The influence of postoperative complications on long-term prognosis in patients with colorectal carcinoma

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Abstract

Background The impact of postoperative complications (POCs) on the long-term prognosis of patients with colorectal carcinoma was analysed with respect to their severity according to the Clavien-Dindo classification (CDC).

Methods The prospectively collected data of 2158 patients who underwent curative resection of a colorectal carcinoma (1168 rectal carcinomas, 990 colon carcinomas) without distant metastases from 1995 to 2014 were analysed. The POCs were documented in a standardized form and graded with the CDC. Patients who died postoperatively (CDC grade V, 1.7%) were excluded.

Results In total, 467 patients (21.6%) had POCs: CDC I, 141 (6.5%); CDC II, 162 (7.5%); CDC III, 112 (5.2%); and CDC IV, 52 (2.4%). More POCs and higher CDC grades were found in men, ASA III-IV patients, rectal carcinoma patients, and patients who underwent abdominoperineal excisions or multivisceral resections. The 5-year locoregional recurrence rate was 5.3% in patients without POCs and 6.6% in patients with POCs. It was highest in CDC III patients (12.9%), which was confirmed in multivariate analysis (HR 2.2; \( p = 0.005 \)). The 5-year distant metastasis rate was 15.9% in CDC 0 patients and 19.5% in CDC I–IV patients. In multivariate analysis, distant metastasis was highest in CDC III patients (HR 1.7; \( p = 0.020 \)). The 5-year overall survival rate was 83.5% in patients without POCs and 73.5% in patients with POCs. It was worst in CDC IV patients (63.1%), which was confirmed by multivariate analysis (HR 1.9; \( p = 0.001 \)).

Conclusion Patients with POCs after colorectal surgery have a poor long-term prognosis. As the CDC grade increases, survival deteriorates.

Keywords Colorectal carcinoma · Postoperative complications · Clavien-Dindo classification · Prognosis

Introduction

Quality management in colorectal carcinoma is usually divided into short- and long-term results. How closely these two are linked was first demonstrated with anastomotic leaks. In 1991 Akyol et al. [1] and in 2001 Merkel et al. [2] showed that anastomotic leaks in rectal carcinoma, a traditional short-term quality indicator, was associated with a poor long-term outcome, i.e., elevated locoregional recurrence rates and poor survival. Moreover, this has also been proven in meta-analyses [3]. Over the last few decades, the frequency of anastomotic leaks has decreased due to improvements in surgical techniques. Whether there is a connection between postoperative complications (POCs) in general and long-term prognosis is still under debate, particularly whether a classification of complications can gradually predict the long-term outcome of patients with colorectal cancer.

In 1992, Clavien et al. [4] classified negative outcomes by differentiating complications, sequelae, and failures. Twelve years later, the classification was re-evaluated and modified by one of the authors, focusing on the grading of life-threatening complications and long-term disabilities due to complications [5]. The use of therapeutic consequences as a basis for the classification of complications remained unchanged. Although new attempts to classify complications appeared, the Clavien-Dindo classification (CDC) has been validated...
and established in international studies across many fields of surgery. Recently, a study of 2266 patients reported that POCs are associated with adverse oncological outcomes, with an increased effect at higher CDC grades [6].

The Erlangen Registry for Colorectal Carcinoma (ERCRC) was established in 1978. Quality management and prognostic factor analysis are the main objectives of this prospective cancer registry. The aim of the current study was to analyse the impact of postoperative complications on long-term prognosis and to assess the severity of complications graded by the CDC and their influence on locoregional recurrence, distant metastasis, disease-free survival, and overall survival.

Methods

The study refers to 2215 consecutive patients who underwent colorectal carcinoma surgery at the Department of Surgery of the University Hospital Erlangen, Germany, between 1995 and 2014. We evaluated the prospectively collected database of the Erlangen Registry for Colorectal Carcinomas (ERCRC) according to the following inclusion criteria: solitary invasive colorectal carcinoma (at least into the submucosa); no appendiceal carcinoma; no other previous or synchronous malignancies; carcinomas not related with familial adenomatous polyposis, ulcerative colitis or Crohn’s disease; no distant metastases; radical elective surgery; and residual tumour classification R0 (no residual tumour at clinical and pathohistological examination). All patients underwent resection with regional lymph node dissection according to the TNM classification system [11].

Node Metastasis (TNM) classification system [11].

Adjuvant chemotherapy was recommended for stage III patients and for select stage II patients.

The detailed documentation allowed for a classification of the carcinomas according to the eighth edition of the Tumour Node Metastasis (TNM) classification system [11].

Postoperative complications (POCs) were documented in a standardized form. To assess the severity of these POCs, the Clavien-Dindo classification (CDC) [5, 12] was retrospectively applied. This classification consists of 5 different grades. Grade I comprises any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. The allowed therapeutic regimens are antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside. Grade II complications require pharmacological treatment with drugs other than those applied for grade I complications, including blood transfusions and total parenteral nutrition. Grade III complications require surgical, endoscopic or radiological intervention (grade III a, intervention not under general anaesthesia; grade III b, intervention under general anaesthesia). Grade IV complications are life-threatening complications requiring intensive care/intermediate care management (grade IV a, single organ dysfunction including dialysis; grade IV b, multi-organ dysfunction). Grade V complications describe the postoperative death of the patient.

Anastomotic leaks were classified according to Rahbari et al. (grade A, no change in patients’ management; grade B, active therapeutic intervention without relaparotomy; grade C, requiring re-laparotomy [13]). Severe late anastomotic leaks diagnosed after readmission were also considered.

The American Society of Anaesthesiologists (ASA) classifies the comorbidities of the patients into 6 levels [14]. The levels were grouped into ASA I-II and ASA III-IV. The ASA classification was missing in 324 patients.

The patients were followed up for at least 5 years, every 3 months for the first 2 years and every 6 months thereafter; the follow-up included a physical examination, carcinoembryonic antigen (CEA) analysis, abdominal ultrasonography, chest X-ray, computed tomography (CT) of the pelvis and rectoscopy/colonoscopy, depending on localization (rectum or colon) and stage of the primary tumour. In 2004, the follow-up examinations were changed...
Statistical analysis

The χ² test and Fisher’s exact test were used to compare frequencies, and the Mann-Whitney U test was used to analyse continuous data. The Kaplan-Meier method was used to calculate the 5-year rates of locoregional recurrence, distant metastasis and survival. Survival curves were compared using a log-rank test. Disease-free survival was defined as the time to the first occurrence of locoregional recurrence, distant metastasis or death by any cause. The endpoint of overall survival was death from any cause. Factors that were found to be significant in the univariate analysis were included in a multivariate Cox regression model. A p value less than 0.05 was considered significant. Statistical analysis was carried out using the statistics software package SPSS® version 21 (IBM, Armonk, New York, USA).

Results

The characteristics of all 2158 patients and their tumours are shown in Table 1. A total of 467 (21.6%) patients had postoperative complications. These complications were distributed across the 4 CDC grades as follows: grade I, n = 141 (6.5%); grade II, n = 162 (7.5%); grade III, n = 112 (5.1%); and grade IV, n = 52 (2.4%). Table 2 shows typical examples of postoperative complications and their respective treatment according to the different CDC grades. The most frequent complications were: for CDC grade I complications, secondary healing (n = 28) and urinary bladder dysfunction (n = 40); for CDC grade II complications, urinary tract infection (n = 40) and central venous catheter infection (n = 23); for CDC grade III, anastomotic leak (n = 27), abdominal wall dehiscence (n = 14) and postoperative bleeding (n = 11); and for CDC grade IV, anastomotic leak (n = 23) and pulmonary complication (n = 12). Compared to other patients, male patients, patients with an ASA level > II, tumour localization in the rectum, abdominopereineal excision and multivisceral resection had significantly more postoperative complications and higher CDC grades.

Quality indicators

The median number of regional lymph nodes examined in all specimens was 25 (1–145). In patients with rectal carcinoma, the median number of regional lymph nodes examined was 22 (2–76). In patients with primary surgery, it was 27 (4–76), and in those with neoadjuvant treatment, it was 18 (2–62). In patients with colon carcinoma, the median number of regional lymph nodes examined was 29 (1–145). In those who underwent standard colon resections, it was 27 (4–76), and in extended resections, it was 37 (12–145).

The pathological circumferential resection margin (pCRM) was positive (≤ 1 mm) in 20 (2.0%) of the 997 rectal cancer specimens who underwent respective examinations.

The quality of TME/PME [16] was evaluated as mesorectal plane or intramesorectal plane of surgery in 911 (98.3%) of 927 specimens, while 16 (1.7%) specimens were classified as muscularis propria plane.

Anastomotic leaks of grade B and C were observed in 45 (4.8%) of 942 patients after rectal resection and in 23 (2.3%) of 985 patients after colon resection.

Adjuvant treatment

Six hundred fifty-eight patients (30.5%) received adjuvant treatment. The higher the CDC grade, the less frequently adjuvant therapy was administered (31.8% to 15.4%; Table 1). While this was not observed for stage II and III rectal cancer patients without neoadjuvant therapy, it was highly significant for stage III colon carcinomas (p < 0.001).

Prognosis

The 5-year locoregional recurrence rate of the entire study group was 5.6% (95% confidence interval 4.6–6.6). The rate was 8.5% for rectal carcinomas compared to 2.2% for colon carcinomas (p < 0.001). The locoregional recurrence rate was significantly higher in men than in women and increased with stage. The rate was higher in patients with POCs (6.6% vs 5.3%; p = 0.068) and was highest in patients with CDC grade III POCs (12.9%; p = 0.007). In the multivariate Cox regression analysis, sex (p = 0.050), tumour site (p < 0.001), stage III tumours (p = 0.005) and CDC grade III POCs were found to significantly influence the locoregional recurrence rate (HR 2.2; p = 0.005; Table 3, Fig. 1).
The 5-year distant metastasis rate of the entire study group was 16.7% (95% CI 15.1–18.3). The rate differed significantly between patients with and without POCs (19.5% vs 15.9%; \( p = 0.009 \)). The univariate analysis also found that ASA classification (\( p = 0.028 \)), tumour site (\( p < 0.001 \)) and tumour stage (\( p < 0.001 \)) were significant factors. The 5-year distant metastasis rate increased as the CDC grade advanced, but this association did not reach significance (\( p = 0.066 \)). In the multivariate analysis, ASA classification (\( p = 0.045 \)), tumour site (\( p < 0.001 \)) and stage III tumours (\( p = 0.020 \)) were found to be independent prognostic factors. In addition, CDC grade III POCs were again significantly associated with the highest risk for distant metastases (HR 1.7; \( p = 0.020 \); Table 4, Fig. 2).

The 5-year disease-free survival rate of the entire study group was 73.4% (95% CI 71.4–75.4). The patients with POCs had a significantly worse disease-free survival (65.2%) than patients without POCs (75.6%; \( p < 0.001 \)). In the univariate analysis, significant differences were found for

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**Table 1** Patients’ and tumour characteristics for 2158 patients

| Clavien-Dindo classification | All \( n = 2158 \) | 0 \( n = 1691 \) | I \( n = 141 \) | II \( n = 162 \) | III \( n = 112 \) | IV \( n = 52 \) | \( p \) |
|-----------------------------|----------------|----------------|-------------|-------------|-------------|-------------|--------|
| Age median (range) (years)  | 64.5 (17–94)   | 64 (17–94)     | 66 (21–87)  | 67 (36–93)  | 65 (35–88)  | 71 (39–90)  | <0.001 |
| Sex                         |                |                |             |             |             |             |        |
| Male                        | 1351 (62.6)    | 1038 (61.4)    | 92 (65.2)   | 99 (61.1)   | 87 (77.7)   | 35 (67)    |        |
| Female                      | 807 (37.4)     | 653 (38.6)     | 49 (34.8)   | 63 (38.9)   | 25 (22.3)   | 17 (33)    | 0.011  |
| ASA *                       |                |                |             |             |             |             |        |
| ASA I–II                    | 1498 (81.7)    | 1200 (83.7)    | 93 (77.5)   | 114 (78.6)  | 65 (69.9)   | 26 (61)    | <0.001 |
| ASA III–IV                  | 336 (18.3)     | 233 (16.3)     | 27 (22.5)   | 31 (21.4)   | 28 (30.1)   | 17 (40)    | <0.001 |
| Tumour site                 |                |                |             |             |             |             |        |
| Colon                       | 990 (45.9)     | 807 (47.7)     | 61 (43.3)   | 62 (38.3)   | 33 (29.5)   | 27 (52)    | <0.001 |
| Rectum                      | 1168 (54.1)    | 884 (52.3)     | 80 (56.7)   | 100 (61.7)  | 79 (70.5)   | 25 (48)    | <0.001 |
| Surgical procedure          |                |                |             |             |             |             |        |
| (Low) anterior resection     | 951 (44.1)     | 747 (44.2)     | 48 (34.0)   | 77 (47.5)   | 57 (50.9)   | 22 (42)    |        |
| Abdominoperineal excision    | 216 (10.0)     | 138 (8.2)      | 30 (21.3)   | 23 (14.2)   | 22 (19.6)   | 3 (6)      |        |
| Colon standard resection     | 787 (36.5)     | 656 (38.8)     | 40 (28.4)   | 50 (30.9)   | 26 (23.2)   | 15 (29)    |        |
| Colon extended resection     | 204 (9.5)      | 150 (8.9)      | 23 (16.3)   | 12 (7.4)    | 7 (6.3)     | 12 (23)    | <0.001 |
| Multivisceral resection      | 246 (11.4)     | 170 (10.1)     | 26 (18.4)   | 23 (14.2)   | 17 (15.2)   | 10 (19)    | 0.003  |
| Multimodal treatment         |                |                |             |             |             |             |        |
| Neoadjuvant treatment        | 550 (25.5)     | 420 (24.8)     | 37 (26.2)   | 43 (26.5)   | 39 (34.8)   | 11 (21.2)  | 0.187  |
| Adjuvant treatment           | 658 (30.5)     | 537 (31.8)     | 44 (31.2)   | 41 (25.3)   | 28 (25.0)   | 8 (15.4)   | 0.032  |
| Adjuvant treatment for rectal carcinoma stage II,III | 162/342 (47.4) | 126/253 (49.8) | 10/29 (34) | 11/34 (32) | 10/17 (59) | 5/9 (56) | 0.150 |
| Adjuvant treatment for colon carcinoma stage III | 215/312 (68.9) | 186/257 (72.4) | 14/17 (82) | 10/15 (67) | 5/12 (42) | 0/11 (0) | <0.001 |
| pT category                  |                |                |             |             |             |             |        |
| pT1.2/ypT0,1.2               | 998 (46.2)     | 790 (46.7)     | 53 (37.6)   | 76 (46.9)   | 59 (52.7)   | 20 (38)    |        |
| pT3/ypT3                    | 1028 (47.6)    | 801 (47.4)     | 80 (56.7)   | 74 (45.7)   | 45 (40.2)   | 28 (54)    |        |
| pT4/ypT4                    | 132 (6.1)      | 100 (5.9)      | 8 (5.7)     | 12 (7.4)    | 8 (7.1)     | 4 (8)      | 0.309  |
| pN category                  |                |                |             |             |             |             |        |
| pN0/ypN0                    | 1491 (69.1)    | 1166 (69.0)    | 95 (67.4)   | 119 (73.5)  | 81 (72.3)   | 30 (58)    |        |
| pN1.2/ypN1.2                | 667 (30.9)     | 525 (31.0)     | 46 (32.6)   | 43 (26.5)   | 31 (27.7)   | 22 (42)    | 0.290  |
| Stage (UICC)                |                |                |             |             |             |             |        |
| Stage I                     | 573 (26.6)     | 454 (26.8)     | 32 (22.7)   | 42 (25.9)   | 33 (29.5)   | 12 (23)    |        |
| Stage II                    | 535 (24.8)     | 424 (25.1)     | 37 (26.2)   | 46 (28.4)   | 17 (15.2)   | 11 (21)    |        |
| Stage III                   | 500 (23.2)     | 393 (23.2)     | 35 (24.8)   | 31 (19.1)   | 23 (20.5)   | 18 (35)    |        |
| Stage y0                    | 73 (3.4)       | 60 (3.5)       | 2 (1.4)     | 4 (2.5)     | 7 (6.3)     | 0         |        |
| Stage y1                    | 164 (7.6)      | 127 (7.5)      | 6 (4.3)     | 17 (10.5)   | 12 (10.7)   | 2 (4)      |        |
| Stage yII                   | 146 (6.8)      | 101 (6.0)      | 18 (12.8)   | 10 (6.2)    | 12 (10.7)   | 5 (10)     |        |
| Stage yIII                  | 167 (7.7)      | 132 (7.8)      | 11 (7.8)    | 12 (7.4)    | 8 (7.1)     | 4 (8)      | 0.045  |

ASA American Society of Anesthesiologists Classification; *ASA missing in 324 patients.
age, sex, ASA classification, tumour site, tumour stage and CDC grade. In the multivariate analysis adjusted for age, all of these factors were found to have a significant influence on disease-free survival. Patients with CDC grade IV POCs were

| Postoperative complication | CDC I | CDC II | CDC III | CDC IV |
|----------------------------|-------|--------|---------|--------|
| Pulmonary complication      |       |        |         |        |
| Mild infection requiring respiratory therapy | | | | |
| Urinary bladder dysfunction requiring leg bags or sanitary pads | | | | |
| Pneumonia requiring antibiotics | | | | |
| Urinary tract infection requiring antibiotics; bladder dysfunction treated by anticholinergics or alpha-blocking agents | | | | |
| Pleural effusion requiring drainage | | | | |
| Urinary bladder dysfunction treated by suprapubic catheterization | | | | |
| Respiratory insufficiency requiring ventilation | | | | |
| Urosepsis requiring intensive care | | | | |
| Urologic complication       |       |        |         |        |
| Urinary bladder dysfunction requiring leg bags or sanitary pads | | | | |
| Urinary tract infection requiring antibiotics | | | | |
| Urinary bladder dysfunction treated by anticholinergics or alpha-blocking agents | | | | |
| Pleural effusion requiring drainage | | | | |
| Urinary bladder dysfunction treated by suprapubic catheterization | | | | |
| Respiratory insufficiency requiring ventilation | | | | |
| Urosepsis requiring intensive care | | | | |
| Wound healing disorder      |       |        |         |        |
| Wound infection opened at the bedside | | | | |
| Wound dehiscence requiring surgical abdominal wall closure | | | | |
| Wound infection leading to sepsis requiring intermediate or intensive care | | | | |
| Wound infection with peritonitis and multi-organ dysfunction requiring relaparotomy and intensive care | | | | |
| Anastomotic leak            |       |        |         |        |
| Anastomotic leak requiring observation | | | | |
| Anastomotic leak requiring antibiotics | | | | |
| Anastomotic leak requiring drainage or relaparotomy | | | | |

| Table 3 | Univariate and multivariate Cox regression analyses of locoregional recurrences |
|---------|---------------------------------|
|         | Univariate analysis | Multivariate model |
|         | n | 5-year rate | 95% CI | p** | Hazard ratio | 95% CI | p |
| All     | 2158 | 5.6 | 4.6–6.6 | | | | | |
| Age (years) | | | | | | | | |
| <65 | 1079 | 5.7 | 4.3–7.1 | 0.718 | 0.7 | 0.4–1.0 | 0.050 | |
| ≥65 | 1079 | 5.6 | 4.2–7.0 | | | | | |
| Sex | | | | | | | | |
| Male | 1351 | 6.5 | 5.1–7.9 | 1.0 | | | | |
| Female | 807 | 4.1 | 2.7–5.5 | 0.010 | 0.7 | 0.4–1.0 | 0.050 | |
| ASA* | | | | | | | | |
| ASA I–II | 1498 | 4.8 | 3.6–6.0 | | | | | |
| ASA III–IV | 336 | 6.4 | 3.5–9.3 | 0.344 | | | | |
| Tumour site | | | | | | | | |
| Colon | 990 | 2.2 | 1.2–3.2 | 1.0 | | | | |
| Rectum | 1168 | 8.5 | 6.7–10.3 | <0.001 | 5.3 | 3.2–8.8 | <0.001 | |
| Stage (UICC) | | | | | | | | |
| Stage I | 573 | 3.5 | 1.9–5.1 | 1.0 | | | | |
| Stage II | 535 | 4.6 | 2.8–6.4 | 2.2 | 1.3–4.0 | 0.006 | |
| Stage III | 500 | 7.7 | 5.2–10.2 | 2.7 | 1.5–4.6 | <0.001 | |
| Stage y0 | 73 | 0 | 0 | 0.954 | | | | |
| Stage yI | 164 | 4.5 | 1.2–7.8 | 0.6 | 0.3–1.5 | 0.296 | |
| Stage yII | 146 | 9.6 | 4.5–14.7 | 1.7 | 0.9–3.3 | 0.118 | |
| Stage yIII | 167 | 10.2 | 5.3–15.1 | <0.001 | 1.9 | 1.0–3.5 | 0.061 | |
| Clavien-Dindo classification | | | | | | | | |
| 0 | 1691 | 5.3 | 4.1–6.5 | 1.0 | | | | |
| I | 141 | 4.4 | 0.7–8.1 | 0.9 | 0.4–1.8 | 0.683 | |
| II | 162 | 4.8 | 1.3–8.3 | 1.0 | 0.5–1.9 | 0.948 | |
| III | 112 | 12.9 | 6.2–19.6 | 2.2 | 1.3–3.9 | 0.005 | |
| IV | 52 | 4.3 | 0–10.2 | 0.007 | 0.8 | 0.2–3.1 | 0.699 | |

ASA American Society of Anesthesiologists Classification; *ASA missing in 324 patients

**Log-rank test
found to have the worst disease-free survival compared to patients without POCs (HR 1.8; \( p = 0.002 \); Table 5, Fig. 3).

The 5-year overall survival rate of the entire study group was 81.3% (95% CI 79.7–82.9). The patients with POCs had a strikingly decreased overall survival (73.5%) compared to patients without POCs (83.5% \( p < 0.001 \)). The univariate analysis was significant for age (\( p < 0.001 \)), sex (\( p = 0.001 \)), tumour stage (\( p < 0.001 \)) and CDC grade (\( p < 0.001 \)). In the

Table 4 Univariate and multivariate Cox regression analyses of distant metastases

|                | n     | 5-year rate | 95% CI     | \( p^{**} \) | Hazard ratio | 95% CI   | \( p \) |
|----------------|-------|-------------|------------|--------------|--------------|----------|--------|
|                | All   | 2158        | 16.7       | 15.1–18.3    |              |          |        |
| Age (years)    | < 65  | 1079        | 16.5       | 14.3–18.7    |              |          |        |
|                | ≥ 65  | 1079        | 16.9       | 14.5–19.3    | 0.598        |          |        |
| Sex            | Male  | 1351        | 17.9       | 15.7–20.1    |              |          |        |
|                | Female| 807         | 14.6       | 12.1–17.1    | 0.051        |          |        |
| ASA*           | ASA I-II | 1498   | 15.5       | 13.5–17.5    | 1.0          |          |        |
|                | ASA III-IV | 336   | 20.0       | 15.3–24.7    | 0.028        | 1.3      | 1.0–1.8 | 0.045 |
| Tumour site    | Colon | 990         | 12.9       | 10.7–15.1    | 1.0          |          |        |
|                | Rectum| 1168        | 19.9       | 17.5–22.3    | < 0.001      | 1.8      | 1.4–2.4 | < 0.001|
| Stage (UICC)   | Stage I | 573    | 6.3        | 4.1–8.5      | 1.0          |          |        |
|                | Stage II | 535   | 13.1       | 10.2–16.0    | 2.5          | 1.7–3.8  | < 0.001|
|                | Stage III | 500  | 28.8       | 24.7–32.9    | 4.7          | 3.3–6.9  | < 0.001|
|                | Stage y0 | 73    | 1.4        | 0–4.1        | 0.1          | 0.0–1.0  | 0.047  |
|                | Stage y1 | 164   | 8.8        | 4.5–13.1     | 1.0          | 0.6–1.8  | 0.941  |
|                | Stage yII | 146  | 14.8       | 7.7–21.9     | 3.3          | 2.1–5.2  | < 0.001|
|                | Stage yIII | 167 | 36.4       | 29.0–43.8    | < 0.001      | 4.8      | 3.2–7.4 | < 0.001|
| Clavien-Dindo classification | 0 | 1691 | 15.9 | 14.1–17.7 | 1.0 |          |        |
|                | I     | 141        | 17.4       | 10.7–24.1    | 1.0          | 0.7–1.6  | 0.878  |
|                | II    | 162        | 19.6       | 13.1–26.1    | 1.4          | 1.0–2.1  | 0.056  |
|                | III   | 112        | 21.0       | 13.2–28.8    | 1.7          | 1.1–2.5  | 0.020  |
|                | IV    | 52         | 23.7       | 11.4–36.0    | 0.066        | 1.2      | 0.6–2.5 | 0.543  |

ASA American Society of Anesthesiologists Classification; *ASA missing in 324 patients. **Log-rank test
multivariate analysis, all of these factors were found to be significant. Patients with CDC grade IV POCs had the worst overall survival (HR 1.9; \( p = 0.001 \); Table 6, Fig. 4).

**Results over time**

If the study time is divided and the two periods, 1995–2004 \(( n = 1097 \) ) and 2005–2014 \(( n = 1061 \) ), are compared, we found fewer POCs in the second period \(( 23.2\% \text{ vs } 20.0\%; \ p = 0.066 \) ), in particular a decrease in POCs of CDC grade IV was observed \(( 3.4\% \text{ vs } 1.4\%; \ p = 0.003 \) ). With regard to long-term outcome, the 5-year locoregional recurrence rate decreased significantly from \( 7.3\% \ (95\% \text{CI} \ 5.7–8.9) \) to \( 3.8\% \ (95\% \text{CI} \ 2.6–5.0; \ p = 0.006) \), while improvements in distant metastasis \(( 18.5\% \text{ vs } 14.8\%; \ p = 0.082) \), disease-free survival \(( 70.9\% \text{ vs } 76.0\%; \ p = 0.092) \) and overall survival \(( 79.5\% \text{ vs } 83.3\%; \ p = 0.239) \) did not reach significance.

**Discussion**

The present study shows that men, ASA III–IV patients, patients with rectal carcinomas, patients who underwent abdominoperineal excisions and patients who underwent multivisceral resections have more POCs and higher CDC grades than other patients. In investigating the influence of postoperative complications on long-term prognosis, a worse prognosis was found in patients with postoperative complications, especially in patients with high CDC grades. In particular, CDC grade III patients were associated with an increased risk for locoregional recurrences and distant metastases. This corresponds to the recurrence rates in the study by Duraes et al. [6], in which CDC grade III patients also had the worst recurrence rate. In addition, patients with CDC grade IV POCs showed significantly worse disease-free and overall survival rates, which is also consistent with the results of the study mentioned above. Postoperative complications usually depend on the extent of the surgical intervention. Sigmoid resection of a small tumour is typically associated with fewer and less serious complications than total pelvic exenteration [17].

Most patients with CDC grade III complications had surgical complications. In our series, 89% (97 of 112 patients) of the patients with CDC grade III POCs had a surgical complication. These patients required endoscopic, radiological or surgical interventions. Anastomotic leak is a typical example of a CDC grade III complication frequently associated with increased rates of locoregional recurrences and even poor overall survival [2, 3]. This can be explained by exfoliated cancer cells that remain after tumour resection, which may lead to local recurrence induced by a pelvic infection with systemic inflammatory and immunomodulatory responses primarily caused by the anastomotic leak.

CDC grade IV complications are life-threatening and require the patient to be admitted to an intermediate or intensive care unit. The results of the present study show that these patients had the worst disease-free and overall survival rates compared to other patients. It should be noted that these severe complications are not necessarily surgical complications.
the present study, 40% of CDC IV patients had non-surgical complications. Preoperative comorbidities, such as chronic heart failure, chronic obstructive pulmonary disease (COPD) and renal failure, represent a particular risk for non-surgical complications. These comorbidities can lead to single- or multi-organ dysfunction after colorectal surgery, which affects survival outcomes regardless of the original oncological prognosis.

Artinyan et al. [18] showed that postoperative complications after the resection of colorectal carcinomas are an independent risk factor for poor long-term survival. In particular, patients with infectious complications, such as deep and superficial surgical site infections, pneumonia or urinary tract infections, have been associated with increased rates of locoregional recurrence and decreased long-term prognosis. This association is especially impressive in view of the fact that the affected patients in the study were young and had few preoperative comorbidities. In our study, severe infectious complications such as peritonitis, colon necrosis or pneumonia were found in 46% of the patients with CDC IV POCs, who had decreased disease-free and overall survival rates. Previous studies have shown that C-reactive protein (CRP) can predict the occurrence of complications [19] and even the severity of postoperative complications in colorectal cancer [20]. Among patients with anastomotic leaks, patients who required reoperations were found to have worse overall survival compared to those for whom conservative treatment was sufficient [21].

The ASA classification, which assesses the preoperative status of the patient, is an independent factor for morbidity and mortality. An older age is frequently associated with more comorbidities and thus with an increased ASA classification. The present study showed that patients with more serious comorbidities (ASA III or IV classification) were associated with more frequent complications and a higher CDC grade. This is reflected in the worse long-term prognosis with shorter disease-free and overall survival when patients with comorbidities do not recover properly from the complications of surgery. Patients who are more ill are more likely to have a higher complication rate and thus a lower survival rate. As a

| Table 5 Univariate and multivariate Cox regression analyses of disease-free survival |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Univariate analysis | Multivariate model adjusted for age |
|                                | n    | 5-year rate | 95% CI | p** | Hazard ratio | 95% CI | p     |
| All                             | 2158 | 73.4       | 71.4–75.4 |    |              |       |       |
| Age (years)                     |      |            |        |     |              |       |       |
| < 65                            | 1079 | 78.7       | 76.2–81.2 | < 0.001 |              |       |       |
| ≥ 65                            | 1079 | 68.0       | 65.3–70.7 | < 0.001 |              |       |       |
| Sex                             |      |            |        |     |              |       |       |
| Male                            | 1351 | 71.6       | 69.2–74.0 | 1.0 |              |       |       |
| Female                          | 807  | 76.3       | 73.4–79.2 | 0.001 | 0.8          | 0.7–1.0 | 0.015 |
| ASA*                            |      |            |        |     |              |       |       |
| ASA I–II                       | 1498 | 77.4       | 75.2–79.6 | 1.0 |              |       |       |
| ASA III–IV                     | 336  | 57.1       | 51.8–62.4 | < 0.001 | 1.8          | 1.5–2.1 | < 0.001 |
| Tumour site                     |      |            |        |     |              |       |       |
| Colon                           | 990  | 76.8       | 74.1–79.5 | 1.0 |              |       |       |
| Rectum                          | 1168 | 70.5       | 68.0–73.0 | 0.047 | 1.4          | 1.2–1.7 | < 0.001 |
| Stage (UICC)                    |      |            |        |     |              |       |       |
| Stage I                         | 573  | 83.8       | 80.7–86.9 | 1.0 |              |       |       |
| Stage II                        | 535  | 74.4       | 70.7–78.1 | 1.4 | 1.1–1.7       | < 0.001 |
| Stage III                       | 500  | 61.0       | 56.7–65.3 | 1.9 | 1.5–2.3       | < 0.001 |
| Stage y0                        | 73   | 97.3       | 93.6–100 | 0.6 | 0.3–1.0       | 0.047 |
| Stage yI                        | 164  | 85.7       | 80.2–91.2 | 0.8 | 0.6–1.1       | 0.171 |
| Stage yII                       | 146  | 65.5       | 57.7–73.3 | 1.6 | 1.2–2.1       | 0.002 |
| Stage yIII                      | 167  | 56.2       | 48.6–63.8 | < 0.001 | 2.1          | 1.6–2.8 | < 0.001 |
| Clavien-Dindo classification    |      |            |        |     |              |       |       |
| 0                               | 1691 | 75.6       | 73.4–77.8 | 1.0 |              |       |       |
| I                               | 141  | 68.3       | 60.5–76.1 | 1.5 | 1.2–2.0       | 0.002 |
| II                              | 162  | 64.0       | 56.6–71.4 | 1.4 | 1.1–1.8       | 0.002 |
| III                             | 112  | 67.8       | 59.2–76.4 | 1.4 | 1.1–1.9       | 0.013 |
| IV                              | 52   | 55.4       | 41.9–68.9 | < 0.001 | 1.8          | 1.2–2.5 | 0.002 |

ASA American Society of Anesthesiologists Classification; *ASA missing in 324 patients. **Log-rank test
complication-free course is important for the overall prognosis, good preoperative preparation is essential, particularly for older and high-risk patients. In addition to ensuring appropriately treated comorbidities, such as good control of diabetes and hypertension, optimal preoperative and postoperative nutrition and physical activity play an important role.

Table 6 Univariate and multivariate Cox regression analyses of overall survival

|                           | Univariate analysis | Multivariate model adjusted for age |
|---------------------------|---------------------|-----------------------------------|
|                           | n                   | 5-year rate | 95% CI | p** | Hazard ratio | 95% CI | p   |
| All                       | 2158                | 81.3        | 79.7–82.9 |    |              |        |     |
| Age (years)               |                     |             |        |     |              |        |     |
| < 65                      | 1079                | 88.3        | 86.3–90.3 | < 0.001 |              |        |     |
| ≥ 65                      | 1079                | 74.4        | 71.9–76.9 |        |              |        |     |
| Sex                       |                     |             |        |     |              |        |     |
| Male                      | 1351                | 80.2        | 78.0–82.4 | 1.0 |              |        |     |
| Female                    | 807                 | 83.2        | 80.7–85.7 | 0.001 | 0.8          | 0.7–0.9 | 0.002 |
| ASA*                      |                     |             |        |     |              |        |     |
| ASA I-II                  | 1498                | 85.2        | 83.4–87.0 | 85.2 | 1.0          |        |     |
| ASA III-IV                | 336                 | 63.6        | 58.3–68.9 | 63.6 | 1.9          | 1.6–2.3 | < 0.001 |
| Tumour site               |                     |             |        |     |              |        |     |
| Colon                     | 990                 | 82.5        | 80.1–84.9 |    |              |        |     |
| Rectum                    | 1168                | 80.3        | 77.9–82.7 | 0.306 |              |        |     |
| Stage (UICC)              |                     |             |        |     |              |        |     |
| Stage I                   | 573                 | 88.2        | 85.5–90.9 | 1.0 |              |        |     |
| Stage II                  | 535                 | 81.7        | 78.4–85.0 | 1.2 | 1.0–1.5      | 0.120  |     |
| Stage III                 | 500                 | 70.9        | 66.8–75.0 | 1.7 | 1.3–2.0      | < 0.001 |     |
| Stage y0                  | 73                  | 98.6        | 95.9–100 | 0.7 | 0.4–1.3      | 0.290  |     |
| Stage y1                  | 164                 | 94.4        | 90.9–97.9 | 0.9 | 0.6–1.3      | 0.504  |     |
| Stage yII                 | 146                 | 74.6        | 67.3–81.9 | 1.8 | 1.3–2.4      | < 0.001 |     |
| Stage yIII                | 167                 | 73.5        | 66.8–80.2 | < 0.001 | 2.3 | 1.7–3.0      | < 0.001 |     |
| Clavien-Dindo classification |                    |             |        |     |              |        |     |
| 0                         | 1691                | 83.5        | 81.7–85.3 | 1.0 |              |        |     |
| I                         | 141                 | 76.2        | 69.1–93.3 | 1.6 | 1.2–2.1      | < 0.001 |     |
| II                        | 162                 | 72.7        | 65.8–79.6 | 1.5 | 1.2–1.9      | 0.001  |     |
| III                       | 112                 | 76.5        | 68.7–84.3 | 1.4 | 1.1–2.0      | 0.022  |     |
| IV                        | 52                  | 63.1        | 50.0–76.2 | < 0.001 | 1.9 | 1.3–2.7      | 0.001  |     |

ASA American Society of Anesthesiologists Classification; *ASA missing in 324 patients
**Log-rank test
Malietzis et al. found an association between muscle mass and postoperative morbidity and mortality. They identified myopenia as an independent risk factor for disease-free and overall survival in patients with colorectal cancer [22]. It has also been found that physical exercise programs improve the symptoms of the side effects of chemotherapy and thus enable an increase in the completion rate of chemotherapy in patients with colorectal carcinoma [23], which ultimately affects disease-free and overall survival.

Patients with complications have an increased risk of not receiving adequate adjuvant therapy. The lack of receiving adjuvant therapy postoperatively is known to increase metastasis rate and to decrease survival. In addition, if adjuvant treatment is indicated after surgery, it should start on time; otherwise, the prognosis will deteriorate [24]. According to the German Evidenced-based Guideline for Colorectal Cancer, colon cancer patients should start adjuvant chemotherapy within 8 weeks [15]. This is supported by a complication-free postoperative course and a favourable long-term outcome. The increasing specialization in colorectal surgery contributes to this conclusion [29].

Our study has some limitations, particularly the single-centre design and its retrospective nature. During the long study time of 20 years, treatment protocols have changed, and multimodal treatment has gained importance. For example, the administration of adjuvant chemotherapy for stage III colon cancer nearly doubled from 44% in 1995–1999 to 79% in 2010–2014.

In conclusion, this study identified postoperative complications as an inverse prognostic factor in colorectal cancer with a strong relationship to the Clavien-Dindo classification. It emphasizes the importance of a complication-free postoperative course, not only in view of the immediate postoperative problems and costs but also for the long-term course. This relevance should be known to the entire treating and caring team during the preoperative preparation, the actual surgery and in the postoperative course. It also should be discussed with the patient, so that he/she will definitely attend all follow-up examinations.
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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent According to the Clinical Ethics Committee of the University Hospital Erlangen, no written consent was required for this retrospective analysis of anonymous data.

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