Associations Between Blood Cultures After Surgery for Colorectal Cancer and Long-Term Oncological Outcomes

Watt, S K; Fransgaard, T; Degett, T H; Thygesen, L C; Benfield, T; Knudsen, J D; Fuursted, K; Jensen, T G; Dessau, R B; Schønheyder, H C; Møller, J K; Gögenur, I

Published in:
British Journal of Surgery

DOI (link to publication from Publisher):
10.1002/bjs.11372

Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

Watt Sara (Orcid ID: 0000-0001-9162-1678)

Title page

Title: Associations between blood cultures after surgery for colorectal cancer and long-term oncological outcomes.

Short running head: Blood cultures after colorectal cancer surgery.

Authors: *Sara Kehlet Watt MD,[1] Tina Fransgaard PhD,[1] Thea Helene Degett MD,[1] Lau Caspar Thygesen PhD,[2] Thomas Benfield DMsc,[3] Jenny Dahl Knudsen DMsc,[4] Kurt Fuursted DMsc,[5] Thøger Gorm Jensen PhD,[6] Ram Benny Dessau PhD,[7] Henrik Carl Schønheyder DMsc[8] Jens Kjølseth Møller DMsc,[9] and Ismail Gögenur DMsc,[1]*

1. Zealand University Hospital Køge/Roskilde, Department of Surgery, Lykkebækvej 1, 4600 Køge, Denmark.
2. National Institute of Public Health, University of Southern Denmark, Studiestræde 6, 1455 Copenhagen K, Denmark.
3. Copenhagen University Hospital, Amager/Hvidovre, Department of Infectious Diseases, Kettegård Allé 30, 2650 Hvidovre, Denmark.
4. Copenhagen University Hospital Hvidovre, Department of Clinical Microbiology, Kettegård Allé 30, 2650 Hvidovre, Denmark.
5. Statens Serum Institut, Department of Bacteria, Parasites and Fungi. Artillerivej 5, 2300 Copenhagen S, Denmark
6. Odense University Hospital, Department of Clinical Microbiology, J. B. Winsloews Vej 21,2 5000 Odense C, Denmark

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/bjs.11372

7. Slagelse Hospital, Department of Clinical Microbiology, Ingemannsvej 46,st. 4200 Slagelse, Denmark
8. Aalborg University Hospital, Department of Clinical Microbiology, Hobrovej 18-22, 9100 Aalborg C
9. Lillebaelt Hospital, Department of Clinical Microbiology, Beriderbakken 4, 7100 Vejle, Denmark

Corresponding author:

Sara Kehlet Watt

Zealand University Hospital, Department of Surgery

Lykkebækvej 1, 4600 Køge

Denmark.

E-mail*:* sakw@regionsjaelland.dk

Phone*: +45 22471921*

Sources of Funding

The work has been supported by a grant from the Novo Nordisk PROCRIN-foundation. The foundation had no influence on the design or conduct of the study, collection, management, analysis or interpretation of the data or preparation, review or approval of the manuscript.

Category for submission: Original article

Keywords: Colorectal cancer; recurrence; inflammation;

Abstract

Background

Systemic inflammation for colorectal cancer may be associated with increased risk of recurrence. This study investigated whether a clinically suspected infection in which blood cultures were sent within 30 days after surgery for colorectal cancer was associated with long-term oncological outcomes.

Method

The study was a register-based national cohort study including all Danish residents undergoing curatively intended surgery for colorectal cancer between January 2003 and December 2013. Patients with recurrence or death within 180 days after surgery were not included. Associations between blood cultures taken within 30 days after primary surgery and overall survival, disease-free survival and recurrence-free survival was estimated by Cox regression models adjusted for relevant clinical confounders (including demographic data, cancer stage, comorbidity, blood transfusion, postoperative complications and adjuvant chemotherapy).

Results

The study included 21,349 patients of whom 3,390 (16%) had blood cultures taken within 30 days after surgery. Median follow-up was 5.6 years. Patients who had blood cultures taken had increased risk of all-cause mortality (HR 1.27; 95% CI 1.20-1.35; $p<0.0001$), poorer

disease-free survival (1.22; 1.16-1.29; $p<0.0001$), and higher risk of recurrence (1.15; 1.07-1.23; $p<0.0001$) than patients that did not have blood cultures taken.

Conclusions

A clinically suspected infection requiring blood cultures within 30 days of surgery for colorectal cancer was associated with poorer oncological outcomes.

INTRODUCTION

Tumour development and recurrence depend on multiple interactions between tumour and host.[1] To metastasize, cancer cells undergo epithelial to mesenchymal transition, immune evasion, and tissue invasion[2]. These events are central elements of the surgical stress response and believed to be important for the initiation of the postoperative metastatic process, which may be accelerated by inflammation.[3–5]

Blood cultures obtained in the postoperative period is a common event, performed when there is a clinical suspicion of bloodstream infection following symptoms such as fever, tachycardia or hypotension. The objective of this study was to investigate whether clinical suspicion of a bloodstream infection, defined by blood cultures taken within 30 days after surgery for colorectal cancer (CRC), was associated with a higher risk of all-cause mortality, disease-free survival or cancer recurrence.

MATERIALS AND METHODS

Study cohort

Patients who had surgery for CRC with a curative intent between January 2003 and December 2013 in Denmark were included through the Danish Colorectal Cancer Group (DCCG) national clinical register.[6] Patients who died, had a recurrence or a new cancer diagnosis within 180 days after surgery were not included. From DCCG demographic data and information regarding type of cancer, surgery, and operative and postoperative details were obtained. Complications were grouped in infectious complications including anastomotic leakage, abscess formation, pneumonia, and sepsis and non-infectious complications including bleeding, ileus, embolism, myocardial infarction, cerebral apoplexy, deep venous thrombosis, heart failure, respiratory insufficiency, kidney insufficiency, and wound dehiscence.

Blood cultures showing growth of gram positive and negative bacteria or fungi were regarded as true bloodstream infection except for the skin commensals: coagulase-negative staphylococci, Propionibacterium, Bacillus, Micrococcus or Corynebacterium species, which were regarded as contamination. Any positive blood culture within 30 days after surgery was combined as one culture positive episode for the statistical analysis.

Data collection

Danish residents have a unique personal identifier that enables linkage of data between registries[7,8] The National Patient Register (NPR) records all visits to hospitals, and from here, information on hospital admissions, discharges, outpatient visits, procedure codes, diagnostic codes and Charlson Comorbidity Index (CCI) grouped in 3 levels: 1, 2 and 3+, was obtained.[9]

The Danish microbiology database (MiBa) records laboratory reports from all department of clinical microbiology beginning in 2010.[10] Information on blood cultures prior to 2010 were obtained directly from each individual department of clinical microbiology. Due to difficulties extracting data from two departments (2003-2006 for one site and 2003-2009 for the other), all patients who had colorectal cancer surgery at these two hospitals were excluded from the study for the specified period.

Data on pathological specimens are coded by clinical pathologists using the Danish version of the Systemized Nomenclature of Pathology (SNOMED) and recorded in the Danish Pathology Registry.[11] This register provided information regarding pathologically diagnosed cancer recurrence.

Study design

The study was an observational register-based open cohort study, and patients were included on day 180 after surgery. Patients who had a blood culture taken within 30 days after surgery were included in the exposed group, and all other patients were included as unexposed. Recurrence was defined through a validated algorithm using data from NPR and the Danish

Pathology Registry[12] Briefly, the presence of at least one of following four criteria should occur:

1: A metastasis code in NPR occurring at least 180 days after the primary CRC operation and with no new primary cancer in the period between primary surgery and registered metastasis code.

2: A cytostatic code registered in NPR with initiation date more than 180 days after primary CRC surgery, and more than 60 days after last adjuvant cytostatic code, and without a new primary cancer in the period from primary surgery to date of new or first cytostatic therapy code.

3: A SNOMED combination indicating recurrence in NPR within 180 days from primary surgery and with no new cancer registered in the period from primary CRC surgery to day of SNOMED registered recurrence.

4: An NPR-registered code for local CRC recurrence at any time after primary diagnosis.

NPR codes for metastasis and cytostatic treatment did not indicate which primary cancer the codes were related to. Therefore, patients with other primary cancers prior to CRC-surgery were excluded except for a diagnosis of non-melanoma skin cancer.

Overall survival was defined as survival from day 180 after surgery to death by any cause. Patients were censored at end of follow-up, recurrence, or a new primary cancer of any type. Disease-free survival was defined as the time from 180 days after surgery to any of the events: recurrence, new primary cancer or death by any cause, and patients were censored at

end of follow-up. Recurrence-free survival was defined as the period from 180 days after surgery to cancer recurrence, and patients were censored at end of follow-up, new primary cancer or death by any cause.

Statistical methods

Follow-up period with presentation of the non-adjusted overall survival for the two groups was illustrated by Kaplan-Meier curves. A Cox proportional regression model was used to estimate overall survival, disease-free survival and recurrence-free survival. The model was adjusted for age, sex, comorbidity, body mass index (BMI), blood transfusion, smoking habits, alcohol consumption, type of surgery (acute or elective), type of cancer (colon or rectum), T-stage (pathological), N-stage (positive lymph nodes in the resected specimen or not), infectious and non-infectious post-operative complications, and time to chemo- or radiotherapy (estimated as therapy initiated within four weeks, between four and eight weeks, and eight weeks after CRC surgery). Missing data on BMI, alcohol, smoking, type of surgery, T-stage, N-stage, and complications was handled with multiple imputation with 20 imputed datasets. Imputation was carried out with all variables included. Competing risk analysis for risk of recurrence taking account of mortality was performed using the sub-distribution hazard regression model by Fine and Gray [13]. Results were presented as hazard ratios (HR) with 95% confidence intervals (CI). Statistical analysis was performed using SAS® Proprietary Software 9.4, SAS institute Inc, Cary, NC.

The study was approved by the Danish Data Protection agency (file no: 2008-58-0020) and the report was written according to recommendations in Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE).[14]

RESULTS

The study included 21,349 patients and 3,390 (15.9%) had blood cultures taken. Of these, 561 (16.5%) were positive, and 2,829 (83.5%) were negative (Figure 1). Median follow-up time was 5.6 years (range: 1 day to 13.5 years) (Figure 2).

In the study period, 8,541 patients died, and 6,583 had recurrent disease. In the non-exposed group, this constituted 39.1% who died, and 30.3% who had recurrent disease. In the exposed, 44.8% died and 33.5% had recurrent disease.

In the exposed group, there were more male patients, more who experienced a post-operative complication, had blood transfusions, had a CCI level of 3 or above, had surgery on acute indication, had cancer infiltrated lymph nodes, initiated chemotherapy more than eight weeks after surgery, and had surgery in the late period from 2011 to 2013 (Table 1). All these factors were included in the Cox regression model.

The group of patients who had blood cultures taken had an adjusted HR of 1.27 (95% CI 1.20-1.35 p<0,0001) for higher risk of all-cause mortality. For poorer disease-free survival adjusted HR was 1.22 (1.16-1.29 p<0,0001 and for higher risk of recurrence, adjusted HR was 1.15 (95% CI 1.07-1.23 p<0.0001), compared with the group of patients that did not have blood cultures taken (Table 2).

Sub-distribution HR for competing risks in the analysis of recurrence was 1.11 (p=0.004) which is comparable to the Cox regression model. Repeating the analyses without adjusting for infectious post-operative complications did not change the HR estimates.

In a subgroup analysis of patients who had blood cultures taken, there was no association between positive versus negative blood cultures and risk of recurrence or disease-free survival, but there was a higher risk of all-cause mortality for patients with positive blood cultures (HR: 1.25, 95%CI: 1.10-1.43, p=0.0007).

DISCUSSION

Patients who had blood cultures taken within 30 days after primary CRC surgery had an increased risk of all-cause mortality, poorer disease-free survival and increased risk of cancer recurrence, compared with patients who did not have blood cultures taken. Similarly, previous studies have found that infectious post-operative complications or merely a systemic

inflammatory response after surgery for CRC, increased the risk of early and late mortality and morbidity.[15–17] This study suggests that an excess systemic inflammatory response may be associated with recurrence.

In a subgroup analysis of patients who had blood cultures performed there was a higher risk of all-cause mortality in patients with positive cultures, similar to a previous study that found a high mortality in patients with bacteraemia after elective surgery.[19] There was no association to recurrence or disease-free survival. The subgroup included only 561 patients with positive cultures, thus limiting the statistical power to draw a firm conclusion.

The causal link between postoperative systemic inflammation and increased risk of recurrence, has been demonstrated in ex vivo and animal studies, and associated to both angiogenesis, growth and increased epithelial permeability, all factors promoting the metastatic process in the postoperative period.[20–25]

There are limitations to the study, which must be considered. There were demographical differences between the two groups, and even though many factors known to be related to cancer outcome were adjusted for in the model, unmeasured confounding may still be present. Patients who had neoadjuvant treatment, or comorbidities such as diabetes and steroid dependent patients may be more prone to postoperative infectious complications, and poor long-term cancer outcomes. Though CCI was implemented in the model, a more precise patient stratification was not possible. Furthermore, patients in the exposed group generally had a later postoperative initiation of chemotherapy, which may further worsen the oncological outcome.[26]

The study carries a high external validity as the patients represented an unselected national cohort of patients who had surgery for CRC with curative intent in Denmark from 2003-2013, including national data regarding blood cultures. There was practically no loss to follow-up, due to the completeness of the national registers, and the risk of selection bias was therefore limited.

Acknowledgement

The authors wish to thank The Danish Colorectal Cancer Group and The Danish Microbiology Database for data extraction. Furthermore, we wish to thank the Novo Nordisk PROCRIN foundation for their research grant.

REFERENCES

1 Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002; **420**: 860–867.

2 Thiery JP, Acloque H, Huang RYJ, Nieto MA. Epithelial-Mesenchymal Transitions in Development and Disease. Cell. 2009.

3 Salvans S, Mayol X, Alonso S, Messeguer R, Pascual M, Mojal S, *et al*. Postoperative Peritoneal Infection Enhances Migration and Invasion Capacities of Tumor Cells In Vitro: An Insight Into the Association Between Anastomotic Leak and Recurrence After Surgery for Colorectal Cancer. *Ann Surg* [Internet]. 2014; **260**: 939–944. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25243554

4 Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative events influence cancer recurrence risk after surgery. *Nat Rev Clin Oncol* [Internet]. 2017; **15**: 205–218. Available from: http://www.nature.com/doifinder/10.1038/nrclinonc.2017.194

5 Horowitz M, Neeman E, Sharon E, Ben-eliyahu S. Exploiting the critical perioperative period to improve long-term cancer outcomes. *Nat Publ Gr*. Nature Publishing Group; 2015; **12**: 213–226.

6 Ingeholm P, Gögenur I, Iversen LH. Danish colorectal cancer group database. Clin. Epidemiol. 2016. p. 465–468.

7 Pedersen CB, Gøtzsche H, Møller JØ, Mortensen PB. The Danish Civil Registration System A cohort of eight million persons. *Dan Med Bull*. 2006; **53**: 441–449.

8 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur. J. Epidemiol. 2014. p. 541–549.

9 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* [Internet]. 2011; **39**: 30–33. Available from: http://sjp.sagepub.com/cgi/doi/10.1177/1403494811401482

10 Voldstedlund M, Haarh M, Mølbak K. The danish microbiology database (MIBA) 2010 to 2013. *Eurosurveillance*. 2014; **19**.

11 Erichsen R, Lash TL, Hamilton-Dutoit SJ, Bjerregaard B, Vyberg M, Pedersen L. Existing data sources for clinical epidemiology: The Danish National Pathology Registry and Data Bank. *Clin Epidemiol*. 2010; **2**: 51–56.

12 Lash TL, Riis AH, Ostenfeld EB, Erichsen R, Vyberg M, Thorlacius-Ussing O. A validated algorithm to ascertain colorectal cancer recurrence using registry resources in Denmark. *Int J Cancer*. 2015; **136**: 2210–2215.

13 Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc*. 2099; **94**: 496–509.

14 Vandenbroucke JP, von Elm E, Altman DG, G??tzsche PC, Mulrow CD, Pocock SJ, *et al.* Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *Int J Surg*. 2014; **12**: 1500–1524.

15 Artinyan A, Orcutt ST, Anaya D a, Richardson P, Chen GJ, Berger DH. Infectious Postoperative Complications Decrease Long-term Survival in Patients Undergoing Curative Surgery for Colorectal Cancer: A Study of 12,075 Patients. *Ann Surg* [Internet]. 2015; **263**: 497–505. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25185465

16 McSorley ST, Watt DG, Horgan PG, McMillan DC. Postoperative Systemic Inflammatory Response, Complication Severity, and Survival Following Surgery for Colorectal Cancer. *Ann Surg Oncol* [Internet]. 2016; **23**: 2832–2840. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27016295

17 Watt DG, McSorley ST, Park JH, Horgan PG, McMillan DC. A Postoperative Systemic Inflammation Score Predicts Short- and Long-Term Outcomes in Patients Undergoing Surgery for Colorectal Cancer. *Ann Surg Oncol*. 2017;

18 Nielsen SL, Lassen AT, Gradel KO, Jensen TG, Kolmos HJ, Hallas J, *et al.* Bacteremia is associated with excess long-term mortality: A 12-year population-based cohort study. *J Infect*. 2015;

19 Velasco E, Soares M, Byington R, Martins CAS, Schirmer M, Dias LMC, *et al.* Prospective evaluation of the epidemiology, microbiology, and outcome of bloodstream infections in adult surgical cancer patients. *Eur J Clin Microbiol Infect Dis*. 2004;

20 Salvans S, Mayol X, Alonso S, Messeguer R, Pascual M, Mojal S, *et al.* Postoperative

Peritoneal Infection Enhances Migration and Invasion Capacities of Tumor Cells In Vitro: An Insight Into the Association Between Anastomotic Leak and Recurrence After Surgery for Colorectal Cancer. *Ann Surg*. 2014; **260**: 939–944.

21 Tai LH, Ananth AA, Seth R, Alkayyal A, Zhang J, de Souza CT, *et al.* Sepsis increases perioperative metastases in a murine model. *BMC Cancer*. 2018;

22 Lee WL, Slutsky AS. Sepsis and Endothelial Permeability. *N Engl J Med*. 2010;

23 Bohle B, Pera M, Pascual M, Alonso S, Mayol X, Salvado M, *et al.* Postoperative intra-abdominal infection increases angiogenesis and tumor recurrence after surgical excision of colon cancer in mice. *Surgery*. 2010; **147**: 120–126.

24 Alonso S, Pascual M, Salvans S, Mayol X, Mojal S, Gil MJ, *et al.* Postoperative intra-abdominal infection and colorectal cancer recurrence: A prospective matched cohort study of inflammatory and angiogenic responses as mechanisms involved in this association. *Eur J Surg Oncol*. 2015; **41**: 208–214.

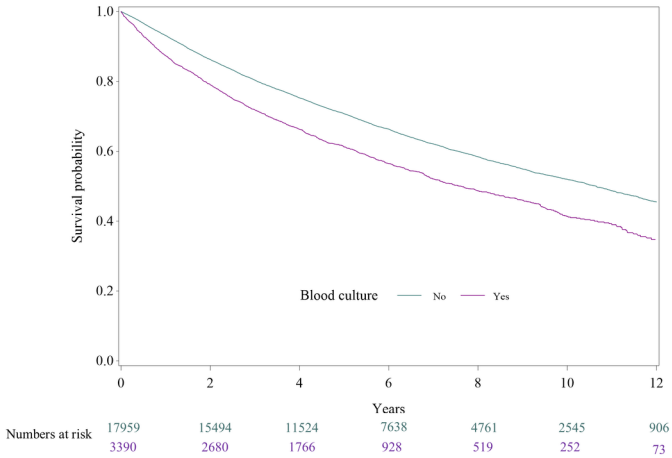
25 Bell SW, Walker KG, Rickard MJFX, Sinclair G, Dent OF, Chapuis PH, *et al.* Anastomotic leakage after curative anterior resection results in a higher prevalence of local recurrence. *Br J Surg*. 2003; **90**: 1261–1266.

26 Klein M, Azaquoun N, Jensen BV, Gögenur I. Improved survival with early adjuvant chemotherapy after colonic resection for stage III colonic cancer: A nationwide study. *J Surg Oncol*. 2015;

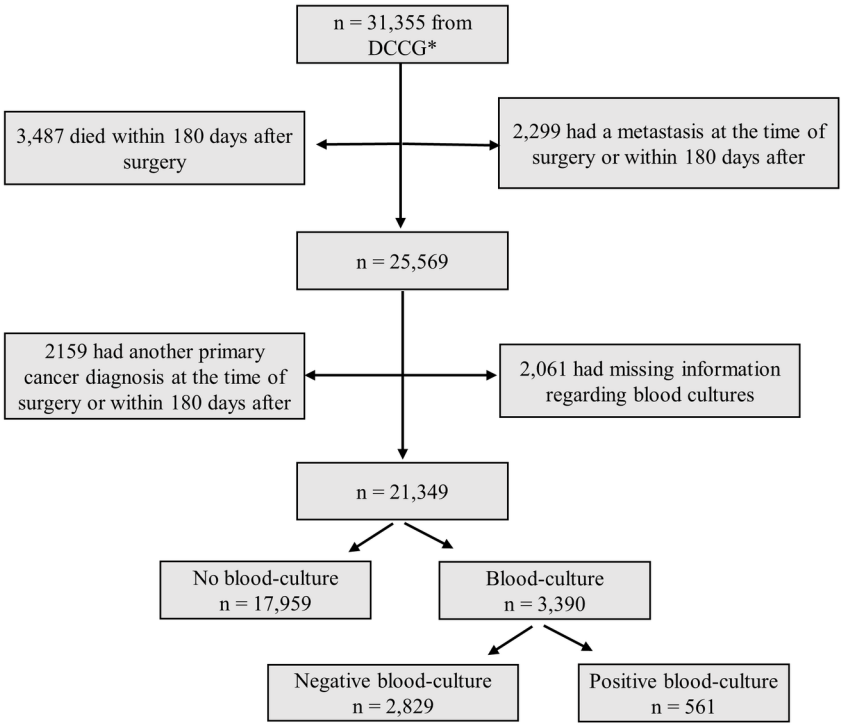
Figure Legend

Figure 1: Flow diagram of study cohort.

Figure 2: Kaplan-Meier curve of unadjusted all-cause mortality for patients undergoing curative surgery for colorectal cancer with initiation year 0 at 180 days after surgery.



BJS_11372_figure 2.tif



* Danish Colorectal Cancer Group. Patients undergoing surgery for colorectal cancer with curative intent between January 1st 2003 and December 31st 2013.

BJS_11372_Figure 1.tif

Table 1: Demographic data in 21,349 patients undergoing colorectal cancer surgery 2003-2013.

		No blood cultures **n = 17959**	**Blood cultures** **n = 3390**
Age, n (%)	<50	835 (4.7)	153 (4.5)
	50-60	2382 (13.3)	445 (13.1)
	60-70	5,169 (28.8)	1,062 (31.3)
	70-80	5,829 (32.5)	1,162 (34.3)
	> 80	3,744 (20.8)	568 (16.8)
Sex, n (%)	Male	9,120 (50.8)	2,111 (62.3)
BMI (kg/m^2), n (%)	<18.5	455 (2.5)	90 (2.6)
	18.5-24	6,613 (36.8)	1,137 (33.5)
	25-30	4,982 (27.7)	1,049 (30.9)
	30-35	1,601 (8.9)	367 (10.8)
	>35	486 (2.7)	134 (3.9)
	Missing information	3,822 (21.3)	613 (18.1)

Smoking, n (%)	Current smoker	2,844 (15.8)	623 (18.4)
	Former smoker	5,912 (32.9)	1,268 (37.4)
	Never smoker	5,225 (29.1)	852 (25.1)
	Missing information	3,978 (22.2)	647 (19.1)
Alcohol, n (%)	0	3,468 (19.3)	625 (18.4)
	1-14	8,065 (44.9)	1,532 (45.2)
	15-21	1,044 (5.8)	251 (7.4)
	>21	1,139 (6.3)	307 (9.1)
	Missing information	4,243 (23.6)	675 (19.9)
Comorbidity n (%)	0	14,124 (78.6)	2,460 (72.6)
	1	2,497 (13.9)	543 (16.0)
	2	879 (4.9)	218 (6.4)
	3	459 (2.6)	169 (5.0)
Cancer type, n (%)	Colon	11,933 (66.4)	2,056 (60.6)
	Rectum	6,026 (33.5)	1,334 (39.3)
Type of surgery, n (%)	Acute	1,265 (7.0)	437 (12.9)
	Elective	16,576 (92.3)	2,916 (86.0)

	Missing information	118 (0.7)	37 (1.1)
T-stage, n (%)	1	1,506 (8.4)	232 (6.8)
	2	2,958 (16.5)	507 (15.0)
	3	10,736 (59.8)	1,997 (58.9)
	4	2,337 (13.0)	589 (17.4)
	Missing information	422 (2.3)	65 (1.9)
Regional lymph node metastasis, n (%)	No	11,202 (62.4)	1,931 (57.0)
	Yes	6,093 (33.9)	1,394 (41.1)
	Missing information	664 (3.7)	65 (1.9)
Non-infectious complications, n (%)	No	17,505 (97.5)	2975 (87.8)
	Yes	352 (2.0)	397 (11.7)
	Missing information	102 (0.6)	18 (0.5)
Blood transfusion, n (%)	No	14,664 (81.6)	2,430 (71.7)
	Yes	2,894 (16.1)	907 (26.8)
	Missing information	401 (2.2)	53 (1.6)

Initiation of chemo- or radiotherapy, n (%)	< 4 weeks	771 (4.3)	103 (3.0)
	4-8 weeks	3,235 (18.0)	675 (19.9)
	> 8 weeks	940 (5.2)	353 (10.4)
	No	13,013 (72.5)	2,259 (66.6)
Year of surgery, n (%)	2003-2006	6,263 (34.9)	865 (25.5)
	2007-2010	6,569 (36.6)	1,139(33.6)
	2011-2013	5,127 (28.6)	1,386 (40.9)

BMI: Body Mass Index

Table 2: Cancer recurrence, disease-free survival and all-cause mortality assessed by Cox proportional regression model in patients who had blood cultures taken within 30 days after primary colorectal cancer surgery, compared to patients that did not.

	HR	95% CI	P	$HR_{adjusted}$*	95% CI	P
Higher risk of recurrence						
No blood-culture	1			1		
Blood-culture	1.30	1.22-1.39	<0.0001	1.15	1.07-1.23	<0.0001
Poorer disease-free survival						
No blood-culture	1			1		
Blood-culture	1.36	1.30-1.43	<0.0001	1.22	1.16-1.29	<0.0001
Higher risk of mortality						
No blood-culture	1			1		
Blood-culture	1.41	1.33-1.49	<0.0001	1.27	1.20-1.35	<0.0001

HR: Hazard Ratio, CI: 95% Confidence Intervals

* Adjusted for age, gender, comorbidity, smoking habits, alcohol consumption, post-operative blood transfusions, type of surgery (acute or elective), BMI, T-stage, lymph node positivity, non-infectious post-operative complications, infectious post-operative complications, year of surgery, and initiation of chemo-/radiotherapy.