ORIGINAL ARTICLE

The Care of Patients With Colon Cancer

Current Treatment, and Evaluation of New Surgical Approaches

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SUMMARY

Background: Multi-center observational studies in surgery can yield important findings, as long as they are appropriately designed and monitored and employ modern methods of statistical analysis.

Methods: In a multi-center quality assurance study carried out in 346 German hospitals from 2000 to 2004, data were collected from a total of 31 055 patients who underwent surgery for colon carcinoma. The current, overall state of medical care for this disease was analyzed, with particular attention to aspects of quality assurance.

Results: 46.7% of the patients were in the advanced, prognostically unfavorable stages UICC III and IV and had an overall 5-year survival of 53.8% in stage III and 9.8% in stage IV. Laparoscopic intention-to-treat procedures were performed on 1401 patients (4.7%), of whom 20.6% required conversion to laparotomy. The patients who required conversion to laparotomy had a worse overall outcome. 28 271 patients were treated with tumor resection and primary anastomosis; in this group, 3% (n = 844) developed an anastomotic leak. Logistic regression analysis identified the following risk factors for anastomotic leakage: duration of surgery, ileus, tumor localization in the left colon, and single-layer suturing.

Conclusion: This multi-center observational study yields valid findings about the epidemiology and overall quality of medical care for colon carcinoma in Germany.

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The importance of contributions made by multi-center observational studies to findings in surgery is now undisputed after many years of controversial discussion (1–4). Many questions about quality assurance aspects of surgical medicine, for example, can only be examined using this type of study as part of clinical health services research. Observational studies are often the means of choice when dealing with the collection of data over longer periods, for example, data about survival rates in oncology (5).

Appropriate study design and monitoring as well as the use of modern biostatistical methods are a prerequisite to prevent biased results in such investigations. Recent reports indicate that observational studies can be carried out under the same exacting and strict standards as randomized controlled studies (3, 4, 6).

Risk stratification is an important basic prerequisite when comparing treatment results in non-selected patient collectives on the basis of registry data. Simple univariate comparison of results for operative mortality, for example, with no consideration of the risk profile can result in misleading statements and is therefore unreliable. It becomes apparent that different scoring systems such as the POSSUM score or the propensity score can be used as practical instruments for risk-adjusted comparison of clinical results as part of benchmarking. Results using these systems are already available from the authors' working group (7).

To ensure external validity and quality of the data, voluntary participation and strictly anonymized handling of the data are important prerequisites. Study monitoring with extensive plausibility tests and checks of the completeness of the data are also very important (2, 12, 13).

The results of these observational studies enable analysis of the current care and management of colon carcinoma, for example, and provide an image of reality. In addition, sufficiently high case numbers from a large number of hospitals with differing profiles can allow for immediate evaluation of surgical techniques. Furthermore, such studies can generate hypotheses that form the basis of planning of randomized studies.

Methods

From 1 January 2000, to 31 December 2004, 31 055 patients who had undergone surgical treatment of colon

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TABLE 1

Distribution of UICC stages during the study

Tumor stage	Entire study n (%)	Study course n (%)				
		2000	2001	2002	2003	2004
UICC 0	414 (1.4)	47 (0.8)	79 (1.3)	107 (1.7)	103 (1.7)	78 (1.3)
UICC I	5487 (18.0)	960 (15.8)	1058 (17.4)	1111 (17.8)	1190 (19.6)	1168 (19.5)
UICC II	9738 (32.0)	1978 (32.6)	1959 (32.2)	1974 (31.6)	1931 (31.7)	1896 (31.7)
UICC III	8711 (26.6)	1791 (29.5)	1774 (29.2)	1815 (29.1)	1681 (27.6)	1650 (27.6)
UICC IV	6122 (20.1)	1297 (21.4)	1215 (20.0)	1239 (19.8)	1179 (19.4)	1192 (19.9)

UICC, Union Internationale Contre le Cancer

Overall survival (probability) of patients with colon carcinoma dependent on tumor stage (n = 17 684)

FIGURE 1

carcinoma were enrolled from 346 German hospitals providing all levels of health care. This was approximately 15% to 20% of all patients who underwent surgery in this period in Germany.

No participating hospital was excluded from the evaluation. As well as capturing perioperative data, a follow-up study with processing of oncological long-term results was carried out up to 31 December 2008. The follow-up rate was 67.6% of all patients who had consented to collection of their follow-up data (n = 17 684).

The data, which were collected using a standardized questionnaire, were analyzed using the statistical program SPSS 12.0. A detailed description of the methodology and of partial results from the entire study have already been published (12, 14, 16, 17, 20). To prevent distortion due to selection bias and confounding effects, any potential confounding of the data was estimated and minimized using analytical strategies such as regression and stratification (8–11). For the

case where there are more than two groups, unifactorial variance analyses (ANOVA) were carried out with a subsequent Tukey multiple comparison test. The overall survival and tumor-free survival were calculated using the Kaplan-Meier method. The survival rates specified are consequently probabilities. Differences in the survival curves were checked for significance using the log-rank test. Potential influencing factors on binary endpoints were examined using logistic regression (Cox regression analysis, Wald statistics). A stepwise forward analysis was used, that is, in the so-called 0th step all covariables were evaluated and in the subsequent forward selection the influencing factors, for anastomotic leakage for example, were determined stepwise.

Results

UICC stages

There was no sustained shift in the distribution of the tumor stages towards prognostically more favorable stages over the course of the study (Table 1). Adjuvant chemotherapy was planned postoperatively for 72.4% (n = 6311) of the patients in UICC stage III (UICC, Union Internationale Contre le Cancer). The 5-year overall survival was determined for advanced tumor stages UICC III and VI as being 53.8% and 9.8%, respectively (Figure 1).

Tumor localization

The analysis revealed differences due to tumor localization in the colon in terms of right colon carcinomas (RCC) versus left colon carcinomas (LCC). Localizations, defined by embryology and blood supply to the bowel sections, affect the biological behavior of the tumors. RCCs were more common in women and with increasing age. RCCs had a higher prevalence of poorly differentiated, locally advanced carcinomas with an admittedly comparable overall probability of developing distant metastases. There were differences in the metastasis pattern (Table 2).

Surgical procedure

The surgical procedure was carried out with a high degree of conformance to guidelines. With a resection

rate of 97.2%, the proportion of radical surgical procedures was 93.5%. Seventy-eight percent of all patients were curatively resected. Primary laparotomy was the standard surgical procedure. Treatment of 4.7% of the patients (n = 1401) was via laparoscopic access with the intent to use a laparoscopically-assisted procedure. For 288 of these patients, it was necessary to switch to an open procedure intraoperatively with a conversion rate of 20.6% (Table 3).

The highly selective mechanism observed meant that the group whose surgery was completed laparoscopically achieved better early postoperative and oncological results compared to the open procedure. Patients in the conversion group had, compared to the open and laparoscopically completed patients, both worse postoperative and worse oncological long-term results (Figure 2). There was also a significant correlation between annual case numbers and the conversion rate. In hospitals carrying out less than 10 procedures this rate was 24.6% compared to 17.1% in hospitals carrying out 10 to 19 laparoscopic procedures per year and 3.6% in hospitals carrying out more than 20 laparoscopic procedures per year.

However, no significant correlation between procedure frequency and early and late results could be found for the entire study of colon carcinoma compared to investigations of rectal carcinoma (15).

Anastomotic leakage

One of the problems that cannot be investigated for ethical or methodological reasons using experimental studies is the question of risk factors for the development of anastomotic leakage (AL) and its effects on perioperative and oncological results. 28 271 colon carcinoma patients underwent tumor resection with primary anastomosis. Postoperative suture leakage occurred in 3% (n = 844) of these cases. Analysis revealed an increase in mortality of a factor of 7.2 compared to patients after colonic resections without leakage (18.6% with AL versus 2.6% without AL) (21). The presence of anastomotic leakage was associated in the present study with a significantly worse oncological long-term course. The probability of 5-year overall survival was significantly lower for patients following anastomotic leakage (51.0% with AL versus 67.3% without AL). The poorer oncological long-term result for patients with anastomotic leakage is not only a consequence of perioperative mortality. The tumor-free

TABLE 2

Differences arising from tumor localization in the colon

Parameter	RCC ¹	LCC ²	p-value
Sex female (%)	55.3	45.9	<0.001
Average age (years)	71	68.5	<0.001
Tumor grade G1/G2	71.4	83	<0.001
Total incidence of synchronous metastases	19.9	20.4	0.409
of which, hepatic metastases	14.9	16.5	0.003
of which, peritoneal carcinoses	5.9	4.9	0.001

¹ right colon carcinoma; ² left colon carcinoma

5-year survival probability in the group with anastomotic leakage was 63.0%, which was significantly lower than in the group without anastomotic leakage (74.6%, p<0.001).

A logistic regression model, which was formed using forward selection, incorporates the risk factors, which are independent of each other, for the development of postoperative anastomotic leakage as listed in Table 4 in the order of their significance. Single-layer suturing is an independent risk factor in the multiple analysis for the development of anastomotic leakage. Of the tumor-related covariables, tumor localization in the left colon is associated with a significantly higher leakage rate. In more advanced tumor stages, there is only a trend towards more leakages but the differences are not significant.

Discussion

The early postoperative and the oncological long-term results for surgical treatment of colon carcinoma can be determined using comprehensive, prospective, multi-center observational studies of evidence level 2b. These data represent the current care and management of these patients in routine clinical practice in Germany. As well as describing important epidemiological aspects, statements can be made about the evaluation of new surgical procedures and the assessment of specific surgical techniques.

TABLE 3

Laparoscopic procedure for colon carcinoma, period 2000 to 2004

Surgical access	Entire study n (%)	Study course n (%)				
		2000	2001	2002	2003	2004
Laparoscopic	1401 (4.5)	184 (3.0)	232 (3.7)	275 (4.3)	305 (4.9)	405 (6.7)
Conversions	288 (20.6)	36 (19.6)	52 (22.4)	64 (23.3)	60 (19.7)	76 (18.8)

Tumor-free survival of open surgery group versus laparoscopic intervention group, with the group whose surgery was completed laparoscopically shown separately from the group with conversion ($p = 0.007$).
From: Kube R et al.: Stellenwert der laparoskopischen Chirurgie des Kolonkarzinoms in der klinischen Routine. Der Chirurg 2008; 79: 1145–50, with kind permission from Springer-Verlag, Heidelberg

FIGURE 2

It must be stated, however, that the colonoscopy screening established during the study period only led to a marginal reduction in advanced tumor stages with reference to UICC stage distribution. Better oncological long-term results can be achieved in the first line, however, by detecting prognostically favorable early stages.

Analysis of the localization of the colon tumor dependent on the topographical location relative to the left colonic flexure (right–left comparison) should be taken into consideration during stratification for clinical studies, particularly for chemotherapy studies. The results also support the requirement for assessment of

the entire colon both during diagnostics and colonoscopy screening (20).

An important finding during the evaluation of the laparoscopic procedure was that patients who were converted intraoperatively from a laparoscopic to an open procedure had worse early postoperative and oncological results (16). The conversion rate, which at 20.6% is too high, must be reduced. This can be achieved by better patient selection and an increase in case numbers for laparoscopic procedures per hospital ($p = 0.021$) (14). This implies, however, meaningful centralization of these procedures. This requirement is supported by evidence of the effect of hospital case volume on the rate of conversion (22).

The statements about anastomotic leakage, a procedure-specific postoperative complication with considerable influence on the overall quality of results, are highly important. Multiple regression analyses were able to identify factors that favor anastomotic leakage. With knowledge of these risk factors surgical techniques and the tactical approach can be specifically changed (18, 19). This yields findings for practical surgery which should not be underestimated. For example, this is relevant for single-layer suturing, which is an independent risk factor in the multiple analysis for the development of anastomotic leakage. In our opinion the identified risk is, however, too low to require double-layer suturing in general. The technical aspects of anastomosis require, however, a high level of attention, particularly during further training. Even if the hospital's internal standard includes single-layer suturing, the double-layer suture technique should also be taught to ensure that surgeons have recourse to this method for appropriate risk constellations. In an emergency situation with ileus in the left colon caused by a carcinoma, primary anastomosis should only be indicated if the accompanying risk profile without simultaneous peritonitis is low and the tumor is easily resectable locally. In case of doubt, with advanced ileus and additional risk factors, decisions should be made knowing that anastomosis itself is a risk factor, which can be actively influenced, for discontinuous resection.

We have been able to identify important early postoperative and oncological long-term results for surgical treatment of colorectal carcinoma on the basis of these comprehensive, prospective, multi-center observational studies (13, 19).

With respect to quality assurance aspects of these investigations as part of clinical health services research, it must be stated that the concepts of voluntary participation and anonymity for all of the participating facilities guarantees the security of the reported data. Once a year the participating hospitals receive an evaluation of the patients they have enrolled compared to the entire study. This yields valid information about the quality of results with reference to the specific facility without the individual department having to fear any restrictions due to the reported data. Instead, based on the results of the study, each hospital is able to determine their own weaknesses and to work on constructively eliminating

TABLE 4

Estimation of the risk of developing anastomotic leakage

Risk factor	Odds ratio	95% confidence interval	p-value
Surgery duration	1.003	1.002–1.004	<0.001
ASA risk score	1.47	1.26–1.72	<0.001
Male sex	1.58	1.37–1.83	<0.001
Ileus	1.9	1.54–2.33	<0.001
Tumor in left colon	1.45	1.28–1.73	<0.001
Cardiovascular diseases	1.35	1.13–1.61	0.0011
Valtrac anastomosis	3.62	1.72–7.60	0.0011
Single-layer manual anastomosis	1.26	1.09–1.46	0.0016
Intraoperative complication	1.56	1.18–2.23	0.0018
Hepatogenic diseases	1.48	1.08–2.04	0.0145
BMI category >30 kg/m ²	1.2	1.01–1.44	0.0366

ASA. American Society of Anesthesiologists

them. Voluntary participation indicates the sincere interest of the participating hospital in benchmarking to improve their own results. Anonymity combined with the use of modern statistical analysis strategies such as regression and stratification are instruments to enable the acquisition of data without selection bias and the confounding variables that skew results.

As a criticism of the methodology it must also be noted, however, that despite extensive plausibility tests, not all question complexes could be completely answered in all cases. An additional potential source of errors is the transfer of the data from the case report forms into the electronic database. In light of the large amount of data collected, incidental errors can be assumed, although a mechanism to check for these errors is missing. It must be noted that among the problems associated with the collection of the long-term results, 13% of the patients declined to consent to collection of follow-up data, for example. Due to the voluntary nature of participation, a definitive statement about whether the data collected are representative for all hospitals in Germany cannot be made.

The present data about quality measurement and transparency derived from health services research could form the basis for fees based on quality, as striven for by health care policy in Germany. The health insurance providers themselves are increasingly uninterested in the flood of dubious certifications but are much more interested in scientifically based, cross-sector quality assurance with ongoing verification of the quality of results (23).

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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KEY MESSAGES

- Data from multi-center quality assurance studies enable statements to be made about comprehensive quality of medical care for colon carcinoma.
- To date, colonoscopy screening has only led to a marginal reduction in advanced tumor stages.
- A correlation between procedure frequency and early and late results could not be demonstrated for colon carcinoma.
- During the evaluation of laparoscopic procedures conversion was identified as a risk for a worse early post-operative and oncological result.
- Anastomotic leakage increases hospital mortality and is associated with a clearly worse oncological long-term course.

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