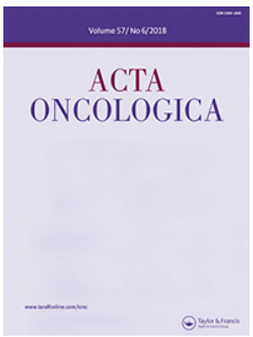

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ORIGINAL ARTICLE

Trends in presentation, treatment and survival of 1777 patients with colorectal cancer over a decade: a Biobank study

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ABSTRACT

Background: Most survival data in colorectal cancer (CRC) is derived from clinical trials or register-based studies. Hospital Biobanks, linked with hospital electronic records, could serve as a data-gathering method based on consecutively collected tumor samples. The aim of this Biobank study was to analyze survival of colorectal patients diagnosed and treated in a single-center university hospital over a period of 12 years, and to evaluate factors contributing to outcome.

Material and methods: A total of 1777 patients with CRC treated during 2001–2012 were identified from the Auria Biobank, Turku, Finland. Longitudinal clinical information was collected from various hospital electronic records and date and cause of death obtained from Statistics Finland.

Results: Cancer-specific, overall and disease-free survival was higher in patients diagnosed during 2004–2008 as compared with patients diagnosed in 2001–2003. Further improvement was not seen during years 2009–2012. Potential factors contributing to the improvement were introduction of multidisciplinary meetings, centralization of rectal cancer surgery, use of adjuvant chemotherapy and systematic preoperative radiotherapy of rectal cancer. The proportion of patients with stage I–IV CRC remained similar over the study period, but a marked decrease in non-metastatic rectal cancer with biopsy only (locally advanced disease) was observed. In stage I–III rectal cancer, Cox multivariate analysis suggested age, comorbidity, R1 resection, T staging and tumor grade as prognostic factors. In colon cancer, prognostic factors were age, comorbidity, gender and presence of lymph node metastases.

Conclusions: Organizational changes in the treatment of CRC patients made since 2004 coincide with improved survival in CRC and a marked reduction in locally advanced rectal cancers. The clinical presentation of CRC has remained similar between 2001 and 2012.

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Introduction

Colorectal cancer (CRC) has an annual incidence of ~45–75/100,000 and rectal cancer accounts approximately for one-third of these cases [1,2]. Controlled quality and centralization of surgery, both in rectal [3,4] and colon cancer [5] and the use of adjuvant chemotherapy [6–8] have improved the survival of patients with CRC. Additionally, in rectal cancer, preoperative radiotherapy or chemoradiotherapy have significantly improved survival [9,10]. Well-known prognostic factors after CRC surgery are age, TNM stage, resection margin, tumor grade and the presence of lymphovascular invasion [11–13]. The amount of dissected lymph nodes should be at least 12 in order to distinguish between stage II and III CRC [2].

Adjuvant chemotherapy is recommended in stage III and stage II high-risk CRC. Stage II CRC is considered a high-risk disease when one of the following high-risk features is present: stage T4, tumor differentiation grade 3, <12 lymph nodes dissected, presence of lymphovascular invasion or tumor obstruction/perforation [1,2]. Intravenous or oral fluoropyrimidine-based compounds, such as fluorouracil/capecitabine remain the backbones of adjuvant chemotherapy. A combination of oxaliplatin with fluorouracil/capecitabine as adjuvant treatment improved both overall survival (OS) and disease-free survival (DFS) in stage III colon cancer during 10 years of follow-up [7,8,14]. By contrast, the addition of oxaliplatin to fluorouracil after chemoradiotherapy resulted only in DFS but not clear OS benefit in a large meta-analytic evaluation and systematic review of patients with stage III rectal cancer [15].

Patients with distant metastases (stage IV) should be evaluated by a multidisciplinary team for their potential to receive a curative resection of their advanced disease. Patients unsuitable for metastasis resection may undergo

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palliative treatments. Currently, chemotherapy is used to treat metastatic CRC in first line, which may be combined with targeted therapy (bevacizumab, panitumumab and cetuximab) [16]. In earlier years, however, cetuximab was recommended only at later lines of treatment [17].

Most of the survival data in CRC is derived from clinical trials or register-based studies. The aim of this study was to evaluate the survival of patients with CRC using a university hospital Biobank as a data-gathering method. The secondary aim was to analyze changes in the clinical presentation of CRC during 2001–2012 and to identify prognostic factors in CRC.

Material and methods

Ethics

Auria Biobank (https://www.auriabiopankki.fi/?lang=en) collects samples and clinical data from patients in the Turku University Hospital district in Finland. The catchment population is ~327,000 people. The Biobank operates in accordance with the Finnish Biobank Act (688/2012) and is licensed by the National Supervisory Authority for Welfare and Health (Valvira). The Biobank obtains clinical data from the operational electronic health record systems of Turku University Hospital. This study was approved by the Scientific Steering Committee of Auria Biobank and research permission was granted by the Institutional Review Board of Turku University Hospital. The study was conducted in accordance with the Declaration of Helsinki. Clinical data was encoded with a study-specific computer-generated code and the identity of the patients was unknown throughout the study.

Study population

Auria Biobank includes all biopsy and surgical samples from tumors of patients diagnosed with CRC in the Turku University Hospital region. All patients with a histologically confirmed diagnosis of adenocarcinoma of the colon or rectum were included in the study. The initial search resulted in 1889 patients diagnosed between 2001 and 2012. Exclusion criteria were non-colorectal adenocarcinoma (four patients with prostate cancer, 15 with gynecological cancer, six with other adenocarcinomas), neuroendocrine carcinoma (three patients), patients referred from other hospitals, i.e., surgery performed elsewhere (78 patients), prior diagnosis of another metastatic malignancy (four patients) or inconsistent data (two patients). The final study cohort included 1777 patients.

Prior to 2004 several hospitals in the Turku region performed CRC surgery, but in 2004 rectal cancer surgery was centralized to Turku University Hospital. Patients were divided into three groups based on year of diagnosis: 2001–2003 (before centralization), 2004–2008 (after centralization) and 2009–2012 (5 years after centralization). Pathology database was used for collection of tumor characteristics, while hospital-based electronic medical records and radiotherapy records were used to collect data on subsequent treatments and patient characteristics. Hospital-based electronic medical records have been linked to biopsy and surgical samples since 2004 and radiotherapy records since 2001. Patients with comorbidities were identified based on the Charlson comorbidity index [18]. Since Auria Biobank includes ICD10 codes given during hospital care only, the index was calculated based on these codes.

All tumor samples were staged by the authors according to the TNM 7th edition classification [19]. Metastatic disease was identified either as: (1) ICD10 code for metastasis; (2) chemotherapy given for metastatic disease including the use of targeted therapy, or chemotherapy with non-adjuvant regimens; (3) palliative radiotherapy; or (4) histological confirmation of liver, lung, ovarian or peritoneal metastasis. Some patients had only a biopsy sample from the primary tumor without confirmation of distant metastases. This 'non-metastatic biopsy-only' category includes patients with inoperable locally advanced tumors, but also those who are unfit for any surgery or with missing ICD10 codes for metastases. Biobank studies cannot specify the true reason for this. Tumors with a 0–1 mm margin (R1 resection) were classified as stage I–III unless the criteria for metastatic disease were met. *RAS* mutation status was obtained from the pathology records. In earlier years, *KRAS* analysis was used, but if the extended *RAS* mutation analysis was also performed on the same patient, the results of extended analysis were used.

Study end-point

The date and cause of death were obtained from the medical records and verified from Statistics Finland, which is an independent national statistical registry. Overall survival (OS) was defined as the period from the date of diagnosis by a pathologist to the date of death or the end of this study in March 2016. Disease-free survival (DFS) was calculated from diagnosis to the first record of metastasis or death. Patients with DFS of less than 3 months were classified as having synchronous metastases. Cancer-specific survival (CSS) was calculated from diagnosis to date of death, where the cause of death was CRC (ICD10 codes C18–C20). OS in stage IV disease was calculated from the date of diagnosis of metastasis to the date of death.

Radiotherapy

Radiotherapy was classified either as preoperative (rectal cancer only), postoperative or palliative based on the given dose and number of fractions, in relation to the date of surgery. The dose was 25 Gy (5×5 Gy) for short-course radiotherapy and 50–50.4 Gy for long course (chemo) radiation. Stage I patients were included in the analyses due to possible downstaging following preoperative treatment, but patients with rectal carcinoma of an adenoma were not.

Adjuvant chemotherapy

Chemotherapy data was available starting from 2004. Adjuvant chemotherapy was classified either as fluoropyrimidine, including intravenous fluorouracil, or oral capecitabine or oxaliplatin combined with fluoropyrimidine. If at least one

Table 1. Demographics and staging of the study population.

	2001–2003	2004–2008	2009–2012	All patients
Patients (*n*)	347	757	673	1777
Age mean (median)	70 (71)	70 (71)	71 (72)	70 (71)
Male	165 (48%)	394 (52%)	355 (53%)	914 (51%)
Female	182 (52%)	363 (48%)	318 (47%)	863 (49%)
Patients with comorbidities[a]	Not available	105 (14%)	141 (21%)	Not available
Primary in colon	229	448	413	1090
Stage I	41 (17%)	81 (18%)	82 (19%)	204 (19%)
Stage II	88 (38%)	147 (32%)	137 (34%)	372 (34%)
Stage III	56 (25%)	115 (26%)	100 (24%)	271 (25%)
Stage IV	41 (18%)	89 (20%)	87 (21%)	217 (20%)
Non-metastatic biopsy-only	3 (1%)	16 (3%)	7 (2%)	26 (2%)
Primary in rectum	118	309	260	687
Stage I	28 (22%)	101 (33%)	80 (31%)	209 (30%)
Stage II	29 (25%)	67 (22%)	62 (24%)	158 (23%)
Stage III	30 (26%)	86 (28%)	81 (31%)	197 (29%)
Stage IV	16 (14%)	31 (10%)	27 (11%)	74 (11%)
Non-metastatic biopsy-only	15 (13%)	24 (8%)	10 (4%)	49 (7%)

[a]Comorbidities were based on the Charlson's comorbidity index requiring hospitalization.

cycle of chemotherapy was given, the patient was considered to have received adjuvant treatment. Similarly, if at least one cycle of oxaliplatin was given, the patient was considered to have received oxaliplatin-based adjuvant therapy. Preoperative chemoradiotherapy was not considered an adjuvant therapy. Patients were divided into two groups based on age 70, which marks the recommendation of the use of oxaliplatin in the adjuvant setting [2,7,8].

Statistics

All statistical analyses were performed with SPSS statistics version 21 (IBM SPSS Statistics, Armonk, NY) software. Between groups 2001–2003, 2004–2008 and 2009–2012, the frequency of categorical covariates such as age group or gender was analyzed using Pearson's chi-square test. OS, DFS and CSS were analyzed with Kaplan–Meier log-rank analysis. Since the last study cohort was from 2009 to 2012 and the study ended in 2016, the survival cutoff was set to 7 years, but occasionally a 10-year cutoff was used to calculate median survival. A cutoff of 5 years was used in metastatic disease. The effect of covariates on survival was analyzed with Cox regression analysis, first one covariate at time, followed by multivariate analysis. In multivariate analysis, the enter method was used with 95% CI. *p* Values of .05 or less were considered significant.

Results

Study population

The demographics of the study population are described in Table 1. Minimum follow-up was 3.3 years and median 8.6 years. The age distribution and male-to-female ratio remained the same, but more cases of rectal cancer were observed during 2004–2012 as compared to 2001–2003 ($p = .009$), reflecting the centralization of rectal cancer surgery in 2004. Hospital-based comorbidities were more frequent in 2009–2012 compared to 2004–2008 ($p = .001$). Patients with colon cancer had more comorbidities (20%) than did patients with rectal cancer (14%, $p = .013$), and colon cancer patients were on average 2 years older ($p = .001$). Identical demographics were observed when analyzing only the subgroup of stage I–III patients.

Since 1953, Finnish Cancer Registry (https://syoparekisteri.fi/) reports comprehensive population-based cancer incidences from the different regions of Finland over time. In comparison to this incidence data, the current Auria Biobank repository contained 78% of colon cancer and 80% of rectal cancer samples from the Turku Region in 2001–2003. Based on this comparison with registry data, the population coverage of colon cancer did not change during our study, but from 2004 onwards 94–99% of rectal cancer samples were included in the Auria Biobank highlighting the improved coverage due to centralization of treatment. The remaining patients were operated in smaller regional hospitals in the Turku region, and were not included in the Auria Biobank.

To validate the cancer-specific survival data of Auria Biobank, the cause of death was obtained from Statistics Finland. The cause of death was CRC in 594 of 1777 (33%) patients. Based on Auria data, 291 patients presented with stage IV and 75 with CRC that was not operated either due to locally advanced disease or patient-related factors. These patients are referred to have 'biopsy-only non-metastatic' disease. A total of 221 patients with stage I–III disease later progressed to stage IV disease. Thus, we found from Biobank a total of 587 patients having probably lethal disease, which was in close agreement with 594 deaths in CRC from records of Statistics Finland.

Tumor staging

The distribution of stage I–IV CRC remained essentially the same throughout 2001–2012, but a decrease in non-metastatic biopsy-only rectal tumors was observed over study period ($p = .007$, Table 1). No differences in T or N staging were observed between 2001 and 2012. Grade 3 rectal cancer was observed in 12–15% of patients during 2001–2008 and in 26% during 2009–2012 ($p = .001$, Supplementary Table 1). The average number of lymph nodes dissected increased in

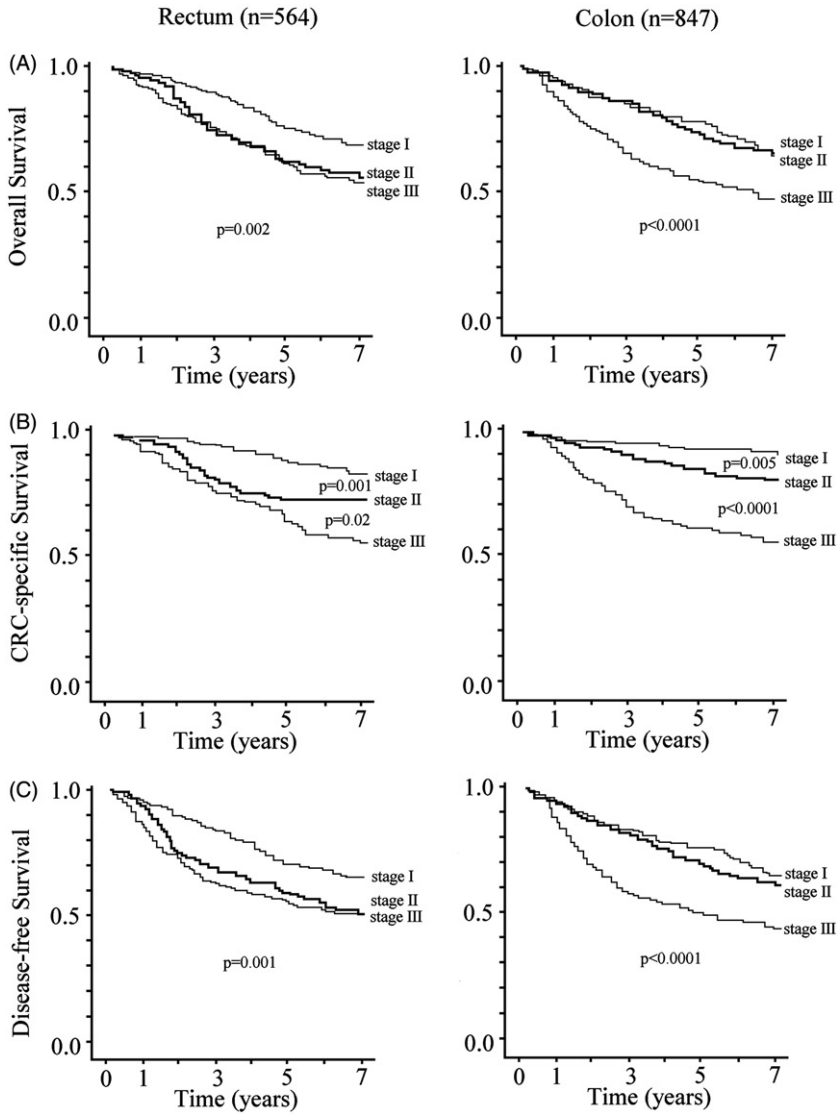

Figure 1. Kaplan–Meier analysis of 7-year survival based on the disease stage; stage I (upper line), stage II (middle bold line) and stage III (lower line) in patients diagnosed during years 2001–2012. (A) Overall survival. (B) Colorectal cancer-specific survival. (C) Disease-free survival.

both colon and rectal cancer steadily during the whole study period ($p < .0001$, Supplementary Table 1), while the average number of metastatic lymph nodes remained the same. Consequently, the number of patients with <12 lymph nodes dissected decreased ($p < .0001$). The proportion of emergency operations of rectal primary tumors fell from 5% in 2001–2003 to <1% in 2004–2012 ($p = .02$).

Survival in stage I–III colorectal cancer

In colon cancer, survival in stage II disease was close to that in stage I, while in rectal cancer survival in stage II was close to that in stage III (Figure 1). A major increase in OS and CSS was observed from 2004 onwards both in rectal and colon cancers (Figure 2(A,B)). DFS in colon cancer started to improve in 2004–2008 as compared to 2001–2003 (Figure 2(C)). A similar trend was seen in rectal cancer but the change remained non-significant. During the study period, a total of 221 patients from the 1411 patients with stage I–III disease (15%) progressed to stage IV disease. Most of the recurrences occurred during the first 3 years (Table 2).

Clinicopathological factors and survival

Analysis of the factors associating with OS was performed for colon and rectal cancer separately (Table 3). The T stage was an independent predictor of OS in rectal cancer ($p = .03$), which was unlike that of colon cancer, where the N staging was a significant covariate ($p < .0001$) while T staging was not. No difference in survival was observed between patients with T4a and T4b tumors.

All colon cancer tumors were classified according to their location either as right-sided (C18.0–C18.4) or left-sided (C18.5–C18.7) tumors. No differences in the distribution of these groups were observed between the three study periods. In stage I–III colon cancer, patients with left-sided primary tumors had a longer OS ($p = .03$). Specifically, in stage III disease the median OS was 3.5 years for patients with

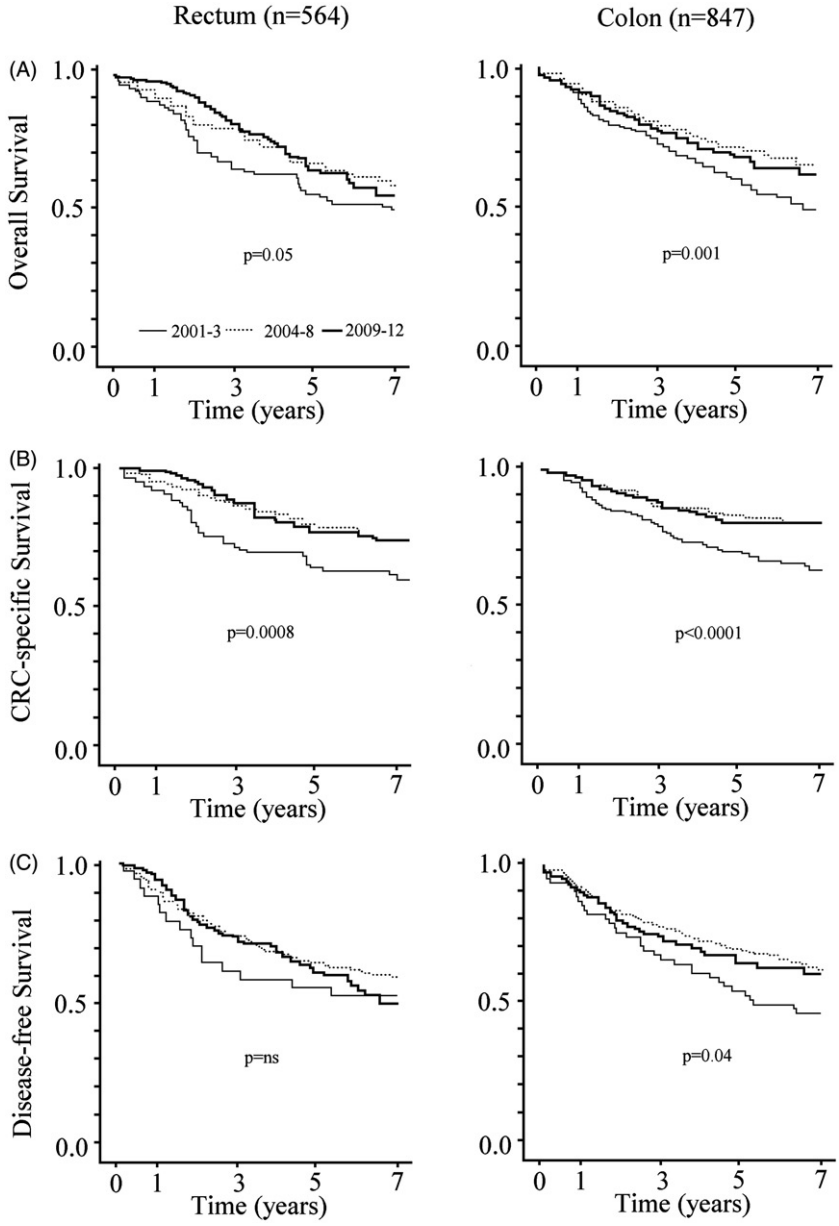

Figure 2. Kaplan–Meier analysis of 7-year survival in stage I–III colorectal cancer based on the year of diagnosis. (A) Overall survival of patients diagnosed in 2001–2003, 2004–2008 and 2009–2012. (B) Colorectal cancer-specific survival. (C) Disease-free survival. The *p* values mark the difference in survival between 2001–2003 and 2004–2008.

right-sided tumors compared to 7.6 years for patients with left-sided tumors ($p = .002$). In stage I or II disease, no differences in OS were observed. It should be noted that the 48 patients who had the primary tumor in the transversal colon (C18.4) had an exceptionally short median OS of 4.7 years.

In 2001–2003, only 20% of patients with stage I–III rectal cancer received preoperative radiotherapy. This increased to 51% in 2004–2012 ($p < .0001$). Correspondingly, the amount of post-operative radiotherapy decreased from 23 to 1% over the same period ($p < .0001$). No change was observed in the ratio of short-course to long-course preoperative radiotherapy.

In stage III CRC patients aged under 70 years, the proportion of patients receiving oxaliplatin-based adjuvant therapy increased from 56 to 70% between 2004–2008 and 2009–2012 ($p = .002$). The proportion of patients who did not receive adjuvant treatment remained at 10–14% and a markedly higher comorbidity index was observed among these patients ($p < .0001$). Their median CSS was 5.1 years, while that of patients who had received adjuvant therapy was not reached ($p < .0001$ both in rectal and colon cancer).

Table 2. Proportion of stage I–III patients who progressed to stage IV disease. The data is sorted based on year of diagnosis, and rectal and colon cancer separately based on the disease stage at the time of diagnosis.

	Patients (*n*)	3-year	5-year	End of study
All stage I–III patients	1411	163 (12%)	192 (13%)	221 (15%)
2001–2003	272	31 (11%)	41 (15%)	51 (19%)
2004–2008	597	62 (10%)	73 (12%)	87 (14%)
2009–2012	542	70 (13%)	78 (14%)	83 (15%)
Rectal cancer				
Stage I	209	14 (8%)	19 (9%)	20 (10%)
Stage II	158	27 (17%)	30 (19%)	33 (21%)
Stage III	197	45 (22%)	52 (26%)	56 (28%)
Colon cancer				
Stage I	204	4 (2%)	5 (2%)	8 (4%)
Stage II	372	22 (5%)	30 (8%)	37 (10%)
Stage III	271	51 (19%)	56 (21%)	66 (24%)

Table 3. Cox multivariate overall survival analysis in stage I–III and stage IV colorectal cancer.

	Colon cancer ($n = 847$) HR (95% CI)	Rectal cancer ($n = 564$) HR (95% CI)	Stage IV cancer ($n = 587$) HR (95% CI)
Age over 70 years	**3.8 (2.5–3.8) $p < .0001$**	**3.0 (2.0–4.4) $p < .0001$**	**2.7 (1.6–4.5) $p < .0001$**
Male gender	**1.7 (1.2–2.4) $p = .03$**	1.1 (0.8–1.6) $p = .6$	1.5 (0.9–2.6) $p = .1$
Comorbidity index >0	**1.8 (1.2–2.7) $p = .001$**	**1.7 (1.1–2.8) $p = .004$**	1.3 (0.7–2.3) $p = .5$
Grade 3 tumor	1.4 (0.9–2.2) $p = .1$	**1.6 (1.1–2.4) $p = .02$**	**2.1 (1.2–3.5) $p = .008$**
T staging 3 or 4	1.1 (0.7–1.8) $p = .7$	**1.6 (1.1–2.4) $p = .03$**	1.1 (0.5–2.4) $p = .7$
N staging >0	**2.0 (1.4–2.9) $p < .0001$**	1.1 (0.8–1.7) $p = .5$	1.5 (0.8–2.8) $p = .2$
Lymphovascular invasion	1.4 (0.9–2.0) $p = .09$	1.2 (1.0–2.0) $p = .07$	1.6 (0.9–2.8) $p = .09$
R1 resection	1.4 (0.3–5.9) $p = .6$	**1.7 (1.1–2.7) $p = .002$**	1.1 (0.5–2.3) $p = .8$
<12 lymph nodes dissected	1.1 (0.8–1.7) $p = .5$	1.2 (0.8–1.8) $p = .1$	1.2 (0.6–2.2) $p = .6$
Bowel obstruction or perforation	1.4 (0.8–2.4) $p = .06$	1.9 (0.2–14.5) $p = .5$	**3.0 (1.5–6.2) $p = .003$**
RAS mutation	–	–	**1.7 (1.1–2.7) $p = .03$**

Significant risk factors appear in bold. HR: hazard ratio; CI: confidence interval.

No difference in CSS was observed between groups receiving fluoropyrimidine or oxaliplatin combined with fluoropyrimidine as an adjuvant therapy.

In stage II high-risk patients aged ≤70 years, 76% had received adjuvant treatment compared with 22% among those aged >70 years. No differences in the usage of adjuvant chemotherapy were observed between 2004 and 2012. A higher comorbidity index was observed in patients who did not receive adjuvant treatment ($p = .04$). CSS was longer in patients who had received adjuvant chemotherapy both in rectal ($p = .02$) and colon cancer ($p = .002$). Median CSS was not reached.

A five-year postoperative follow-up was used in our hospital and no changes in the follow-up routines occurred during the study period. Based on follow-up visits, 80–90% of stage I–III patients operated during 2004–2012 attended follow-up in our hospital.

Survival in stage IV colorectal cancer

No differences in OS of patients with stage IV disease were observed between the three study periods (median OS 18 months), nor in the subgroup of stage IV patients who did not receive chemotherapy (median OS 6 months). This finding was similar in the 320 stage IV patients who had received at least one cycle of chemotherapy (median OS 23 months). The amount of stage IV patients who had received chemotherapy increased from 48 to 67% between 2004–2008 and 2009–2012 ($p < .0001$).

In the 221 patients who progressed to stage IV disease after surgery, the median OS increased from 13 to 23 months between 2001–2008 and 2009–2012 ($p = .02$). Between 2004–2008 and 2009–2012, the proportion of stage IV patients who received targeted therapy (bevacizumab, cetuximab or panitumumab) increased from 26 to 41% ($p = .006$). Cetuximab or panitumumab was rarely used as first-line treatment, but the median OS of patients treated with bevacizumab in the first-line setting was 34 months. The proportion of patients who underwent metastasectomy remained the same (13%) during the study period. It should be noted that a specialized liver surgeon began to work in our hospital starting from year 2012.

In stage IV CRC, age over 70 years, grade 3 tumor, emergency operation of the primary tumor, and presence of *RAS* mutations were identified as negative prognostic factors (Table 3). The presence of synchronous versus metachronous metastases had no effect on OS ($p = .08$). In left-sided stage IV cancer, the median OS was 17 months while that in right-sided cancer was 11 months. This trend was not significant in our patients.

Discussion

During the recent years, several changes in the treatment of CRC have been associated with an improved survival of the patients. These changes include centralized and improved surgery, multidisciplinary teams [3–5], preoperative radiotherapy in rectal cancer [9,10] and more precise adjuvant treatments [6–8]. However, also the regional healthcare systems have changed accordingly, and based on a single clinical trial or study registry, it is challenging to analyze the impact of different changes in the treatment results of CRC. Instead, by combining multiple databases of single hospital district it is easier to analyze these changes *per se*, especially if a single set of databases covers the majority of population of the region. This Biobank study observes the outcomes of CRC during a period of 12 years and analyzes the improved survival in CRC over time. Additionally, the study describes prognostic factors for CRC based on real-life data.

The Finnish Biobank Act allows the scientific use of all pathology samples stored at the Department of Pathology of Turku University Hospital. A minority of patients were diagnosed outside Turku University Hospital due to the marked role of previously less centralized public healthcare, but concurrent with the organizational changes after 2004. Almost every rectal and ~80% of new colon cancer patients were diagnosed in our hospital after 2004. The Finnish electronic medical records system tracks every patient until death, ensuring that no patients in this study were lost during follow-up. The 5-year survival rates in this study are comparable to those in larger studies reported previously [13,20–23].

A major improvement in OS and CSS was observed during period 2004–2008, which coincides with the centralization of rectal cancer surgery from multiple hospitals to Turku University Hospital, and introduction of multidisciplinary CRC teams. DFS did not show a statistical improvement at the time. One reason for this may be the incomplete information of ICD10 codes or contemporary chemotherapy, on which

DFS was based, in 2001–2003. The centralization and multidisciplinary meetings also resulted in a relatively low recurrence risk (Table 2), especially after 3 years of follow-up, as compared to a large meta-analysis [20]. These are results of a single university hospital but may reflect good surgery and extensive use of adjuvant chemotherapy. Other factors potentially contributing to improved OS and CSS include introduction of preoperative rectal cancer radiotherapy in 2004, resulting in a marked decrease of unresectable rectal cancer. The standardized pathology has also yielded in higher number of examined lymph nodes. The results of this study suggest that the clinical presentation of CRC at the time of histological diagnosis remained essentially the same between 2001 and 2012. It should be noted that some rectal cancers may be down-staged following preoperative radiotherapy. Since no stage migration was observed, we estimate that the study cohort is not affected by the possibly earlier detection of CRC in Finland. Of note is that comprehensive screening of CRC was not performed in the Turku region during 2001–2012. Grade 3 rectal cancer became more frequent over time, and represents the pathologist's interpretation of the tumor. The change is most likely related to the updated, and more precise, WHO classification published in 2010.

Comorbidities had an effect on survival, and the finding that colon cancer patients had more comorbidities than those with rectal cancer, is most likely related to patient selection, and to the fact that patients must be fitter for rectal cancer surgery. The selection bias also affects the observed OS in stage IV disease, since outcome of our patients exceeded that observed in population-based studies in the Nordic countries [24]. The retrospective nature of our study and selection bias may also affect our findings in the adjuvant chemotherapy in stage III CRC, where only a slight non-significant CSS benefit was observed in the oxaliplatin combined with fluoropyrimidine-group as compared to the fluoropyrimidine-group.

In this study, the local depth of invasion (T staging) played a marked role in rectal cancer, as compared to colon cancer, where the presence of lymph node metastases was a significant prognostic factor. Half of the patients with rectal cancer had received preoperative radiotherapy, which could have resulted in eradication of lymph node metastases, and, therefore, affecting these results. A poorer prognosis for right-sided than left-sided colon cancer has been shown in stage IV CRC [25], but in stage I–III disease conflicting results are reported [26–28]. Right-sided colon cancer has been associated with poor differentiation grade and T4 stage, but is less likely to be node-positive, than left-sided colon cancer [27]. In this study, only in stage III colon cancer tumor laterality affected OS, but this may be due to the abovementioned discrepancies.

In stage IV CRC, only a limited number of patients had received targeted therapy in the first-line setting, representing contemporary clinical practice. However, 13% of stage IV patients underwent metastasectomy even if targeted therapy was not offered. The OS of stage IV patients with metachronous metastases improved in 2009, at the same time when the use of targeted therapy became more frequent, similar to findings observed elsewhere [29,30]. A more recent study from our hospital suggests higher successful metastasectomy rates once a liver surgeon had started working in our hospital, along with the early use of targeted therapy in stage IV disease [31]. In this study, some patients with stage IV CRC were cured, but due to the low number of patients the impact of metastasectomy on OS of the whole study population remains uncertain.

In conclusion, this Biobank study has decent population coverage and shows a major improvement in survival of CRC patients from 2004 onwards. This coincides with the centralization of rectal cancer surgery, the introduction of multidisciplinary teams, higher number of lymph nodes examined and implementation of preoperative radiotherapy in rectal cancer. The use of adjuvant chemotherapy in stage III CRC also became slightly more frequent. This study also suggests that the clinical presentation of CRC has remained essentially the same between 2001 and 2012.

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Disclosure statement

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