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ORIGINAL ARTICLE

Cumulative incidence of first recurrence after curative treatment of stage I–III colorectal cancer. Competing risk analyses of temporal and anatomic patterns

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ABSTRACT

Background: Updated knowledge about the rates of recurrence and time to recurrence following curative treatment of colorectal cancer is essential to secure better patient information on prognosis, to serve as a premise in the discussion on adjuvant chemotherapy, and help to properly scale the intensity and length of follow-up.

Methods: This is a population-based study investigating aspects on first recurrence after radical treatment of clinical stages I-III of colorectal cancer in Central-Norway during 2001–2015. To reveal any time-trends, data were stratified by the time periods 2001–2005, 2006–2010 and 2011–2015. The cumulative incidence of first recurrence was calculated, treating death of unrelated causes as a competing event. Multivariable Cox analyses were done to calculate cause specific hazard ratios (HR) for risk of recurrence.

Results: At a minimum follow-up of six years, a first recurrence was detected in 1,113/5,556 patients at risk (20.0%). The recurrence rate was reduced from 23.6% in the first time period, through 20.0% in the second, and to 17.2% in the last, $p < 0.001$. The reduction applied to all tumor locations, to pathological disease stages II and III, to both gender, across different tumor differentiations, and to both elective and emergency surgery. In multivariable analyses time period, gender, disease stage, and tumor differentiation were significant determinants for risk of recurrence.

Conclusions: The rate of first recurrence after curative surgery for colorectal cancer was substantially reduced from 2001 to 2015. The reason for the reduction could not be attributed to a single factor only. A combined effect of several incremental improvements, such as an increased use of preoperative radiation for rectal cancers, improved adjuvant chemotherapy for colon cancer, and a reduced proportion of emergency surgery, is suggested.

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Colorectal cancer; population based study; competing risk analysis; first reccurence; stage I–III colorectal cancer

Introduction

For patients with early stage colorectal cancer (CRC) five-year relative survival is above 95%. When tumors involve adjacent structures this declines to 80%, and with stage IV disease to approximately 20% [1,2]. Surgical treatment for metastatic disease may be curative, with liver resections associated with a five-year overall survival of more than 50% in recent studies [3,4]. Synchronous metastases are found in 16–21% of the patients, with liver as the predominant site. Metachronous metastases are found in 19–22% of patients, with 80% detected within three years of the CRC primary [5,6]. Studies based solely on cancer registries have limitations, such as being unable to provide detailed information on individual patients. Others fail to explain how incomplete follow-up was handled and disregard competing risks, i.e. death from other causes, when estimating the cumulative risk of recurrence [7–9]. Updated knowledge on the rate of recurrence, the anatomic site of recurrence, and time to first recurrence following curative treatment of CRC is essential to improve the basis for treatment guidelines and follow-up recommendations. The present study is a large population-based study on recurrence following curative treatment for CRC, clinical stages I-III. The study spanned 15 years, divided into three five-year periods to reveal any time trends. The aims were first, to explore cumulative incidence of first recurrence taking into account competing risk, second, by multivariable analyses to identify factors associated with the risk of recurrence.

Material and methods

This is a population-based study from Central-Norway from 2001 to 2015 with an average catchment area of 680,000

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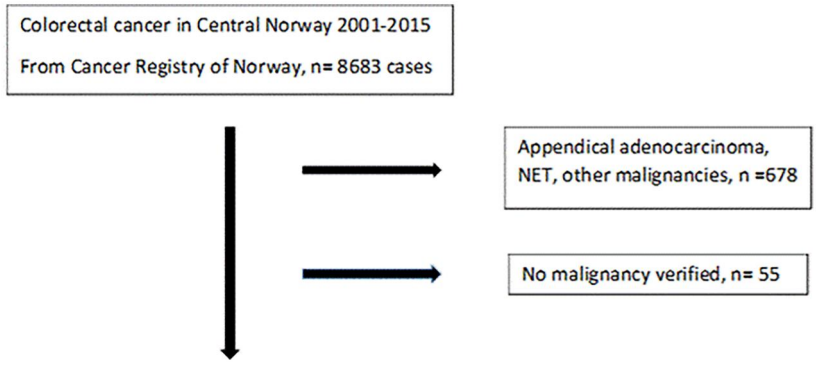
subjects, some 14% of the Norwegian population. Patients diagnosed with clinical or histological cancer are, according to Norwegian legislation, subject to mandatory reporting to the Cancer Registry of Norway (CRN), with a reported compliance close to 99% [10]. A search of the ICD 10 codes C18 (colon cancer), C19 (rectosigmoid cancer), and C20 (rectal cancer) in the CRN database served to identify 8,206 unique patients from January 1, 2001 through December 31, 2015. For patients later experiencing a second/third CRC primary ($n = 453/12$), this was registered accordingly as a new case, adding up to a total of 8,683 cases to be studied. By a detailed search in the individual Electronic Patients' Journals (EPJs) for all patients, entries other than adenocarcinoma of colorectal origin could be excluded. For the remaining patients, all demographic and tumor variables, data on recurrence, and lifetime data were collected from the EPJs exclusively. For patients with two simultanous CRCs ($n = 178$), only the most advanced disease stage was recorded. Synchronous metastases were defined as detected within 30 days of the CRC primary [11]. Patients that died within 90-days of operation or patients too frail for surgery were excluded, leaving $n = 5,556$ cases of radically treated CRC clinical stages I-III to constitute the study cohort (Figure 1).

Completeness of follow-up after radical resection can be divided into three categories. First, 3,312 patients (60%) had a standardized five-year follow-up, declining from 1,078/1,671 (64.5%) in the first period, to 1,132/1,836 (61.7%) in the middle, and 1,102/2,049 (53.8%) in the last, $p < 0.001$. A second group of 1,895 patients (34%) had a non-systematic follow-up. This proportion increased from 475/1,671 (28.4%) during the first period to 584/1,836 (31.8%) during the middle, and 836/2,049 (41.8%) during the last, $p < 0.001$. Patients in this group had CT or MRI scans performed as part of imaging for non-related disease or due to symptoms raising concern for recurrence. For those with no confirmed recurrence, date of death was set as a competing event, otherwise, the patient was censored at the end of study, 31.12.2021. A third group consisted of 349 patients (6%) with a median age of 83 (45–101) years, who had no adequate postoperative imaging done. For these, status on recurrence was unknown; 7.1% during the first time period, 6.5% during the middle, and 5.4% during the last. Date of death was set as a competing event, otherwise, the patient was censored at the end of study. Site of recurrence was recorded with the mutually exclusive categories «liver ± other», «lung ± other», «liver and lung ± other», «retroperitoneal lymph nodes», «peritoneal carcinomatosis», and «other». The latter included locoregional recurrence defined as recurrence in the anastomosis, in the surgical bed of the colorectal primary, or in the area of regional lymphnodes [12–14]. Analyses were stratified by the time periods 2001–2005, 2006–2010 and 2011–2015 to reveal any time trends, and by the variables gender, age-category, CRC-primary location, pathological disease stage, and time to recurrence ($\leq$ 12 months, 12–24 months, 24–36 months and $>$ 36 months). All curves on cumulative incidence of recurrence (CIFs) were stacked on site of recurrence. The study was approved by the Regional Ethics Committee (ref 2018/392 REKnord) and the manuscript prepared in accordance with the STROBE guidelines [15].

Statistics

Continuous variables were summarized by the median (range), and compared using the Kruskal-Wallis test.



	Total	2001-2005	2006-2010	2011-2015
Number of CRC cases	7950	2424	2602	2924
Synchronous metastases	1848 (23.3%)	571 (23.6%)	588 (22.6%)	689 (23.6%)
No radical treatment due to age and fragility	306 (3.9%)	97 (4.0%)	104 (4.0%)	105 (3.6%)
Death within 90 days after treatment of CRC primary	240 (3.0%)	85 (3.5%)	74 (2.8%)	81 (2.8%)
Study population (cases)	5556 (69.9%)	1671 (68.9%)	1836 (70.6%)	2049 (70.1%)

Figure 1. Flowchart identifying the $n = 5,556$ cases at risk of recurrence following radical treatment of colorectal cancer clinical stages I-III during 2001-2015. Stratified by time period.

Categorical data were crosstabulated and analysed by the Pearson chi-square test. Cumulative incidence functions (CIF) were calculated using the Aalen-Johansen estimator [16], treating death as a competing event, and compared using the Gray's test [17]. The effect of this approach, as opposed merely to present the 1-Kaplan-Meier estimate with death as a censored event, is depicted based on the present dataset (Figure S1). Cause specific hazard ratios (HRs) for recurrence were calculated with 95% confidence intervals (CI) using a multivarible Cox proportional hazard model, entering time period, gender, age, tumor location, (yr)pTNM disease stage, and tumor differentiation as covariates. According to recent recommendations [18] we did not test for proportional hazards, but instead advise that the reported HRs should be interpreted as a weighted average of the true hazard ratios over the follow-up period. A p-value of 0.05 was set as threshold for statistical significance.

Results

Patient demographics, tumor characteristics, and (neo)adjuvant treatment

The 5,556 cases at risk of recurrence had a median age of 73.0 years (20–101), with no difference across the time periods, $p = 0.512$. The pattern of the CRC primary location was similar across all time periods, but for the remaining variables statistically significant differences occurred (Table S1). A total of 610/5,556 (11.0%) cases were subjected to emergency surgery, defined as resection within 24 hrs of diagnosis, reduced from 13.9% in the first period, through 10.4% in the middle, and 9.0% in the last, $p < 0.001$. According to national guidelines, patients below 75 years, with UICC stage III or high risk stage II colon cancer (e.g. intraoperative tumor perforation), were offered a six-months period of adjuvant chemotherapy with 5-fluorouracil and folinic acid (FLV) [19] or, since 2006, with the addition of oxaliplatin (FLOX) for patients below 70 years [20]. For disease stage II, 4.5% received adjuvant chemotherapy, reduced from 5.1% during the first period to 2.6% during the last, $p = 0.008$. For disease stage III and age $\leq$ 75 years, 87% started adjuvant chemotherapy in the first time period, 85% in the middle, and 90% in the last period. An increasing proportion received less than half the number of scheduled cycles, i.e. stopped or shifted to a less toxic regimen such as from FLOX to FLV. For the first time period, this amounted to 10.3% of those who started chemotherapy, for the second period 15.7%, and for the third period 21.5%, $p = 0.013$. For rectal cancer, the use of preoperative MRI was not recorded, but practice in Central Norway is reflected in contemporary national numbers, showing a steady increase from less than 10% in 2001 to above 85% in 2006 [21]. No adjuvant treatment was given for rectal cancers, but for patients that received formal resection, 482/1,475 patients (32.7%) received preoperative radiation, with a steady increase from 13.4% during the first time period to 45.2% during the last, $p < 0.001$, in line with the national trend [22]. During the first time period this implied long-course radiochemotherapy with $\geq$ 2 Gy x 25 for 90.8% and 5 Gy x 5 short-course treatment for 9.2%. The corresponding proportion receiving long-course radiochemotherapy in the second period was 98.9% and in the last period 94.9%, $p = 0.011$. Within six years of diagnosis a total of 1,013 cases (18.2%) had died without any known recurrence (competing events), 314/1,671 (18.8%) during the first time period, 333/1,836 (18.1%) during the second, and 366/2,049 (17.9%) during the last, $p = 0.760$.

Cumulative incidence of first recurrence

At a minimum of six years follow-up 1,113/5,556 cases (20.0%) had a first recurrence, with a substantial reduction from 23.6% during the first period, through 20.0% in the second, and 17.2% for the last (Table 1), χ^2 $p < 0.001$, CIF Figure 2, Gray's test $p = 0.021$. Crude rates were strongly associated with several variables (Table 1). Females had a lower rate of recurrence at 17.7% compared to males at 22.3%, χ^2 $p < 0.001$, CIF Figure S2a, Gray's test $p < 0.001$. Right-sided colon cancers had a lower rate of recurrence compared to rectal cancers, 18.4% *vs* 21.9%, respectively, χ^2 $p = 0.009$, but not compared to left-sided colon cancers with a recurrence rate of 19.9%, χ^2 $p = 0.265$. Left-sided colon cancers came out no different from rectal cancers, χ^2 $p = 0.177$, CIF Figure 3a, Gray's global test $p = 0.008$. With advancing disease stages there was a steady increase in the rate of recurrence, for stage I 7.4% compared to stage II 16.0%, χ^2 $p < 0.001$, and stage IIIa + b 33.5% compared to stage IIIc 54.5%, χ^2 $p < 0.001$, CIF Figure 3b, Gray's global test $p < 0.001$. Pathological disease stage ypT0N0 represents rectal cancers with a complete response following upfront radiotherapy, with a noticeable recurrence rate of 15%, predominantly as distant recurrence. No tumor with initial stage TisN0M0 was entered. The recurrence rate for low differentiation was 24% compared to 10% for well differentiated tumors, $p < 0.001$. Emergency surgery had a higher rate of recurrence compared to elective surgery, 27.7% *vs* 19.1%, respectively, $p < 0.001$. Recurrence-free survival at six years of follow-up was 963/1,671 (57.6%) for the first time period, 1,136/1,836 (61.9%) for the middle, and 1,331/2,049 (65.0%) for the last period, $p < 0.001$.

Site of first recurrence

The decline in first recurrence was primarily driven by site «liver ± other», reduced from 8.0% during the first time period to 5.6% in the last, $p = 0.007$, and by site «other only», from 6.2% during the first period to 3.7% during the last, $p < 0.001$ (Figures 2,3, S2, Table S2). The site «other only» includes locoregional recurrence, which was stable at 1.3% for right-sided and 3.8% for left-sided tumors. For rectal cancer, locoregional recurrence was reduced from 6.4% during the first period to 3.1% during the last, $p = 0.020$. Of note, these are *first* recurrences, and total sum of local recurrences for rectal cancer was somewhat higher. Right- and left-sided colon cancers showed a similar anatomic pattern of recurrence, whereas rectal cancers had a higher rate of pulmonary recurrence at 6.4% compared to an average of 3.5% for colon cancers, $p < 0.001$, and a recurrence at «other

Table 1. Number of first recurrence (cumulative incidence rates) at a minimum of six years follow-up for $n = 5556$ cases of radically treated colorectal cancer, clinical stages I-III, between 2001 and 2015.

	Total	2001- 2005	2006- 2010	2011- 2015
Total	1113/5556 (20.0%)	394/1671 (23.6%)	367/1836 (20.0%)	352/2049 (17.2%)
Gender				
Male	623/2795 (22.3%)	223/851(26.2%)	192/873(22.0%)	208/1071 (19.4%)
Female	490/2761 (17.7%)	171/820 (20.9%)	175/963 (18.2%)	144/978 (14.7%)
Age				
< 55	79/402 (19.7%)	26/126 (20.6%)	25/138 (18.1%)	28/138 (20.3%)
55- 64	214/944 (22.7%)	86/304 (28.3%)	66/293 (22.5%)	62/347 (17.9%)
65- 74	341/1628 (20.9%)	116/452 (25.7%)	117/565 (20.7%)	108/611 (17.7%)
≥ 75	479/2582 (18.6%)	166/789 (21.0%)	159/840 (18.9%)	154/953 (16.2%)
Tumor location				
Right colon	410/2223 (18.4%)	126/622 (20.3%)	141/768 (18.4%)	143/833 (17.2%)
Left colon	305/1535 (19.9%)	112/478 (23.4%)	98/489 (20.0%)	95/568 (16.7%)
Rectal	354/1620 (21.9%)	139/515 (27.0%)	114/520 (21.9%)	101/585 (17.3%)
Multiple	44/178 (24.7%)	17/56 (30.4%)	14/59 (23.7%)	13/63 (20.6%)
Pathological stage				
ypT0N0*	16/103 (15.5%)	4/11 (36.4%)	5/44 (11.4%)	7/48 (14.6%)
(y)p I	106/1442 (7.4%)	28/395 (7.1%)	36/447 (8.1%)	42/600 (7.0%)
(y)p II	364/2280 (16.0%)	155/747 (20.7%)	115/768 (15.0%)	94/765 (12.3%)
(y)p IIIa + b	452/1350 (33.5%)	154/407 (37.8%)	143/430 (33.3%)	155/513 (30.2%)
(y)p IIIc	151/277 (54.5%)	36/61 (59.0%)	63/114 (55.3%)	52/102 (51.0%)
X	24/104 (23.1%)	17/50 (34.0%)	5/33 (15.2%)	2/21 (9.5%)
Differentiation				
Well [G1]	36/376 (9.6 %)	12/87 (13.8%)	6/76 (7.9%)	18/ 213 (8.4%)
Moderate [G2]	738/3521 (21.0%)	265/1120 (23.7%)	249/1215 (20.5%)	224/1186 (18.9%)
Low [G3]	290/1221 (23.8%)	100/345 (29.0%)	104/425 (24.5%)	86/451 (19.1%)
Unknown	49/438 (11.2%)	17/119 (14.3%)	8/120 (6.7%)	24/199 (12.1%)
Mucinous differentiation				
Yes (> 50%)	91/436 (25.9%)	29/109 (26.6%)	32/159 (20.1%)	30/168 (17.9%)
No	1022/5120 (20.0%)	365/1562 (23.4%)	335/1677 (20.0%)	322/1881 (17.1%)
Preoperativ radiation rectal cancer **				
No	213/1092 (19.5%)	113/454 (24.9%)	55/311 (17.7%)	45/327 (13.8%)
Yes	146/556 (26.3%)	28/71 (39.4%)	61/215 (28.4%)	57/270 (21.1%)
Surgical planning				
Elective	944/4946 (19.1%)	316/1438 (22.0%)	318/1644 (19.3%)	310/1864 (16.6%)
Emergency	169/610 (27.7%)	78/233 (33.5%)	49/192 (25.5%)	42/185 (22.7%)
Treatment				
Formal resection	1084/5272 (20.6%)	382/1601 (23.9%)	359/1749 (20.5%)	343/1922 (17.9%)
Polyppectomy	8/169 (4.7%)	2/42 (4.8%)	2/48 (4.2%)	4/79 (5.1%)
TAMIS/ TEM***	10/50 (20%)	4/15 (26.7 %)	3/15 (20.0%)	3/20 (15%)
Radiation only	2/44 (4.5%)	0/3	1/20 (5.0%)	1/21 (4.8%)
Other resection ****	9/21 (42.9%)	6/10 (60.0%)	2/4 (50.0%)	1/7 (14.3%)

Note: Stratified by time period.
*Following preoperative radiochemotherapy for selected rectal cancers.
**Including 19 with multiple locations and rectal cancer, and 9 with lower sigmoid location.
***TAMIS/TEM: Trans Anal Minimally Invasive Surgery/Transanal Endoscopic Microsurgery.
****Total colectomies.

only» at 6.0% compared to an average of 3.8% for colon cancers, $p < 0.001$ (Figure 3a), driven by number of locoregional recurrences. For disease stage, a proportional increase for all sites of recurrence stage by stage was found, with the exemption of ypT0N0 that had a high proportion of first recurrence detected at «other sites» (Table 1, Figure 3b). With increasing recurrence-free survival all sites of first recurrence were proportionally reduced, i.e. early recurrence (<12 months) displayed the same anatomic pattern as late recurrences (>36 months), except for «lung ± others» that constituted an increased proportion among the late recurrences (Figure 3c). Finally, first recurrence at a single organ site only, occured in 871/1,113 (78.3%) of all recurrences, with no difference across the time periods, $p = 0.281$. A total of 288/5,556 (5.2%) had a liver only recurrence, corresponding to 26.0% of all first recurrences and 193/5,556 (3.5%) had a pulmonary only recurrence, corresponding to 17.3% of all first recurrences. Number of local recurrence alone was 133, corresponding to 11.9% of first recurrences.

Time to first recurrence

Median time to first recurrence at any location was 15 months (95% CI 14–17), ranging from 12 months (95% CI 11–14) for «liver ± other» to 22 months (95% CI 19–25) for «lung ± other». A total of 415/1,113 (37.3%) of first recurrences was observed within 12 months, 30.4% between 12 and 24 months, 15.9% between 24 and 36 months, and 16.4% beyond 36 months after treatment of the CRC primary, corresponding to 3.3% of the cases at initial risk. A total of 61 first recurrences occurred beyond six years of radical treatment (Table S3). Comparing the proportion of first recurrences occurring within 24 months *vs* beyond 24 months, neither gender, $p = 0.948$, age distribution, $p = 0.283$, nor tumor location, $p = 0.051$, showed any differences, although right-sided colon cancers had a trend towards first recurrence earlier compared to the left-sided cancers, 71.0% within 24 months compared to 64.3%, respectively, $p = 0.057$. With advancing disease stages a steady increase in the proportion

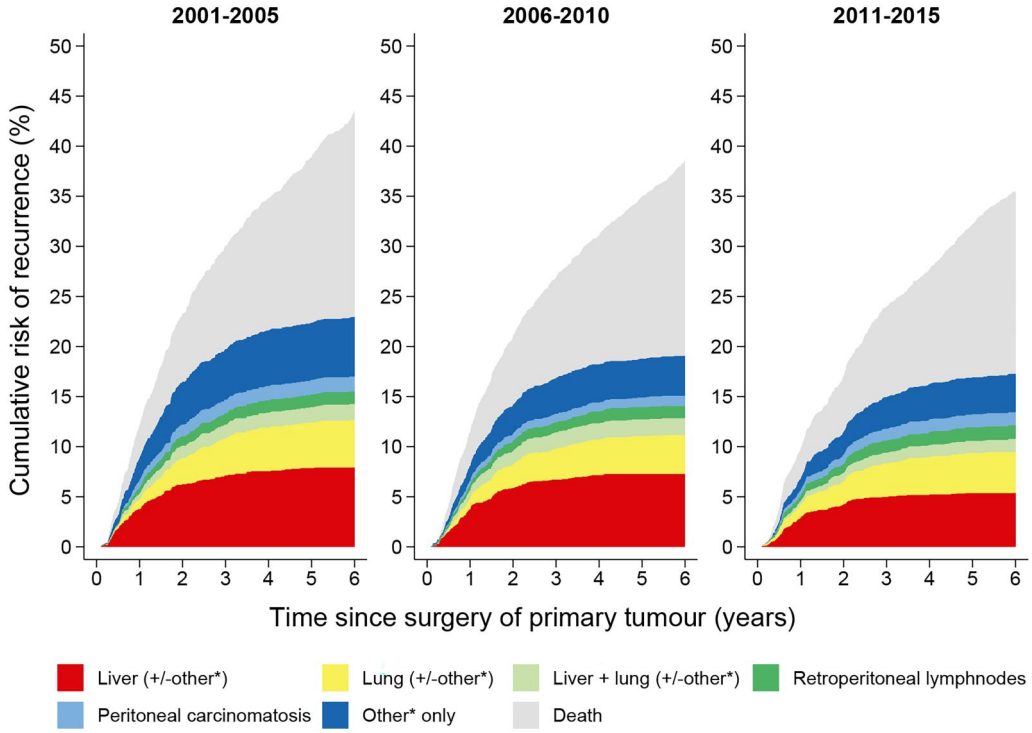


Figure 2. Stacked plot of cumulative incidence of first recurrence following radical treatment of clinical stages I-III colorectal cancer during 2001-2015. Stratified by time period, Gray's global test $p = 0.021$.
* Locoregional, distant lymphnodes, brain, abdominal wall, skeletal, urogenital, adrenal.

of first recurrences within 24 months was found. For stage I this was 50.9% compared to 63.7% for stage II, $p < 0.001$ and for stage IIIa + b 69.5% compared to 82.8% for stage IIIc, $p < 0.001$. For differentiation, 58.3% of the recurrences occurred within 24 months for well differentiated tumors, 64.8% for moderately differentiated tumors, and 77.2% for low differentiation, $p < 0.001$ (Table S3).

Cause specific HRs for first recurrence

In multivariable Cox regressions, no significant differences in HRs emerged between colon and rectal cancers, and in further tabulations common HRs were calculated (Table 2). Time period *per se* emerged as a significant determinant of recurrence, HR 0.69 (95% CI 0.57–0.90) for 2011–2015 compared to 2001–2005. Females had a lower risk of recurrence compared to males, HR 0.71 (95% CI 0.58–0.88), a sustained finding across the time periods. HRs for recurrence increased steadily with advancing disease stages, a sustained pattern across all time periods. With low differentiation as reference, moderate differentiation had a HR 1.40 (95% CI 1.07–1.82) for the entire cohort, driven by a HR 2.41 (95% CI 1.41–4.12) for the last time period. For well differentiated tumours a HR 0.86 (95% CI 0.46–1.60) was found, a sustained finding across all time periods. Only grade of differentiation was included with no quantification of the mucinous component, since a percentage above 50% by default was counted as low differentiated [23].

Discussion

The main finding of the present study was a statistically significant reduction in the cumulative rate of first recurrence for radically treated CRC from 23.8% during 2001–2005 to 17.2% during 2011–2015. This was a sustained finding across all primary tumor locations, across all pathological disease stages, for both gender, and for both elective and emergency surgery. These observations are in line with data from the 1990s and the first decade of the current century on rectal cancer in Norway [22], and on both colon and rectal cancer in Denmark [24]. They concur with a recent study from Australia restricted to colon cancer, describing a steady decline in recurrence for all disease stages individually [25]. The present study confirms and extends these findings, showing that a reduced recurrence rate over time is a persistent finding extending into the twenty first century for both colon and rectal primaries. The possibility of a spurious finding must be considered, i.e. that numbers of observed recurrences could deviate from numbers of actual recurrences differentially across the time periods. However, if a larger proportion of actual recurrences had gone undetected during the last time period, numbers of deaths counted as competing events would be expected to rise. As numbers prove, the opposite was true. Further, the possibility of a stage migration bias due to imprecise preoperative workup in the early time periods could be envisioned. Some patients that were considered to harbour stage I–III disease might in reality have suffered from stage IV disease. However, the proportion with synchronous metastases was stable at around 23% across the three time periods, and resection rates for cure were stable at some 70%. Taken together with a significant increase in five-year recurrence-free survival from 57.6% during the first timeperiod to 65.0% in the last, a true reduction in rates of first recurrence can be concluded. The reason for this decline may be multifactorial.

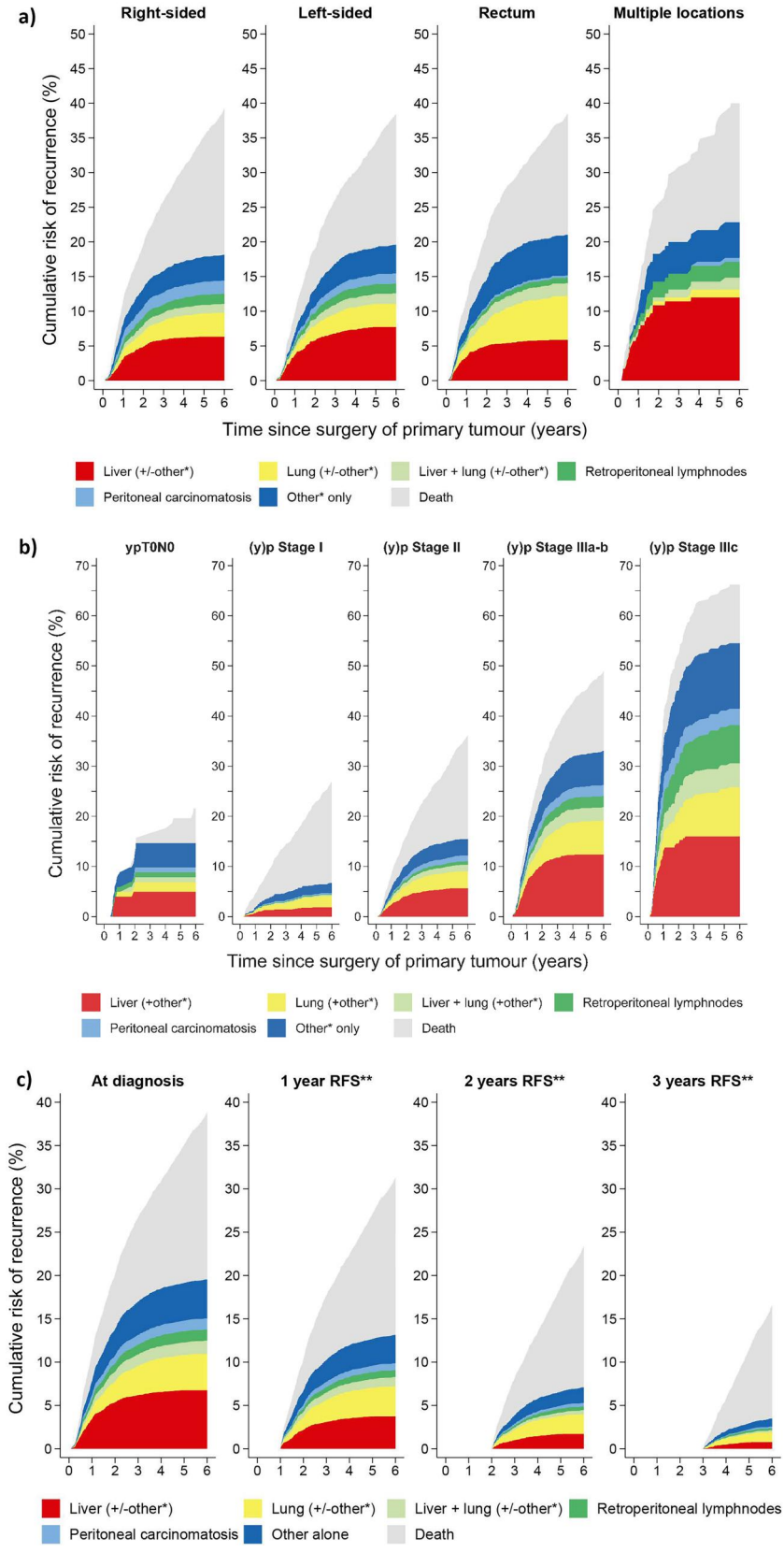


Figure 3. Stacked plot of cumulative incidence of first recurrence following radical treatment of clinical stages I-III colorectal cancer during 2001-2015. Stratified by tumor location (3a), Gray's global test $p = 0.008$, pathological disease stage (3b), Gray's global test $p < 0.001$, and years of recurrencefree survival (3c).
* Locoregional, distant lymphnodes, brain, abdominal wall, skeletal, urogenital, adrenal.
**RFS: recurrence-free survival.

The first factor is improved surgical strategies. Of note, though, the observed reduction in recurrence included both right-sided and left-sided colon cancers, with no change in the surgical approach during the study period. For rectal cancer, total mesorectal excision was firmly established as standard of care well ahead of 2001 [26]. A statistically

Table 2. Cause specific hazard ratios (HRs) and 95% confidence intervals (CI) for first recurrence following radical treatment of colorectal cancer, clinical stages I-III, during 2001–2015.

	Total	2001–2005	2006–2010	2011–2015
Time period				
2001–2005	1	–	–	–
2006–2010	0.95 (0.74–1.21)	–	–	–
2011–2015	0.69 (0.53–0.90)	–	–	–
Gender				
Male	1	1	1	1
Female	0.71 (0.58–0.88)	0.69 (0.48–1.00)	0.66 (0.46–0.93)	0.82 (0.55–1.21)
Age group				
< 55	1	1	1	1
55–64	1.11 (0.71–1.73)	1.54 (0.73–3.24)	1.63 (0.74–3.59)	0.40 (0.17–0.92)
65–74	1.02 (0.67–1.57)	1.14 (0.54–2.41)	1.18 (0.55–2.55)	0.70 (0.34–1.42)
≥ 75	1.12 (0.74–1.70)	1.18 (0.57–2.43)	1.58 (0.75–3.32)	0.63 (0.31–1.27)
Tumour location				
Right colon	1	1	1	1
Left colon	1.15 (0.89–1.49)	1.15 (0.74–1.80)	1.28 (0.84–1.96)	0.96 (0.60–1.54)
Rectum	1.15 (0.87–1.51)	1.33 (0.84–2.09)	1.20 (0.76–1.90)	0.90 (0.52–1.54)
Multiple	2.00 (1.26–3.16)	1.39 (0.55–3.54)	1.84 (0.83–4.05)	2.59 (1.25–5.39)
Pathological stage				
ypT0N0	3.58 (1.22–10.45)	0	4.25 (0.84–21.46)	5.21 (1.06–25.50)
(y)p I	1	1	1	1
(y)p II	3.11 (1.98–4.87)	2.88 (1.40–5.91)	3.90 (1.65–9.24)	2.67 (1.22–5.85)
(y)p III a-b	7.43 (4.78–11.57)	5.17 (2.51–10.65)	10.84 (4.64–25.34)	7.69 (3.62–16.34)
(y)p IIIc	13.65 (8.15–22.89)	9.64 (3.91–23.75)	18.41 (7.20–47.05)	12.93 (5.26–31.75)
Differentiation				
Well [G1]	0.86 (0.46–1.60)	0.44 (0.10–1.89)	0.64 (0.15–2.73)	1.69 (0.71–4.00)
Moderate [G2]	1.40 (1.07–1.82)	1.05 (0.68–1.63)	1.22 (0.80–1.86)	2.41 (1.41–4.12)
Low [G3]	1	1	1	1

Note: Stratified by time period.

significant reduction in local recurrence for rectal cancer from 6.2% to 3.7% is likely due to the increased use of preoperative radiation therapy in the late time periods. However, this reduction in conjunction with a proportion of rectal cancers at 29%, is too low alone to account for the total reduction in first recurrence. The second factor is adjuvant chemotherapy. Compliance with guidelines in the study cohort was high across all time periods. Of notice, though, in 2006 the guidelines changed following the results of the MOSAIC-trial [20]. This RCT demonstrated a statistically significant reduction in the hazard of recurrence by adding the more toxic oxaliplatin to the traditional FLV-regimen, global HR = 0.77, $p = 0.002$. Findings were for stage II disease HR 0.80 (95% CI 0.56–1.15) and for stage III disease HR 0.76 (95% CI 0.62–0.92). This emerges as an interesting explanatory factor for the reduced recurrence rates. However, it should be noted that for curatively resected patients with stage II disease, only 4.5% received adjuvant chemotherapy, significantly reduced from the earlier time periods to the last. Still, recurrence rates were statistically significantly lowered even for disease stage II. A similar reduction in recurrence was observed for both elderly patients and for patients with rectal cancers, for whom adjuvant chemotherapy played no part. Hence, adding oxaliplatin to the FLV-regimen may be part of, but not the sole reason for the observed reduction in recurrence. The third factor is the difference in demographic variables and tumor characteristics across the three time periods. However, when scrutinizing the absolute numbers, no variable could singularly account for the entire reduction observed. Taken together, no demographic, tumor, or treatment variable alone was able to explain the significant reduction in first recurrence from the first to the last time period. Rather, a reduced proportion of emergency surgery, improved adjuvant treatment for colon cancers, and a reduction in local recurrence for rectal cancers, may have acted together to reduce the cumulative recurrence rate.

In multivariable analyses, gender and tumor stage emerged as statistically significant risk factors for first recurrence, whereas age or tumor location did not, which concurs with findings in previous studies [6,7,27,28]. For tumor grading numbers were ambigious. Although several studies report low differentiation of the CRC primary to be an independent risk of recurrence [7,28], grading is prone to interobserver variation [29], and two recent population-based studies from the Netherlands [6] and Sweden [27] found no impact on risk of recurrence. Concerning other variables, vascular/neural invasion and KRAS/BRAF mutations were in some studies found to be significant determinants for recurrence [28], whereas microsatellite instability (MSI) was not [30]. However, due to the time span of the present study, no reliable information on these variables was available, and any development towards less aggressive or more chemosensitive CRC primaries with time could not be assessed. The clinical implications of a study like the present are several. Updated knowledge on rates of recurrence will secure better patient information on prognosis, and help to properly scale the intensity and length of the outpatient follow up after treatment of a CRC primary. A second consideration is the ongoing debate on adjuvant chemotherapy for colon cancer [31]. Current guidelines are based on rather old data from an RCT conducted during 1999–2001 [20]. The position has been voiced that the FLOX-regimen for patients with disease stage III or high risk stage II, might be an overtreatment, in particular when considering worrisome side effects. It has

been speculated that if the RCT had been conducted under the auspices of modern recurrence rates, results might well have proven the FLOX-regimen to be no better than the traditional FLV-regimen in preventing recurrence [20]. Properly conducted observational studies can enlighten the discussion on whether to use less toxic regimen of chemotherapy, a shortened number of cycles, or for subsets, maybe refrain from adjuvant treatment at all. It should be kept in mind that the MOSAIC trial did not show a statistically significant reduced recurrence for stage II disease [20]. A limitation of the present study is its retrospective nature, with the possibility of inaccurate tumor staging or grading as several pathologists were involved over an extended time period. Further, it should be noted that throughout the analyses the final (yr)pTNM stage was utilized, not the initial clinical stage. The strengths include this as a large population-based study, with a completeness of reporting to the CRN documented to be close to 99% [10]. The study was conducted within a geographically confined aera, making a manual review of the individual EPJs a feasible task. This allowed detailed information on each patient to be obtained, and elimination of entries other than CRC primaries, refinements that studies based solely on registry data are deprived from. Lastly, the mode of follow-up was detailed and death due to causes other than CRC recurrence was treated within the proper framework to allow unbiased estimates of the cumulative incidence functions (of recurrence) to be presented and compared.

Conclusions

The cumulative rate of first recurrence after curative surgery for colorectal cancer declined from 23.6% to 17.2%, $p < 0.001$, corresponding to a 27% reduction in risk of recurrence over a 15-year period. The reduction was primarily driven by a reduced recurrence in the liver, and was a sustained finding across gender, age categories, tumor locations, disease stages, degrees of tumor differentiation, and for both elective and emergency surgery. The reason for the observed reduction could not be attributed to any particular demographic, tumor, or treatment variable alone.

Disclosure statement

No potential conflict of interest was reported by the authors.

Disclaimer

The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

Data availability statement

The datasets generated and analysed during the current study are not publicly available due to hospital policy, but are available from the corresponding author on reasonable request.

References

[1] Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014; 383(9927):1490–1502. doi:10.1016/S0140-6736(13)61649-9.

[2] Cancer in Norway 2020: cancer incidence, mortality, survival and prevalence in Norway. 2021. https://www.kreftregisteret.no/globalassets/cancer-in-norway/2021/cin_report.pdf.

[3] Storli PE, Johnsen G, Juel IS, et al. Impact of increased resection rates and a liver parenchyma sparing strategy on long-term survival after surgery for colorectal liver metastases. A population-based study. Scand J Gastroenterol. 2019;54(7):890–898. doi:10.1080/00365521.2019.1641215.

[4] Mise Y, Aloia TA, Brudvik KW, et al. Parenchymal-sparing hepatectomy in coorectal liver metastasis improves salvageability and survival. Ann Surg. 2016;263(1):146–152. doi:10.1097/SLA.0000000000001194.

[5] van der Pool AEM, Damhuis RA, Ijzermans JNM, et al. Trends in incidence, treatment and survival of patients with stage IV colorectal cancer: a population-based series. Colorectal Dis. 2012; 14(1):56–61. doi:10.1111/j.1463-1318.2010.02539.x.

[6] Elferink MA, de Jong KP, Klaase JM, et al. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. Int J Colorectal Dis. 2015;30(2):205–212. doi:10.1007/s00384-014-2085-6.

[7] Qaderi SM, Galjart B, Verhoef C, et al. Disease recurrence after colorectal cancer surgery in the modern era: a population-based study. Int J Colorectal Dis. 2021;36(11):2399–2410. doi:10.1007/s00384-021-03914-w.

[8] Rahbari NN, Carr PR, Jansen L, et al. Time of metastasis and outcome in colorectal cancer. Ann Surg. 2019;269(3):494–502. doi:10.1097/SLA.0000000000002564.

[9] van Gestel YR, de Hingh IH, van Herk-Sukel MP, et al. Patterns of metachronous metastases after curative treatment of colorectal cancer. Cancer Epidemiol. 2014;38(4):448–454. doi:10.1016/j.canep.2014.04.004.

[10] Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the cancer registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009;45(7):1218–1231. doi:10.1016/j.ejca.2008.10.037.

[11] Adam R, de Gramont A, Figueras J, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer Treat Rev. 2015;41(9):729–741. doi:10.1016/j.ctrv.2015.06.006.

[12] Read TE, Mutch MG, Chang BW, et al. Locoregional recurrence and survival after curative resection of adenocarcinoma of the colon. J Am Coll Surg. 2002;195(1):33–40. doi:10.1016/s1072-7515(02)01224-3.

[13] Elferink MA, Visser O, Wiggers T, et al. Prognostic factors for locoregional recurrences in colon cancer. Ann Surg Oncol. 2012; 19(7):2203–2211. doi:10.1245/s10434-011-2183-4.

[14] Wisselink DD, Klaver CEL, Hompes R, et al. Curative-intent surgery for isolated locoregional recurrence of colon cancer: review of the literature and institutional experience. Eur J Surg Oncol. 2020;46(9):1673–1682. doi:10.1016/j.ejso.2020.04.021.

[15] von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observationa. Lancet. 2007; 370(9596):1453–1457. doi:10.1016/S0140-6736(07)61602-X.

[16] Allignol A, Schumacher M, Beyersmann J. A note on variance estimation of the Aalen-Johansen estimator of the cumulative incidence function in competing risks, with a view towards left-truncated data. Biom J. 2010;52(1):126–137. doi:10.1002/bimj.200900039.

[17] Dignam JJ, Kocherginsky MN. Choice and interpretation of statistical tests used when competing risks are present. J Clin Oncol. 2008;26(24):4027–4034. doi:10.1200/JCO.2007.12.9866.

[18] Stensrud MJ, Hernan MA. Why test for proportional hazards? JAMA guide to statistics and methods. JAMA. 2020;323(14):1401–1402. doi:10.1001/jama.2020.1267.

[19] Francini G, Petrioli R, Lorenzini L, et al. Folinic acid and 5-fluorouracil as adjuvant chemotherapy in Colon cancer. Gastroenterology. 1994;106(4):899–906. doi:10.1016/0016-5085(94)90748-x.
[20] Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350(23):2343–2351. doi:10.1056/NEJMoa032709.
[21] Norwegian Rectal Cancer Registry, Norwegian Gastrointestinal Cancer Group (NGICG), annual report. 2009.
[22] Guren MG, Kørner H, Pfeffer F, et al. Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993-2010. Acta Oncol. 2015;54(10):1714–1722. doi:10.3109/0284186X.2015.1034876.
[23] WHO. Classification of tumours of the digestive system. 4th ed. Lyon: IARC Publications; 2010.
[24] Holmes AC, Riis AH, Erichsen R, et al. Descriptive characteristics of colon and rectal cancer recurrence in a danish population-based study. Acta Oncol. 2017;56(8):1111–1119. doi:10.1080/0284186X.2017.1304650.
[25] Gately L, Jalali A, Semira C, et al. Stage dependent recurrence patterns and post-recurrence outcomes in non-metastatic colon cancer. Acta Oncol. 2021;60(9):1106–1113. doi:10.1080/0284186X.2021.1943519.
[26] Wibe A, Møller B, Norstein J, et al. A national strategic change in treatment policy for rectal cancer – implementation of total mesorectal excisison as routine treatment in Norway. A national audit. Dis Colon Rectum. 2002;45(7):857–866. doi:10.1007/s10350-004-6317-7.
[27] Osterman E, Glimelius B. Recurrence risk after up-to-date colon cancer staging, surgery, and pathology: analysis of the entire swedish population. Dis Colon Rectum. 2018;61(9):1016–1025. doi:10.1097/DCR.0000000000001158.
[28] Böckelman C, Engelmann BE, Kaprio T, et al. Risk of recurrence in patients with Colon cancer stage II and III: a systematic review and meta-analysis of recent literature. Acta Oncol. 2015;54(1):5–16. doi:10.3109/0284186X.2014.975839.
[29] Chandler I, Houlston RS. Interobserver agreement in grading of colorectal cancers – findings from a nationwide web-based survey of histopathologists. Histopathology. 2008;52(4):494–499. doi:10.1111/j.1365-2559.2008.02976.x.
[30] Toh J, Chapuis PH, Bokey L, et al. Competing risks analysis of microsatellite instability as a prognostic factor in colorectal cancer. Br J Surg. 2017;104(9):1250–1259. doi:10.1002/bjs.10542.
[31] Osterman E, Hammarstrøm K, Imam I, et al. Recurrence risk after radical colorectal cancer surgery – less than before, but how high is it? Cancers (Basel). 2020;12(11):3308. doi:10.3390/cancers12113308.