoscopic and the open techniques were shown to be at least equivalent with regards to overall and recurrence-free survival. Depending on the characteristics of the observed patient collective, laparoscopy might be slightly superior if the same surgical standards are applied.

## Corresponding address

**Dr. med. Vinzenz Völkel**
Tumorzentrum Regensburg—Institut für Qualitätssicherung und Versorgungsforschung der Universität Regensburg
Am BioPark 9, 93053 Regensburg, Germany
vinzenz.voelkel@ur.de

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## Compliance with ethical guidelines

**Conflict of interest.** V. Völkel, T. Draeger, M. Gerken, M. Klinkhammer-Schalke, S. Benz, and A. Fürst declare that they have no competing interests.

This publication does not contain any experiments with patients or animals.

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**Table 5 Tumor recurrence**

| Laparoscopic Local and distant metastasis | Open Local and distant metastasis | Significance | Type of study |
|----------------------------------------|----------------------------------|-------------|--------------|
| **Kuhry (Cochrane review)** | | **Meta-analysis** | |
| Locoregional recurrence | OR: 0.84 | Reference | n.s. |
| Distant recurrence | OR: 0.82 | Reference | n.s. |
| **CLASSICC** | | **RCT** | |
| Locoregional recurrence | 7.3% | 5.7% | n.s. |
| Distant recurrence | 11.4% | 12.9% | n.s. |
| **Kaiser** | | **RCT** | |
| Locoregional recurrence | 3.6% | 0% | n.s. |
| Distant recurrence | 7.1% | 5.0% | n.s. |
| **Lacy** | | **RCT** | |
| Locoregional recurrence | 6.6% | 13.7% | n.s. |
| Distant recurrence | 6.6% | 8.8% | n.s. |
| **Liang** | | **RCT** | |
| Locoregional recurrence | 0% | 0% | n.s. |
| Distant recurrence | 15.6% | 19.4% | n.s. |

**5-year disease-free survival**

| CLASSICC | 57.6% | 64.0% | n.s. |
| COLOR | 66.5% | 67.9% | n.s. |
| COST | 69.2% | 68.4% | n.s. |

**5-year recurrence-free survival**

| Kubé | | **RETRO** | |
| **Descriptive** | 83.2% | 72.5% | s. |
| Conversions: 67.6% | |
| **Völkel** | | **RETRO** | |
| **Descriptive** | 75.9% | 70.3% | n.s. |
| Risk adjusted: | HR: 0.94 | Reference | n.s. |

s. significant (p < 0.05), n.s. not significant, HR hazard ratio, RCT randomized controlled trial, RETRO representative retrospective cohort study.

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