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Time trends in treatment patterns and survival of older patients with synchronous metastatic colorectal cancer in the Netherlands: A population-based study

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Abstract

New treatment strategies have improved survival of metastatic colorectal cancer in trials. However, it is not clear whether older patients benefit from these novel therapies, as they are often not included in pivotal trials. Therefore, we investigated treatment patterns and overall survival over time in older patients with metastatic colorectal cancer in a population-based study. We identified 22.192 Dutch patients aged ≥70 years diagnosed with synchronous metastatic colorectal cancer between 2005 and 2020 from the Netherlands Cancer Registry. Changes in treatment over time were assessed with logistic regression models. Survival was assessed by Cox proportional hazard ratios (HR). Results showed that chemotherapy use increased between 2005 and 2015, but declined from 2015 onwards, while more patients received best supportive care. Over time, fewer patients underwent primary tumor resection alone. Although survival of both metastatic colon and rectal cancer improved until 2014, survival of colon cancer decreased from 2014 onwards (HR 1.04, 95% confidence interval [CI] 1.01-1.05), which was seen in all age groups. Survival of metastatic rectal cancer patients remained unchanged from 2014 onwards (HR 1.00, 95% CI 0.98-1.03) in all age groups. In conclusion, treatment patterns of Dutch older patients with synchronous metastatic colorectal cancer rapidly changed from 2005 to 2020, with increasing percentages of patients receiving best supportive care. Survival of metastatic colon cancer decreased from 2014 onwards. The implementation of a colorectal cancer screening program and patient selection might explain why only a subset of older patients seem to benefit from the availability of novel treatment options.

Abbreviations: APC, annual percentage change; CI, confidence interval; CT, computerized tomography; HR, hazard ratio; IKNL, Netherlands Comprehensive Cancer Organisation; IQR, interquartile range; NCR, Netherlands Cancer Registry; OS, overall survival.

KEYWORDS
metastatic colorectal cancer, older adults, population-based study, survival, treatment patterns

What's new?

New therapeutic approaches for metastatic colorectal cancer (mCRC) have yielded significant survival gains in clinical trials. Most trials, however, excluded patients over the age of 70 due to comorbidity and functional impairment. This population-based study, which sought to better understand mCRC treatment and outcomes among older patients in the Netherlands, reveals shifts in treatment patterns between 2005 and 2020, whereby older patients more often received best supportive care. Survival decreased after 2014, suggesting that only a subset of older patients benefits from novel therapies. These findings warrant further study of older mCRC patients in order to optimize treatment strategies.

1 | INTRODUCTION

Treatment of metastatic colorectal cancer has rapidly changed the past decades, with advances in surgical methods of hepatic resection and ablation,[1,2] development of targeted drugs[3] and effective polychemotherapy schedules,[4] leading to improved survival in clinical trials. Although more than half of the patients diagnosed with metastatic colorectal cancer are aged ≥70 years,[5] previous trials that investigated these treatment modalities mostly excluded older patients based on comorbidities or functional limitations.[6] Moreover, trial data generally do not result in knowledge about most older patients seen in daily practice, as they often live with more frailty and multimorbidity, affecting treatment effectiveness.[7] To investigate if the marked improvement of survival seen in trials is reflected in the real-world older population, it is fundamental to study outcomes in population-based studies.

A previous Dutch population-based study found that, compared to their younger counterparts, survival of older patients diagnosed with metastatic colorectal cancer between 1991 and 2005 did not improve,[8] which is in line with community-based studies in other countries.[8-13] Nonetheless, these studies were all conducted before the implementation of national colorectal cancer screening programs in these countries. In the Netherlands, a screening program was implemented in 2014 for patients aged 55-75 years. Among patients aged 70-75 years, the program achieved participation rates of 71% in 2016, 72% in 2018 and 75% in 2020[14,15] and led to a decrease in colorectal cancer incidence.[16] As both the screening and novel treatment options might have changed treatment patterns and survival, up-to-date survival data are needed.

This population-based study aims to investigate time trends in treatment patterns and overall survival of Dutch older patients with synchronous metastatic colorectal cancer, diagnosed between 2005 and 2020.

2 | METHODS

This is a nationwide population-based cohort using data from the Netherlands Cancer Registry (NCR). The NCR registers all patients with newly diagnosed cancer in the Netherlands, based on notification by the national pathology database (PALGA). Importantly, the NCR only registers patients with synchronous metastatic colorectal cancer. Information on patient and tumor characteristics, such as topography and grade, and primary treatment were collected from medical records by specially trained registry staff. Data on WHO performance status were available from 2015 onwards. Information on vital status (dead/alive) and date of death was obtained from municipal demography registries and nationwide population registries network on a yearly basis.[17] The estimated completeness of the NCR is 96%.[18]

All registered patients with synchronous metastatic colon or rectal cancer, aged ≥70 years, and diagnosed between January 1, 2005, and December 31, 2020, were selected. Follow-up time for vital status was calculated from date of diagnosis until date of death or end of follow-up.

2.1 | Statistical analyses

Analyses were stratified by tumor type (colon or rectal cancer), except for the systemic treatment analyses. Descriptive statistics using chi-square tests were used to summarize patient and tumor characteristics, categorized into year of diagnosis (2005-2013 and 2014-2020) and age. We calculated national incidence rates of metastatic colorectal cancer per year using data from Statistics Netherlands.[19] The number of patients with newly diagnosed metastatic colorectal cancer per year was divided by the number of older adults of the same age living in the Netherlands in the year of diagnosis. We analyzed trends in incidence with Joinpoint Regression Program V4.9.0.1.[20-22] Joinpoint regression models assess changes in incidence trends, identify time points at which the change is observed, and compute annual percentage change (APC) and 95% confidence intervals (CI) between time periods.

To describe trends in treatment modalities, we graphically depicted the percentage of patients receiving different treatment types per age group. Second, logistic regression models were calculated to analyze trends in treatment, adjusted for age, sex, number of metastatic sites and liver-only disease. We used the Kaplan-Meier method to estimate median overall survival (OS) with interquartile

ranges (IQR) per year of diagnosis. As we hypothesized that OS might have been affected by the implementation of the colorectal cancer screening program, we separately calculated hazard ratios (HR) with 95% CI for patients diagnosed from 2005 to 2013 and from 2014 to 2020 in Cox proportional hazards models. Time and age were included as a continuous variable, and sex, number of metastatic sites, and liver-only disease as categorical variables. Survival analyses were stratified by age and number of metastatic sites. To investigate if data on incidence, treatment patterns and survival were confounded by the COVID-19 pandemic in 2020, we performed sensitivity analyses in which we excluded patients diagnosed in 2020. Analyses were performed in SPSS V.25 and a two-sided $P < .05$ was considered statistically significant.

3 | RESULTS

Our study population consisted of 22.192 patients aged ≥70 years (median age at diagnosis of colon cancer 78 years (IQR 73-82) and rectal cancer 77 years (IQR 73-82)), diagnosed with synchronous metastatic colorectal cancer between 2005 and 2020. Primary tumors were located in the colon (76%) and rectum (24%) and approximately 40% had liver-only disease (Tables 1 and 2 and S1-S6). Compared to patients diagnosed in 2005-2013, patients diagnosed between 2014 and 2020 were older, had increased numbers of metastatic sites, more lung metastases and less liver-only disease. From 2014 onwards, WHO performance status was registered in 53%. Approximately 30% of those with a registered WHO status had a WHO of 2 or higher.

3.1 | Trends in incidence

Incidence rates of synchronous metastatic colon cancer increased from 49 cases/100.000 persons to 62 cases/100.000 persons from 2005 to 2013 (APC 3.0%; 95% CI 2.0-4.1, $P < .001$) but lowered to 47 cases/100.000 persons in 2020 (APC −4.6%; 95% CI −5.6 to −3.5, $P < .001$) (Figures 1A and S1), simultaneously with the introduction of the screening. Metastatic rectal cancer incidence rates remained similar from 2005 to 2016 (from 20 cases/100.000 persons to 18 cases/100.000 persons, APC −0.66%; 95% CI 0.4 to −1.4, $P = .191$), but decreased to 12 cases/100.000 persons in 2020 (APC −12.9%; 95% CI −4.8 to −1.6, $P = .005$), a few years after the implementation of the screening (Figures 1B and S1). A decrease in

TABLE 1 Baseline characteristics of patients with metastatic colon cancer

Variables	Categories	Total (%) (N = 16.768)	Time of diagnosis 2005-2013 (N = 8.848)	Time of diagnosis 2014-2020 (N = 7.920)	*P*-value*
Male	Yes	52.3	52.3	52.3	.985
Age	Median (IQR)	78 (73-82)	77 (73-82)	78 (73-83)	
	70-74	31.3	31.0	31.6	<.001
	75-79	29.0	31.1	26.7	
	≥80	39.7	37.9	41.6	
WHO status	0	6.4	N/A	16.2	N/A
	1	7.7		20.3	
	≥2	6.0		17.4	
	Unknown	79.9		46.2	
Tumor grade	1	2.2	2.9	1.5	<.001
	2	40.9	37.7	44.5	
	3	15.2	17.7	12.3	
	Undifferentiated	0.2	0.2	0.3	
	Unknown	41.5	41.6	41.5	
Number of metastatic sites	1	60.4	62.4	58.2	<.001
	2	25.8	24.8	27.0	
	≥3	11.4	8.4	14.8	
	Unknown	2.3	4.4	0.0	
Metastatic site	Liver	70.5	70.3	70.8	.460
	Lung	21.9	19.2	25.0	<.001
	Peritoneum	27.7	24.3	32.7	<.001
Liver only	Yes	39.8	42.5	36.7	<.001

Abbreviations: IQR, interquartile range; N/A, not available; WHO, World Health Organisation.

*P-value refers to differences between two time periods (2005-2013 and 2014-2020) and were calculated using chi-square test.

TABLE 2 Baseline characteristics of patients with metastatic rectal cancer

Variables	Categories	Total (%) (N = 5.424)	Time of diagnosis 2005-2013 (N = 3.005)	Time of diagnosis 2014-2020 (N = 2.419)	*P*-value*
Male	Yes	59.0	58.4	59.8	.306
Age	Median (IQR)	77 (73-82)	77 (73-81)	77 (73-82)	
	70-74	35.0	35.1	34.8	<.001
	75-79	29.7	31.8	27.2	
	≥80	35.3	33.1	38.0	
WHO status	0	7.8	N/A	17.2	N/A
	1	10.3		22.9	
	≥2	6.0		13.2	
	Unknown	76.0		46.7	
Tumor grade	1	1.5	1.8	1.2	<.001
	2	43.1	32.1	56.8	
	3	10.7	11.4	9.7	
	Undifferentiated	0.1	0.0	0.2	
	Unknown	44.6	54.6	32.1	
Number of metastatic sites	1	61.9	64.5	56.4	<.001
	2	26.2	23.6	30.4	
	≥3	9.5	7.8	13.1	
	Unknown	2.3	4.2	0.0	
Metastatic site	Liver	71.3	71.2	71.4	.885
	Lung	35.0	30.8	40.1	<.001
	Peritoneum	9.9	9.7	10.2	.580
Liver only	Yes	41.1	44.5	36.9	<.001

Abbreviations: IQR, interquartile range; N/A, not available; WHO, World Health Organisation.
*P-value refers to differences between two time periods (2005-2013 and 2014-2020) and were calculated using chi-square test.

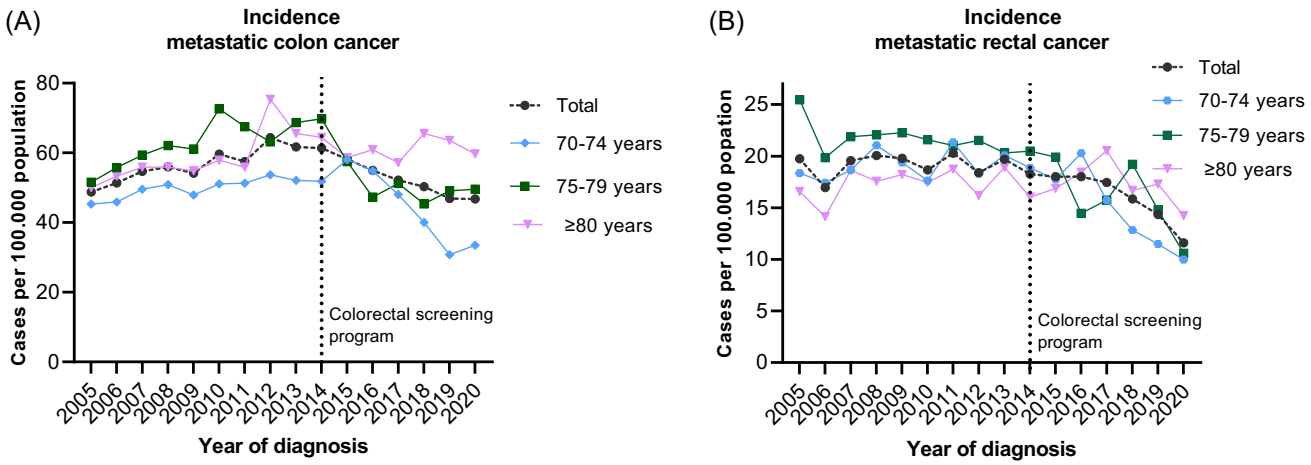

FIGURE 1 (A) Incidence rates per 100.000 persons for metastatic colon cancer, stratified by age. (B) Incidence rates per 100.000 persons for metastatic rectal cancer, stratified by age

incidence of both tumor types was observed in patients aged 70-74 years ($P < .001$ for both tumor types) and 75-79 years ($P < .001$ for both tumor types), but not in patients aged ≥80 years ($P = .325$ for colon and $P = .361$ for rectal cancer) (Figure S2A-C).

3.2 | Trends in treatment

Figure 2 shows local and systemic treatment patterns of synchronous metastatic colorectal cancer over time, and treatment patterns per

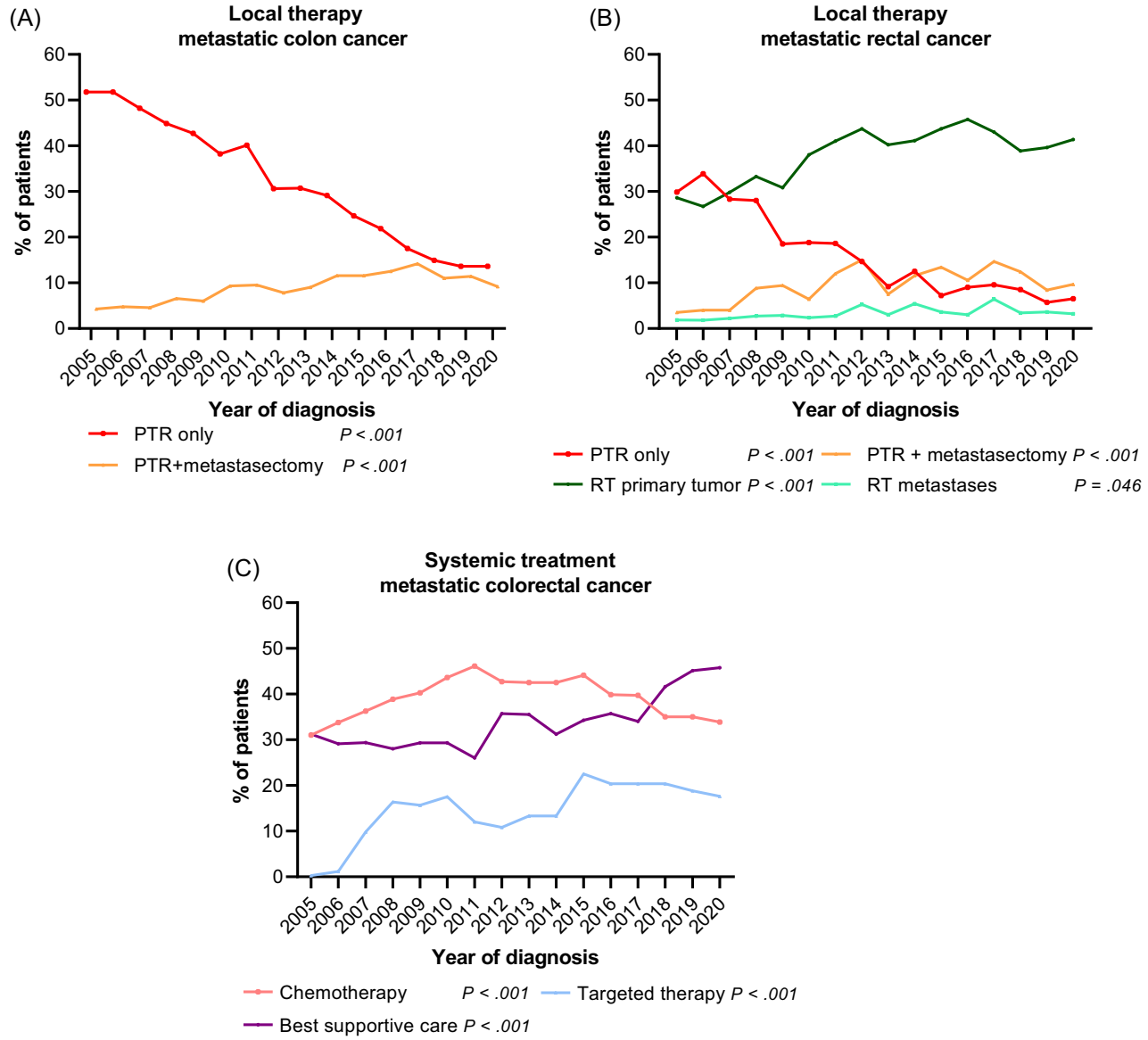

FIGURE 2 (A-C) All figures represent unadjusted percentages of patients receiving the specific treatment modality. *P*-values were calculated using logistic regression, adjusted for sex, number of metastatic sites and liver-only disease, and represent *P* for trend for year of diagnosis. (A) Trends in local treatment patterns over time for metastatic colon cancer. (B) Trends in local treatment patterns over time for metastatic rectal cancer. (C) Trends in systemic treatment patterns over time for both metastatic colon and rectal cancer. BSC, best supportive care; PTR, primary tumor resection; RT, radiotherapy

age group are shown in Figures S3-S5. Regarding local treatment of metastatic colon cancer, the proportion of patients undergoing primary tumor resection or metastasectomy strongly changed over time in all age groups. In 2005, 52% of all patients received primary tumor resection alone, whereas this percentage declined to 14% in 2020 ($P < .001$ for trend for year of diagnosis). The percentage of patients undergoing both primary tumor resection and metastasectomy increased from 4% in 2005 to 9% in 2020 ($P < .001$). Patients with synchronous metastatic rectal cancer also underwent less primary tumor resection only, as this percentage dropped from 30% in 2005 to 6% in 2020 ($P < .001$) and this decline was seen in all age groups. Similarly, patients in all age groups more frequently underwent both primary tumor resection and metastasectomy (4% in 2005 to 10% in 2020, $P < .001$). More patients with synchronous metastatic rectal cancer received radiotherapy to the primary tumor over time (29% in 2005 to 41% in 2020, $P < .001$), and this increase was observed in all age groups.

Systemic treatment patterns in patients with synchronous metastatic colorectal cancer vastly changed as well. Chemotherapy use initially rose from 31% in 2005 to 44% in 2015, but this percentage dropped to 34% in 2020 ($P < .001$). This decline was only seen in patients aged 70-74 and 75-79 years. From 2005 to 2015, patients increasingly received targeted therapy as first-line treatment in combination with chemotherapy (0% of the patients in 2005 to 23%

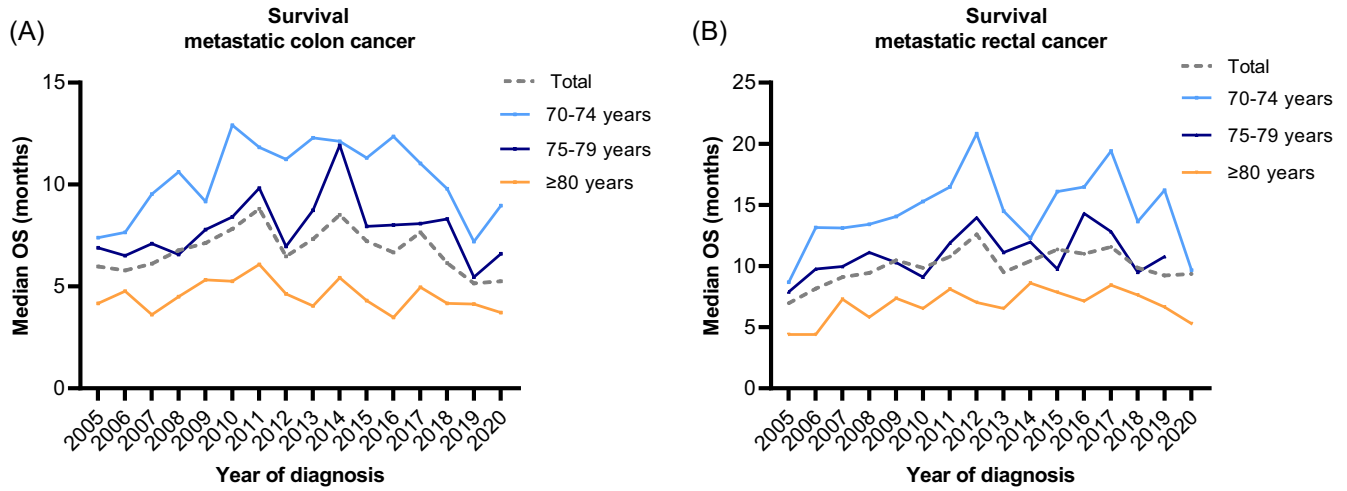

FIGURE 3 (A) Median OS per year of diagnosis for metastatic colon cancer, stratified by age. Median OS was derived from Kaplan Meier curves. (B) Median OS per year of diagnosis for metastatic rectal cancer, stratified by age. Median OS was derived from Kaplan Meier curves

[meaning 51% of the patients treated with chemotherapy] in 2015), which applied to all age groups. This percentage slightly dropped to 18% in 2020 ($P < .001$), again only seen in patients aged 70-74 and 75-79 years. Moreover, patients received best supportive care more frequently over time, as this proportion rose from 31% in 2005 to 46% in 2020 ($P < .001$). This increase was observed in all age groups.

3.3 | Trends in survival

In older patients with metastatic colon cancer, median OS increased from 5.9 months (IQR 1.8-15.9) in 2005 to 8.5 months (IQR 2.3-21.5) in 2014 (HR 0.98; 95% CI 0.97-0.98), but declined to 5.3 months (IQR 1.4-not reached) in 2020 (HR 1.04; 95% CI 1.03-1.06), after the screening was implemented (Figure 3A). This decrease in survival was seen in all age groups (HR 1.05; 95% CI 1.02-1.07 for 70-74 years, HR 1.06; 95% CI 1.03-1.08 for 75-79 years and HR 1.03; 95% CI 1.01-1.05 for ≥80 years) (Table S7). Although improvement of survival from 2005 to 2013 was only seen in patients with one metastatic site (HR 0.97; 95% CI 0.96-0.98), the decreased survival from 2014 onwards was seen in both patients with one (HR 1.03; 95% CI 1.01-1.05), two (HR 1.04; 95% CI 1.02-1.07) or three or more (HR 1.05; 95% CI 1.02-1.09) metastatic sites (Table S8).

Median OS of metastatic rectal cancer improved from 7.0 months (IQR 3.1-16.0) in 2005 to 10.4 months (IQR 4.1-23.7) in 2014 (HR 0.97; 95% CI 0.95-0.98), but in 2020, a few years after the introduction of the screening, survival remained similar (OS 9.3 months, IQR 2.6-not reached, HR 1.00; 95% CI 0.98-1.03) (Figure 3B). Survival between 2014 and 2020 remained similar in all age groups (HR 0.99; 95% CI 0.94-1.04 for 70-74 years, HR 0.97; 95% CI 0.92-1.01 for 75-79 years and HR 1.03; 95% CI 0.99-1.08 for ≥80 years) (Table S7). Improvement of survival between 2005 and 2013 was only seen in patients with one metastatic site (HR 0.96; 95% CI 0.94-0.98), and survival between 2014 and 2020 remained similar regardless of number of metastatic sites (HR 1.03; 95% CI 0.97-1.04 for one site, HR 1.00; 95% CI 0.95-1.04 for two sites and HR 1.01; 95% CI 0.95-1.08 for three or more sites) (Table S8).

3.4 | Sensitivity analysis regarding the COVID-19 pandemic

When excluding all patients diagnosed in 2020, the first year of the pandemic, all analyses yielded similar results, except for the decrease in incidence of metastatic rectal cancer, as this trend was no longer statistically significant (APC −7.9; 95% CI −15.1 to 0.0, $P = .05$) (Figure S6).

4 | DISCUSSION

This Dutch population-based study shows that the incidence of synchronous metastatic colorectal cancer in older patients decreased since the introduction of the colorectal cancer screening program in 2014 and treatment strategies vastly changed over time. Fewer patients underwent primary tumor resection alone and the percentage of patients receiving chemotherapy or targeted therapy increased at first, but declined since 2015, while more patients received best supportive care. Although survival of older patients with both synchronous metastatic colon and rectal cancer improved up until 2014, unexpectedly, thereafter no further improvement was seen for patients with synchronous metastatic rectal cancer, while survival even declined for patients with synchronous metastatic colon cancer.

Possibly, these results were explained by the introduction of the colorectal cancer screening program. It is well known that fit older patients with few comorbidities and higher socioeconomic status attend screenings more frequently than patients with frailties or poor socioeconomic backgrounds.[23,24] Consequently, the proportion of frail

older patients presenting with clinically detected metastatic colorectal cancer rises, leading to increased use of best supportive care and deteriorated survival, as shown in a previous Dutch study.[25] The substantial decline in incidence of synchronous metastatic colorectal cancer in patients aged 70-74 years since 2014 indeed suggests an effect of the screening on early detection. The decrease in incidence rates of patients aged 75-79 might also be affected by the screening, as patients aged 75 years were the first invited to participate. In addition, tumors are detected earlier and in younger patients, causing a decreased incidence in patients aged 75-79 years. Patients aged ≥80 years did not participate in the screening, and the incidence in this age group remained unchanged in the first 6 years after implementation of the screening, which strengthens this hypothesis.

Trends in treatment patterns might also be influenced by the increased use of new diagnostic imaging tools, such as computerized tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). Dutch studies observed a substantial rise in the use of CT scans in the past decades, which potentially led to higher detection of small metastases.[26] The expanded diagnostic possibilities to detect metastatic colorectal cancer might also have resulted in increased detection of tumors in frail older patients with multimorbidity, who might have remained undiagnosed a few years ago due to limited diagnostic tools. Previous literature indeed showed a growing prevalence of multimorbidity over time in Dutch patients with colorectal cancer.[27] This shift might have generated a higher percentage of patients not eligible for antitumor treatment due to frailty or comorbidities.

Interestingly, only a subset of older patients received chemotherapy. The development of effective polychemotherapy regimens initially resulted in an increase in chemotherapy use, but we observed a decline since 2015. Besides patient selection due to the screening and increased frailty, this low percentage of patients receiving chemotherapy might also reflect undertreatment of older patients, possibly due to fear of chemotherapy-related toxicity among oncologists. Despite the evidence that fit older patients derive similar survival benefits of chemotherapy,[28] they are less likely to receive systemic treatments.[29] Observational studies show that, when older patients receive chemotherapy, many patients indeed experience toxicity and discontinue treatment early,[30] suggesting that standard-dose chemotherapy is too high for older patients with frailty. More tailored treatment options for this population are essential to reduce risk of toxicities and maximize treatment efficacy.

Other substantial shifts in treatment modalities have been taking place in the last decade as well. First, less patients underwent primary tumor resection alone, which is consistent with previous population-based studies in Dutch patients with metastatic colorectal cancer.[8,31] This can be explained by the fact that recent studies showed that primary tumor resection without metastatectomy is only indicated in case of symptoms.[32,33] Second, more older patients underwent both primary tumor resection and surgical resection of isolated hepatic or lung metastases.[34,35] Third, Dutch guidelines recommended the administration of bevacizumab in combination with chemotherapy as first-line treatment in 2008,[36] resulting in a growing percentage of patients receiving targeted therapy.

This is the first large population-based study that provides insights on current treatment patterns and survival of unselected patients with synchronous metastatic colorectal cancer up until 2020. Data were derived from the well-registered, quality-assured database of the NCR. Due to the high registration rate, selection bias of our study is low. Thus, our findings give a representative overview of the treatment of older patients with synchronous metastatic colorectal cancer and can be extrapolated to real world patients seen in daily practice.

A few limitations should be addressed. Due to missing information on tumor characteristics, such as screening-detected or clinically detected cancer, and patient characteristics, such as comorbidities, physical functioning and frailty, our study has limited potential to address underlying reasons for changes in treatment and survival. Future studies should focus on further identifying the individuals receiving best supportive care and possible predictors of survival. Information about the effect of the screening on incidence and survival of patients aged <70 years or in other countries may also help to clarify our findings. In addition, our results only depict potential short-term effects of the screening program. Last, data from patients with metachronous metastatic colorectal cancer were not available and might differ from data on synchronous metastatic colorectal cancer. Although studies suggest survival of metachronous and synchronous metastatic colorectal cancer is similar,[37,38] the screening might have had a different effect on survival of metachronous disease compared to synchronous disease.

To increase the proportion of patients being offered chemotherapy and potentially improve survival, future trials should investigate tailored treatment options for frail older patients. Two previous trials showed that upfront dose reduction of chemotherapy in older frail patients with metastatic colorectal cancer improved treatment tolerability and quality of life, without compromising survival.[39,40] Geriatric measurements might aid in selecting those who benefit from primary dose reduction.[41,42] The recently published GAP70+ trial demonstrated that geriatric assessment-based interventions led to an increase in primary dose reductions and decrease in severe chemotherapy-related toxicity in older patients with advanced cancer, while survival remained unchanged.[42] More trials studying dose-reduced chemotherapy are needed to reduce undertreatment and develop individualized treatment strategies for this large and growing population.

In conclusion, treatment patterns of Dutch older patients with synchronous metastatic colorectal cancer rapidly changed from 2005 to 2020, with increasing percentages of patients receiving best supportive care. Survival of metastatic colon cancer decreased from 2014 onwards, suggesting that only a subset of older patients benefits from the availability of novel treatment options. Future studies using geriatric measurements are needed to provide evidence-based, tailored treatment options for older patients with metastatic colorectal cancer and optimize the balance between over- and undertreatment.

AUTHOR CONTRIBUTIONS

Joosje C. Baltussen: Data curation; Formal analysis; Investigation; Methodology; Investigation; Visualization; Writing—original draft; Writing—review & editing. **Nienke A. de Glas:** Conceptualization;

Methodology; Supervision; Visualization; Writing—original draft; Writing—review & editing. **Gerrit-Jan Liefers:** Writing—review & editing. **Marije Slingerland:** Writing—review & editing. **Frank M. Speetjens:** Writing—review & editing. **Frederiek van den Bos:** Writing—review & editing. **Marissa Cloos-van Balen:** Writing—review & editing. **Arjan J. Verschoor:** Writing—review & editing. **Anouk Jochems:** Writing—review & editing. **Leontine E. A. M. M. Spierings:** Writing—review & editing. **Cynthia Holterhues:** Writing—review & editing. **Leander A. van Gerven:** Writing—review & editing. **Simon P. Mooijaart:** Formal analysis; Investigation; Methodology; Investigation; Visualization; Supervision; Writing—original draft; Writing—review & editing. **Johanneke E. A. Portielje:** Conceptualization; Formal analysis; Investigation; Methodology; Investigation; Visualization; Supervision; Writing—original draft; Writing—review & editing. **Marloes G. M. Derks:** Formal analysis; Investigation; Methodology; Investigation; Visualization; Supervision; Writing—original draft; Writing—review & editing. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

The author declares no potential conflict of interests.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the NCR (information can be found on their website: www.iknl.nl/en/ncr/apply-for-data) on reasonable request. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

Pseudonymized clinical data on demographic characteristics, tumor characteristics and treatment information (type, response) were obtained from the NCR. The privacy rights for patients were maintained. The study was performed in accordance with the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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