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ORIGINAL ARTICLE

Ralf Joachim Rieker
Eva Hammer
Roland Eisele
Eberhardt Schmid
Josef Högel

The impact of comorbidity on the overall survival and the cause of death in patients after colorectal cancer resection

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Dedicated to Prof. Dr. Karin Sorger, Department of Pathology, Klinik am Eichert, Göppingen

R.J. Rieker (✉)
Department of Pathology,
Im Neuenheimer Feld 220/221,
University of Heidelberg,
69120 Heidelberg, Germany
e-mail: ralf_rieker@med.uni-heidelberg.de
Tel.: +49-6221-56 2666
Fax: +49-6221-56 5251

E. Hammer
Christophsbad Göppingen,
Faurndauerstrasse 6-28,
73035 Göppingen, Germany

R. Eisele · E. Schmid
Department of Internal Medicine
and Department of Surgery,
Klinik am Eichert, Eichertstrasse 3,
73035 Göppingen, Germany

J. Högel
Department of Biometry
and Medical Documentation,
University of Ulm, Schwabstrasse 13,
89075 Ulm, Germany

Abstract *Background:* Retrospective investigation to identify associations between certain patient characteristics and survival in 531 patients with resected colorectal cancer (CRC). Special reference is given to a standardized comorbidity. *Methods:* To compare different levels of exposure we determined hazard ratios (HR) in Cox proportional hazards models for survival times and odds ratios (OR) in logistic regression models. *Results:* Overall survival was associated with tumor stages (III+IV vs. I+II; HR 7.48), tumor differentiation (low vs. high; HR 1.84), blood transfusions (>2 vs. ≤2; HR 1.88), and comorbidity (Charlson Comorbidity Index >2 vs. ≤2; HR 1.77). Low tumor stage (I+II vs. III+IV; OR 11.1), elevated Charlson Comorbidity Index (>2 vs. ≤2; OR 3.83), and longer ICU stay (>2 days vs. ≤2 days; OR 3.40) more frequently lead to non-cancer-related death than to cancer-related death. *Conclusion:* Standardized comorbidity should be considered as a factor in survival studies of CRC.

Keywords Colorectal cancer · Overall survival · Multivariable analysis · Charlson Comorbidity Index · Noncancer-related death

Introduction

There is general agreement that tumor stage is the most important single factor for death from colorectal carcinoma (CRC). Blood transfusion has been reported to favor cancer recurrence and curtail survival after curative cancer resection [1, 2, 3, 4, 5, 6]. Meta-analyses by Chung et al. [7] and Amato and Pescatori [8] who evaluated 32 of 132 papers on this subject confirmed this suspicion and concluded that the deleterious effect depends on the number of blood units given. On the other hand, several recent studies deny or minimize a detrimental effect of blood transfusion [9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20].

Furthermore, age over 70 or 80 years is considered a risk factor [6]. In survival analyses patients dying from causes other than CRC were considered only in a few studies and their survival times were treated as censored

observations [11, 15, 17, 19]. Especially studies of elderly patients find coexisting illnesses to play a crucial role. Therefore Edna and Bjerhkeset [4] evaluated the American Society of Anesthesiologists' classification as a prognostic marker in patients with CRC. However, to our knowledge no studies with a multivariable statistical approach, i.e., with simultaneous assessment of several possible risk factors for earlier death, have been published on this subject investigating the role of well-defined comorbidity such as the Charlson Comorbidity Index (CCI) [21]. As an isolated factor this score was recently evaluated by Di Marco et al. [22], who found that comorbidity according to the CCI is negatively associated with short-term survival.

Patients and methods

This retrospective study collected data from 531 consecutive patients with resection of CRC between 1 January 1991 and 31 December 1995 at the Klinik am Eichert in Göppingen, Germany (290 men, 241 women; mean age 68 years, range 30–94). The patients for this retrospective study were identified from the surgery files of the Department of Surgery and from files maintained by the hospital administration. Patients who were not resected were excluded from the study. If a patient was operated on for a second time between 1991 and 1995, only the first hospital stay was taken into account for evaluation. Of the 531 patients 137 persons received one or two red blood cell units, 176 received three or more units, and 218 were not exposed to allogeneic blood. Nine patients (1.7%) died after resection during their hospital stay; eight of these nine had been given blood transfusions. Follow-up was carried out until 31 December 1998 (median 38.5 months; first quartile 15.4 months, third quartile 58.9 months). Information from subsequent hospital stays and from the attending practitioners was collected to provide a complete follow-up and to distinguish cancer-related deaths and non-cancer-related deaths,. These data were assessed by an experienced gastroenterologist (E.S.).

Apart from survival times, data on 13 selected characteristics were evaluated (see Table 1 for the frequency distributions; the categories used as reference categories for hazard ratios and odds ratios are italicized):

- Age (>70 vs<*70 years*)
- Sex (male vs. *female*)
- CCI (>2 vs. *0–2*, see Table 2)
- Perioperative blood transfusion (yes vs. *no*)
- Preoperative ileus at hospitalization (yes vs. *no*)
- Bowel perforation at hospitalization (yes vs. *no*)
- Cancer localization (rectum vs. *colon*)
- One-step operation (no vs. *yes*)
- Additional operations (yes vs. *no*)
- UICC tumor stage (III+IV vs. *I+II*) [23]
- Grade (3+4 vs. *1+2*)
- Major postoperative complications either surgical or medical (yes vs. *no*)
- Length of stay in the intensive care unit (>2 vs. *0–2 days*)

Reasons for additional operations were: leakage of the anastomosis, insufficiency of sutures, bleeding, wound infections, abscesses, and surgically treated postoperative ileus. Examples of postoperative complications are: infections including sepsis, cardiac insufficiency, respiratory insufficiency, renal insufficiency, and prolonged neurological distortion. Perioperative blood transfusions included all transfusions before an operation (e.g., bleeding carcinoma), during the operation, and postoperatively given transfusions in cases of prolonged bleeding until additional operations were performed.

Associations between patient characteristics were assessed using contingency tables, odds ratios (ORs), and their 95% confi-

Table 1 Frequency distribution of selected characteristics in 531 patients

	n	%
Age		
>70 years	243	45.8
≤70 years	288	54.2
Sex		
Male	290	54.6
Female	241	45.4
Charlson Comorbidity Index		
0–2	353	66.5
>2	174	32.8
Incomplete data	4	0.7
Cancer localization		
Rectum	338	63.7
Colon	193	36.3
Ileus		
Yes	61	11.5
No	470	88.5
Bowel perforation		
Yes	23	4.3
No	508	95.7
One-step operation		
Yes	54	10.2
No	477	89.8
Additional operations		
Yes	137	25.8
No	394	74.2
Blood transfusions		
Yes	313	59.0
No	218	41.0
Stage		
I and II	257	48.4
III and IV	274	51.6
Grade		
1 and 2	297	55.9
3 and 4	234	44.1
Postoperative complications		
Yes	199	37.5
No	332	62.5
Length of ICU stay		
0–2 days	469	88.3
>2 days	62	11.7

Table 2 Weighted index of comorbidity: weights assigned for each patient condition. The total equals the score

Condition	Assigned weight for disease
Myocardial infarct	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes with end organ damage	2
Any tumor	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
Acquired immunodeficiency syndrome	6

Table 3 Multivariable Cox model (n=527): hazard ratios for overall survival (e.g., patients with a stage of III or IV have a 7.48-fold risk of dying compared with patients in stage I or II)

Variable	Hazard ratio	95% confidence interval
CCI: >2 vs. 0–2	1.77	1.29–2.42
Blood transfusions: yes vs. no	1.88	1.37–2.59
Stage: III or IV vs. I or II	7.48	4.85–11.54
Grade: 3 or 4 vs. 1 or 2	1.84	1.34–2.53

Table 4 Multivariable logistic model for the comparison of CRC-related deaths (n=180) and non-CRC-related deaths (n=83) (e.g., patients with a high comorbidity score have a 3.83-fold risk of dying of a non-CRC-related cause compared with patients with a low comorbidity score)

Variable	Odds ratio	95% confidence interval
CCI: >2 vs. 0–2	3.83	1.98–7.38
Stage: III or IV vs. I or II	0.09	0.04–0.17
ICU stay: >2 vs. 0–2 days	3.40	1.49–7.77

dence intervals (95% CIs). Prognostic factors for the patients' survival were analyzed descriptively using Kaplan-Meier estimates for survival curves in different subgroups of patients (P values given with these estimates relate to log rank tests) [24]. Simultaneous assessment of prognostic factors was performed under the proportional hazards model according to Cox. (The hazard is a measure for a patient's risk of dying. A Cox model computes the ratio of the hazard between patients under a certain exposure and a reference category.) A final prognostic model was selected using a backward elimination of variables from the original set which had shown at least a slight association with overall survival in univariate log rank tests. The impact of the variables in the final model was considered statistically significant, if P<0.05, and quantified by hazard ratios (HR) [25]. Survival times of persons dying of other causes than CRC were regarded as censored observations in the analyses. For the comparison of CRC-related and non-CRC-related deaths logistic regression was performed [26], and ORs were derived. Special attention was paid to interaction between stage and comorbidity.

For the sake of model simplicity and a clearer interpretation of the results patient characteristics are dichotomized (for the categories used as reference categories for HRs and ORs see above). Computations were carried out using the software SAS, program release 8.

Results

Postoperative medical and surgical complications were observed more frequently when at least one blood transfusion was administered (P<0.001, OR=4.59, 95%CI=3.05–6.91). Blood transfusions were more often given in patients aged over 70 years (P<0.002, OR=1.76, 95% CI=1.24–2.50), with CCI higher than 2 (P<0.021, OR=1.56, 95% CI=1.07–2.28), having rectal cancer (P<0.003, OR=1.75, 95% CI=1.21–2.53), in advanced tumor stage (P<0.007, OR=1.62, 95% CI=1.15–2.30), undergoing additional surgical interventions (P<0.063, OR=1.47, 95% CI=0.98–2.20), and staying longer in the intensive care unit (P<0.001, OR=25.61, 95% CI=6.19–106).

CCI was calculated as 0–2 in 66%, 3 or 4 in 25%, and 5 or higher in 8% of the patients (n=527). A comorbidity score greater than 2 was associated with advanced age (P<0.001, OR=2.91, 95% CI=2.00–4.24), at least one blood transfusion administered (P<0.021, OR=1.56, 95% CI=1.07–2.28), postoperative complications (P<0.001, OR=2.18, 95% CI=1.50–3.16), and stay in the intensive care unit for more than 2 days (P<0.001, OR=3.28, 95% CI=1.91–5.64). The proportion of patients surviving was 59% among those with a CCI of 0–2 but only 32% among those with a CCI of 3 or higher (P<0.001).

CRC death occurred in 10% of patients with stage I or II disease, in 35% of those with stage III, and in 82% after palliative resection in stage IV (P<0.001). In stages I and II about twice as many persons died from other causes than from CRC (53 vs. 26). In stages III and IV most patient deaths were due to cancer (158 vs. 30). In a Cox proportional hazards model HRs were determined to quantify the impact of factors associated with death from CRC. Starting with 13 patient characteristics listed above, advanced tumor stages III and IV, low tumor differentiation, blood transfusions and a CCI higher than 2 were associated with increased mortality (Table 3).

Finally, the characteristics were investigated with respect to their capacity to distinguish between death from other causes (n=83) and from CRC (n=184; 4 patients with incomplete data). Tumor localization, preoperative perforation and ileus, age, sex, operations in more than one step or additional surgery, postoperative complications, tumor grade, and blood transfusions showed no independent effect on the cause of death. Death from other

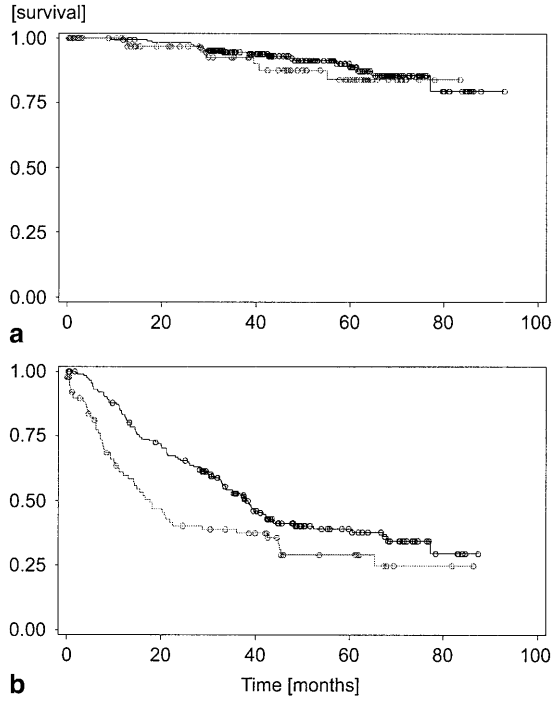

Fig. 1 Survival estimates according to Kaplan and Meier for the two CCI subgroups (*black line* 0–2; *gray line* >2) in UICC stages I and II (**a**) and stages III and IV (**b**). *0* Censored data

causes appeared more often when the CCI was higher than 2, in tumor stages I and II, and if intensive care stay lasted for more than 2 days (Table 4).

Figure 1 presents the interaction between CCI and stage. These two variables constituted prognostic factors for overall survival and for non-CRC-related death. Kaplan-Meier survival estimates among patients with CRC showed no differences in UICC stages I and II between different levels of CCI (log rank $P>0.63$, Fig. 1a). In stages III and IV, however, patients with higher CCI died earlier than those with a CCI of 0–2 (log rank $P<0.005$, Fig. 1b).

Discussion

Between 40% and more than 80% of patients with resected CRC receive blood transfusions [7, 27]. The study by Burrows and Tarter [3] in 1982 led to many publications about the deleterious effects of perioperative blood transfusion and CRC. The results of these studies, however, are conflicting. Samples of patients in some reports are too small to avoid a large type II error, or they neglect possible covariates. Recent studies using multivariable statistical methods with an adequate number of patients [11, 12, 15, 16, 20], not evaluated in the latest meta-analysis [8], showed no deleterious or only a minimal negative effect of blood transfusions after elimination of confounding factors.

Immunomodulation by perioperative blood or blood products has been discussed as a causal mechanism for earlier relapses and/or poorer survival. Hermanek et al. [27] and Marsh et al. [28] have pointed out that plasma proteins in full blood or fresh-frozen plasma, not erythrocytes, are responsible. This conclusion has been challenged by both Modin et al. [14] and Nathanson et al. [29]. Autologous blood was tolerated better than allogenic blood in the study by Heiss et al. [30]. The prospective multicenter study by Busch and coworkers [31] found no difference between the two types of blood, but nontransfused patients had a better prognosis. A similar finding was published by Houbiers [32]: nontransfused subjects fared better with regard to survival than transfused subjects either who received buffy-coat free or leukocyte-reduced blood units. However, patients with cancer of the rectum, especially cancer requiring an abdominoperineal resection [29], are at greater risk of receiving transfusions. This has been confirmed especially in advanced stages [16] by several authors [5, 9, 10, 11, 12, 14, 19, 20, 32, 33]. Experience of the surgeon and mobilization of the tumor are of additional importance. After including other known prognostic variables in the analysis the factor of blood transfusion loses its statistical significance in the effect on survival rates. Bentzen et al. [34] therefore call it a "proxy variable." In our study blood transfusions, together with stage, grade, and comorbidity, had a major impact on overall survival, when comparing patients with two or fewer and more than two transfusions administered. On the other hand, they were closely associated with advanced age, advanced tumor stage, additional surgical intervention, and in rectal cancer. Thus in our study a final conclusion cannot be reached as to whether blood transfusions are a proxy variable. However, in our opinion, transfusions should be restricted, as several studies indicate a causal relationship.

Only some authors [11, 17, 19] have considered death from other causes as an important feature. Molland et al. [15] regards generally poor condition of the patient at the time of surgery an eminent risk factor. The study by Edna and Bjerhkeset [4] found age and American Society of Anesthesiologists classification but not blood transfusion to be associated with non-cancer-associated death. Our comparison of CRC-related deaths and deaths from other causes showed different distributions of CCI, tumor stage, and length of intensive care stay.

The prognostic power of standardized comorbidity has not yet been evaluated in multivariable analyses in CRC. In our series it was a crucial factor when considering overall survival and the cause of death. Together with tumor stage, with which it was closely associated, it had remarkably strong prognostic importance. Comorbidity therefore should be included among the possible prognostic factors in multivariable models for survival in studies using a standardized index [35].

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