

Morbidity and Mortality Following Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Data from the DGAV StuDoQ Registry with 2149 Consecutive Patients

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ABSTRACT

Background. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are performed for well-selected patients with peritoneal surface malignancies. This combined treatment is potentially associated with an increased rate of complications.

Objective. The aim of this paper was to analyze the morbidity and mortality of CRS and HIPEC in the German national registry.

Methods. We present a retrospective analysis of 2149 consecutive patients from 52 hospitals. The data were prospectively documented in the DGAV StuDoQ Registry between February 2011 and December 2016.

Results. Almost two-thirds of all patients had a colorectal malignancy; therefore, the most frequently performed resections were colectomies (54%) and rectal resections (30%). Only 36.2% of all patients had no anastomosis, and fewer than 20% of all patients were older than 70 years of age (16.4%). Enteric fistula and anastomotic leaks occurred in 10.5% of all cases. The reoperation rate was 14.6% (95% confidence interval [CI] 11.51–18.1). Major grade 3 and 4 complications (Clavien–Dindo classification) occurred in

19.3% of all patients, half of which were due to surgical complications. The overall 30-day postoperative hospital mortality was 2.3% (95% CI 1.02–3.85). Multivariate analysis showed an increased risk for morbidity associated with pancreatic resections (odds ratio [OR] 2.4), rectal resection (OR 1.5), or at least one anastomosis (OR 1.35), and mortality with reoperation (OR 8.7) or age > 70 years (OR 3.35).

Conclusions. CRS and HIPEC are associated with acceptable morbidity and low mortality. These results show that CRS and HIPEC can be safely performed nationwide when close mentoring by experienced centers is provided.

For patients with peritoneal surface malignancies, the treatment strategy has evolved over the last decades, suggesting that a locoregional approach, often combined with systemic treatment, may improve the prognosis of selected patients with isolated peritoneal low-volume disease in whom a complete resection of the peritoneal disease is possible. Combining cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC)^{1,2} has changed the prognosis of several patients, particularly those with peritoneal metastases from colorectal malignancies.

The first meta-analysis published in 2009 showed that this combined treatment is associated with morbidity rates of up to 52% and mortality rates as high as 17%, being significantly lower in tertiary referral centers.^{3–7} The

higher mortality rates recorded by many centers starting new programs for HIPEC suggest that experience and learning curve play an important role in the observed outcomes.

A recently published analysis based on data from 76 studies showed mean morbidity and mortality rates for CRS and HIPEC of 33% and 2.8%, respectively; however, the authors did not find any statistically significant differences in a subgroup of 15 controlled studies comparing CRS and intraperitoneal treatment versus treatment including surgery and systemic chemotherapy.⁸

Interestingly, the underlying primary disease made a difference among the various subgroups of patients. In patients with gastric cancer, for instance, the mortality rate was higher, and lower in ovarian cancer,⁹ than the average mortality rate.

Implementation differs in various countries, as does the registration of treatment.¹⁰ Therefore, it is difficult to create a homogenous data bank or registry including thousands of patients. Most published reports on morbidity and mortality originate from a single institution. Some reports refer to larger series (e.g. multinational register for pseudomyxoma peritonei), but only focus on one entity without analysing in detail the figures related to complications. Consequently, we analyzed the data of the StuDoQ-HIPEC Registry, which was initiated in 2011 by the German Peritoneal Surface Oncology Group of the German Society for General and Visceral Surgery (DGAV). The registry includes all relevant parameters and is operated by an independent administrator of the German Society for General and Visceral Surgery.

The purpose of this study was to present the experience of the German HIPEC register in relation to CRS and HIPEC, specifically regarding associated surgical complications and mortality. To the best of our knowledge, the patient group in this current paper is the largest ever published national register and focuses on accurate analysis of morbidity and mortality related to this treatment strategy.

MATERIALS AND METHODS

For this study, the database including 3078 patients consecutively treated with CRS and HIPEC was retrospectively analyzed. These data were documented in the DGAV StuDoQ Registry, administered by the German Society for General and Visceral Surgery, from February 2011 to December 2016. A total of 52 hospitals contributed to the HIPEC Register.

Because of the anonymized data and the retrospective nature of this study, Institutional Review Board approval was not mandatory; however, all patients had to sign an informed consent form with regard to the inclusion of their

clinical data in the registry. In addition, all patients had a multidisciplinary team (MDT) treatment approved prior to surgery; some patients were also included in ongoing clinical trials.

The database includes all relevant parameters related to a patient's characteristics, type and extent of peritoneal disease, previous treatments, and details of the CRS and HIPEC procedures performed, including short- and long-term outcomes.

CRS performed to achieve a complete macroscopic cytoreduction achieved by parietal and visceral peritonectomy procedures, as described by Sugarbaker.¹ Depending on the protocol, a closed or open circuit HIPEC procedure at 42 °C for 30 or 60 min was performed. The most used intraperitoneal drugs were oxaliplatin, cisplatin, doxorubicin, mitomycin C, and gemcitabine.

For the analysis, only complete data sets for each patient have been considered. Figures for all required parameters were present for 75% of participating hospitals. As a result, the final analysis included 2149 patients. The data of all patients were analyzed using the Chi square test, Fisher's exact test, or Mann–Whitney–Wilcoxon test (the open source R-Project for Statistical Computing, version 3.2.3 [Vienna, Austria]). A p value < 0.05 was considered to be significant. As descriptive measures for categorical data, frequencies and percentage values were reported. For continuous data, mean, standard deviation, median, minimum, maximum, and interquartile range were used for describing location and spread. The dependency between two categorical parameters was investigated using cross tabulation and the Chi square test. The effects of multiple parameters (all binary) on a binary outcome variable (death and complication) were analyzed using logistic regression models. In the models, the effect of every parameter controlled for the other parameters is reported using odds ratios (ORs), p value, and 95% confidence intervals (CIs). For all statistical tests, a level of significance of 5% was used.

RESULTS

This analysis was performed on the data of 2149 treated patients who were suffering from various primary or metastatic malignancies of the peritoneal surface, as shown in Table 1.

The demographic data indicate the following make-up for the studied group of patients: 883 males (41.1%) and 1266 females (58.9%); 352 (16.4%) of the treated patients were older than 70 years of age. Age over 70 years was statistically significant for the mortality rate ($p < 0.001$),

TABLE 1 Distribution of the tumor entities

Organ	N	%
Appendix cancer	319	14.8
Small bowel cancer	40	1.9
Colon cancer	575	26.8
Stomach cancer	259	12.1
Mesothelioma	157	7.3
Ovary cancer	294	13.7
Pseudomyxoma	183	8.6
Rectal cancer	83	3.9
Others (e.g. CUP, sarcomas, desmoplastic small round cell tumor)	239	11.1

CUP cancer of unknown primary

but non-significant for the morbidity rate ($p = 0.536$). A total of 1749 patients (81.4%) were treated in centers with experience of more than 50 cases.

All 2149 patients received a parietal peritonectomy and/or visceral peritonectomy procedure of different extent. Distribution regarding the type of surgery is reported in Table 2.

The median duration of hospitalization was 18 days (ranging from 1 to 217 days), and the median intensive care unit stay was 3 days (ranging from 0 to 218 days). A total of 1378 (64.1%) patients had already undergone oncological surgery and 1078 (50.2%) patients had already undergone chemotherapy prior to surgery. A complete surgical cytoreduction (CC-0 or CC-1) was attained in 1416 patients (65.89%).

A total of 414 patients (19.3%) experienced at least one combined grade III/IV complication. The recorded combined grade III/IV morbidities were pancreatitis (1.7%), fistula (4.8%), anastomotic leak (5.7%), pulmonary embolism (3.4%), deep venous thrombosis (1.5%), and hematological toxicity (7.2%). Of all patients, 308 (14.3%) had to be reoperated due to a complication. The causes of reoperation were fascial dehiscence, hemorrhage,

anastomotic leak, bile leak, surgical site infection, planned second look, small bowel leak, pancreatitis/pancreatic fistula, prolonged ileus, peritonitis, hemothorax or pleural empyema, knee empyema, ureteral leak, gastric perforation, gastric ulcer, and cecal perforation.

Fifty patients (2.3%) died because of treatment-related complications, such as infection (22%), pneumonia (14%), renal failure (2%), pulmonary embolism (2%), tumor-related complications (14%), and other postoperative complications that were not further assessed (46%). Among the 50 patients who died due to complications, 30 were reoperated, representing 9.7% of all reoperated patients. The correlation between reoperation rate and death was statistically significant ($p < 0.001$).

In 778 patients (36.2%), no anastomosis was performed during CRS. A single anastomosis was performed in 811 patients (37.7%), two anastomoses were performed in 425 patients (19.8%), three anastomoses were performed in 96 patients (4.5%), four anastomoses were performed in 32 patients (1.5%), five anastomoses were performed in six patients (0.3%), and one patient received (0.05%) six anastomoses. A total of 1236 patients (57.5%) received platinum-based intraperitoneal chemotherapy, while 913 patients (42.5%) received mitomycin C as intraperitoneal chemotherapy. For 1148 patients (53.4%), surgery lasted longer than 6 h. Four hundred ileostomies (18.61%) and 154 colostomies (7.16%) were performed, of which 86 (21.5%) were permanent ileostomies and 88 (57.14%) were permanent colostomies.

Multivariate analysis using a logistic regression model was performed to determine which procedures or clinical variables correlated with the presence of grade III/IV morbidity, mortality, and the experience of the center (more or less than 100 treated patients). The results are presented in Tables 3, 4 and 5. In Fig. 1, we delineated the number of complications and the mortality rate with case volume.

DISCUSSION

In Germany, first CRS with HIPEC activities started in the late 1990's, with safety data being published in 1997, followed by the first report on long-term results for appendiceal carcinoma in 2001.^{11,12} Four years later, the Peritoneal Surface Oncology Group (Organgruppe Peritoneum) was established as one of the oncologic groups within the German Society for General and Visceral Surgery, with a focus on peritoneal surface malignancies.¹³ The Peritoneal Surface Oncology Group has coordinated all activities related to HIPEC, including proctoring and mentoring new centers. Due to the increasing use of these protocols across the country, the German StuDoQ-HIPEC

TABLE 2 Distribution of parietal and visceral procedures

Characteristic	N (%)
	(N = 2149)
Parietal peritonectomy and omentectomy	1431 (66.6)
Colon resection	1157 (53.8)
Anterior resection of the rectum	661 (30.8)
Splenectomy	432 (20.1)
Pancreatic resection	114 (5.3)
Gastrectomy	259 (12.1)
Hysterectomy	342 (15.9)

TABLE 3 Multivariate regression analysis for morbidity

	aOR	95% CI	<i>p</i> value
Pancreatic resection	2.4	1.55–3.66	< 0.001
Anterior resection of the rectum	1.56	1.22–1.99	< 0.001
Gastrectomy	1.17	0.8–1.7	0.407
Preoperative chemotherapy	0.92	0.73–1.17	0.497
Mitomycin versus platinum derivatives	1.08	0.82–1.42	0.585
More than 100 patients/center	0.78	0.62–0.98	0.032
History of operations	0.95	0.74–1.22	0.686
At least one anastomosis	1.35	1.04–1.75	0.022
Age > 70 years	1.03	0.76–1.38	0.844
Sex	1.1	0.87–1.38	0.435
HIPEC < 60 min versus > 60 min	1.24	0.89–1.72	0.207
Colorectal anastomosis	1.09	0.84–1.41	0.531
Mucinosi histopathology	0.82	0.62–1.06	0.131
Signet ring cell histopathology	0.48	0.29–0.78	0.004
G3 histopathology	0.98	0.75–1.27	0.86

Bolded data are of particular relevance for the clinical practice

aOR adjusted odds ratio, CI confidence interval, HIPEC hyperthermic intraperitoneal chemotherapy

TABLE 4 Multivariate regression analysis for mortality

	aOR	95% CI	<i>p</i> value
Pancreatic resection	2.14	0.85–4.91	0.087
Low anterior resection	1.67	0.84–3.26	0.14
Gastrectomy	1.72	0.7–3.98	0.219
Chemotherapy (yes vs. no)	0.74	0.38–1.42	0.362
Mitomycin versus platinum derivatives	0.78	0.38–1.63	0.511
Patients per center ≥ 100	0.48	0.25–0.89	0.021
Previous surgery	1.84	0.93–3.8	0.086
More than one anastomosis	0.84	0.4–1.71	0.641
Age ≥ 70 years	3.31	1.71–6.29	0.001
Sex (male vs. female)	0.49	0.26–0.91	0.026
HIPEC, min (≥ 60 vs. < 60)	0.74	0.33–1.76	0.489
Reoperation	8.69	4.75–16.21	0.001

Bolded data are of particular relevance for the clinical practice

aOR adjusted odds ratio, CI confidence interval, HIPEC hyperthermic intraperitoneal chemotherapy

Register was initiated to monitor short- and long-term results. The aim was to collect data of all patients treated by CRS and HIPEC in Germany. Nevertheless, participation was not mandatory. More than 50 hospitals entered their data into the registry, operated by an independent administrator. Up to 2016, data from 3000 patients have been documented. To our knowledge, this is the largest national register addressing CRS and HIPEC.

As expected, the main indications for CRS and HIPEC were colorectal malignancies, reported in approximately two-thirds of all patients, consistent with other data from the literature.¹⁴ The most frequently performed peritonectomy procedures were colectomies (in more than half of the patients), and anterior rectal resections (in one-third of all patients). This resulted in a high number of anastomoses: two-thirds of patients received at least one anastomosis, of whom more than half received at least one additional anastomosis. The incidence of 6% for anastomotic leakages is similar to that previously reported.^{3–6,15} In particular, the presence of a rectal anastomosis was an independent prognostic factor in the multivariate analysis of our series (OR 1.5). However, pancreatic resections had the greatest impact on morbidity, with an OR of 2.4. This has also been reported by other groups, however pancreatic resections had no significant impact on postoperative mortality.^{16–18} Nevertheless, pancreatic resections were seldom necessary, being performed in just 5% of all patients. Different to previous data from other countries, gastrectomy was, in the case of CRS and HIPEC, not associated with increased morbidity and mortality, which is in line with other reports from Germany.¹⁹

Non-surgical grade III/IV complications included pulmonary embolism (3.4%), deep venous thrombosis (1.5%), and hematological toxicity (7.2%), in the range of previously published results,^{3,8} suggesting that HIPEC does not significantly increase the risk of bone marrow toxicity or nephrotoxicity.

Looking at the multivariate analysis of mortality data, reoperation was the most relevant independent factor to influence mortality, with an OR of 8.74. This indicates that major surgical complications needing a redo procedure are associated with significantly higher mortality. The second most relevant parameter was age > 70 years. For these patients, the OR was 3.34, which is also consistent with other reported data. Nevertheless, the overall mortality was in line with reports from high-volume centers, with reported mortality rates of approximately 2%.^{20–22}

Interestingly, the mortality figures were not high but did differ significantly between centers, having performed more or less than 100 operations including HIPEC. Although patients treated in experienced centers had more oncological pretreatment, more rectal resections, and more bone marrow toxicity, the mortality was significantly lower, suggesting reduced failure to rescue as the rate of reoperations did not differ. This may also be related to the significant lower digestive fistula rate in the more experienced centers. However, neutropenia was more common in these centers due to heavily pretreated patients who were submitted to surgery.

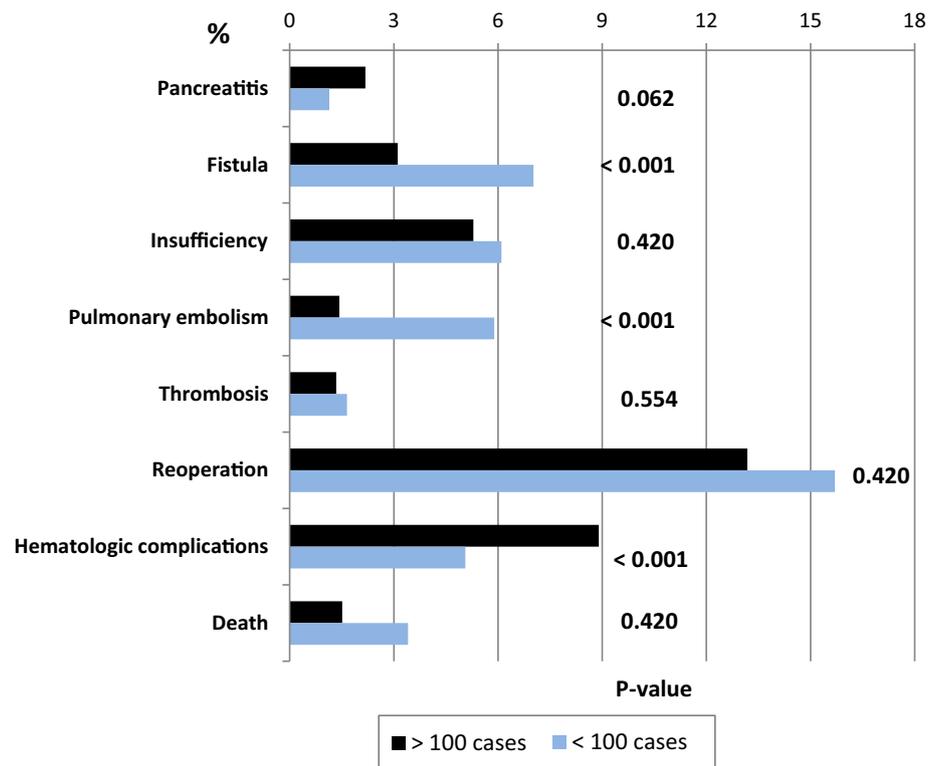
The mortality rate of 3.4% in centers with < 100 procedures is low relative to an aggressive treatment strategy.

TABLE 5 Multivariate regression analysis to compare centers with less or more than 100 treated patients

Parameter	> 100 cases [n = 1191] (%)	< 100 cases [n = 967] (%)	p value
Sex	481 (40.39)	40 (41.88)	0.482
Anterior rectal resection	396 (35.04)	267 (29.28)	0.006
Pancreatectomy	60 (5.33)	54 (5.96)	0.539
Cholecystectomy	489 (42.48)	431 (47.41)	0.025
Pancreatitis	26 (2.18)	11 (1.14)	0.062
Fistula	37 (3.11)	68 (7.02)	0.001
Anastomotic leakage	63 (5.29)	59 (6.1)	0.42
Pulmonary embolism	17 (1.43)	57 (5.89)	0.001
Deep vein thrombosis	16 (1.34)	16 (1.65)	0.554
Reoperation	157 (13.18)	152 (15.7)	0.096
Bone marrow depression	106 (8.9)	49 (5.06)	0.001
Mortality	18 (1.51)	33 (3.41)	0.004
Age > 70 years	168 (14.11)	186 (19.21)	0.001
Previous cancer surgery	777 (66.24)	606 (67.94)	0.417
Previous chemotherapy	665 (57.78)	453 (52.49)	0.018

Bolded data are of particular relevance for the clinical practice

FIG. 1 Relationship between complications, mortality and case volume



Overall mortality was low in this registry, which included many hospitals. This shows a low failure rate of rescuing patients with complications. A possible explanation could be the adequate proctoring and mentoring of new centers within the Peritoneal Surface Oncology Group members. The high-volume centers are undergoing a certification process performed by the German Society for

General and Visceral Surgery, and are also offering courses of live surgery (demonstrating the procedure on both animals and patients), seminars on perioperative management, patient selection, and treatment of complications, all combined with clinical attachments and proctoring for their first own cases. This is similar to other reports on the learning curve.²³ Nonetheless, the fact that hospital volume

(> 100 patients treated, as recommended by other groups)^{4,24} was an independent predictive factor for low morbidity (OR 0.78) shows that many hospitals were in the learning curve phase during the collection of data in the HIPEC registry.

These figures may be relevant for medical oncologists criticizing the aggressiveness of this concept. The (low) mortality rate is similar to that following systemic chemotherapy combined with targeted agents, e.g. for patients with metastatic colorectal cancer. Systemic chemotherapy is the therapeutic alternative for this group of patients if surgery cannot be performed or does not seem reasonable due to oncological criteria. However, morbidity is as high as it is for other major abdominal surgeries, e.g. Whipple procedure. This is acceptable and suggests that, similar to other oncologic patients with gastrointestinal malignancies, adjuvant systemic chemotherapy can still be performed following surgery.

Due to some bias, a few aspects cannot be definitively answered. First, the documentation of all cases operated in Germany was desirable but not mandatory, albeit all cases operated in certified centers (eight) were documented. Second, data were missing for some variables, and improvement of the quality of the database would have only been possible by using statistical methods. Nevertheless, we considered the risk of basing the analysis on imputed information of a potentially non-representative sample with misleading clinical interpretation as being too high. However, this is a common problem of large databases with many contributors for the data input, as up to 30% of data may be missed.²⁵ Third, these data include the learnings from many low-volume centers; however, we believe that adequate proctoring offered by the German Peritoneal Surface Oncology Group contributed to a shorter learning curve than expected. Fourth, the low mortality data are justified by the accurate patient selection and appropriate indication for CRS and HIPEC. Due to the increased medical awareness, patients are subjected to surgery at an earlier stage of disease, with low tumor burden (and PCI) and less toxicity due to previous oncologic treatment. Fifth, the register does not document patients with CRS without HIPEC, which makes the interpretation of the presented data difficult with respect to the particular impact of HIPEC on postoperative morbidity and mortality.

CONCLUSION

Data from this large national registry demonstrate that CRS and HIPEC are associated with acceptable morbidity and low mortality. CRS and HIPEC can be safely performed nationwide, particularly if close mentoring by experienced centers is provided.

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