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Impact of colorectal cancer screening on survival after metachronous metastasis

Patricia A.H. Hamers [a,b], Geraldine R. Vink [a,c], Marloes A.G. Elferink [c], Leon M.G. Moons [d], Cornelis J.A. Punt [b], Anne M. May [b,1], Miriam Koopman [a,*,1]

[a] Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[b] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[c] Department of Research and Development, Netherlands Comprehensive Cancer Organisation, Utrecht, the Netherlands
[d] Department of Gastroenterology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

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ABSTRACT

Background: An increasing proportion of colorectal cancer (CRC) cases in Europe are detected by screening with faecal immunochemical testing (FIT). Previous studies showed that population screening with FIT leads to a decrease in CRC incidence and to detection at an earlier stage. However, approximately twenty percent of patients with CRC without metastases at initial diagnosis still develop metachronous metastases. We investigated the association between detection mode of the primary tumor and overall survival (OS) after metachronous metastasis in patients with CRC.

Methods: Nationwide registry-based data was obtained of 794 patients who developed metachronous metastases after being diagnosed with stage I-III CRC between January and June 2015. With multivariable Cox PH regression modelling, we analyzed the (causal) association between detection mode of the primary tumor (FIT screen-detected versus non-screen-detected) and OS after metachronous metastasis while adjusting for potential confounders.

Results: Median OS and five-year OS after metachronous metastasis were significantly higher for patients with screen-detected (n = 152) vs. non-screen-detected primary tumors (n = 642): 38.3 vs. 19.2 months, and 35.4% vs. 18.8%, respectively, $p < 0.0001$). After adjustment for potential confounders, the association between detection mode and OS after metachronous metastasis remained significant (HR 0.70 [95% CI 0.56–0.89]).

Conclusions: Screen-detection of the primary tumor was independently associated with longer OS after metachronous metastasis. This may support the clinical utility of the population screening program and it shows the prognostic value of detection mode of the primary tumor once metachronous metastasis is diagnosed.

1. Background

In the past twenty years, many European countries have commenced population screening programs for colorectal cancer (CRC) [1], and consequently an increasing proportion of CRC cases are detected by screening [2]. The aim of population screening is to reduce CRC-related mortality. Previous studies have demonstrated that this reduction can be achieved by a decrease in CRC incidence by removing polyps, as well as by detecting CRC at an earlier stage, which likely increases chances of cure [1,3,4].

Approximately twenty percent of patients with CRC without metastases at initial diagnosis develop metachronous metastases, the majority within 3 years [5]. Initial stage (pTN) and differentiation grade of the primary tumor were found to be associated with survival after metachronous metastasis [5–7]. It is yet unknown whether detection of the primary tumor via screening affects survival after development of metastasis at a later time point. Our hypothesis is that the early primary tumor resection in patients with screen-detected tumors might be beneficial to the biologic behavior of metachronous metastases. Therefore we investigated whether detection mode of the primary tumor, screen-detected versus non-screen-detected, is associated with overall survival (OS) after development of metachronous metastasis in patients

* Correspondence to: Internal mail no: Q 05.4.300, P.O. Box 85500, 3508 GA Utrecht, the Netherlands.
E-mail address: M.Koopman-6@umcutrecht.nl (M. Koopman).
[1] These authors contributed equally to this work.

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with CRC.

2. Methods

2.1. Study design and study population

We performed a retrospective, observational, nationwide, registry-based study. We obtained data from the Netherlands Cancer Registry (NCR) on all patients ≥ 18 years who were diagnosed with stage I-III CRC from January 2015 to June 2015 in the Netherlands, and subsequently developed metachronous metastases before October 2019. Metachronous metastases were defined as metastases that would be designated as distant (non-regional) metastases according to the TNM classification [8]. Metachronous metastatic CRC (mCRC) was defined as stage I-III CRC at diagnosis, with the detection of metachronous metastasis after primary tumor resection. In the literature, metachronous metastases are also referred to as 'distant recurrences'. Patients who underwent endoscopic instead of surgical resection of the primary tumor and patients with rectal cancer who opted for a wait-and-see approach after neoadjuvant chemoradiation (and therefore did not undergo surgical resection with curative intent) were excluded.

2.2. Data collection

All data used in this study were extracted from the NCR. Clinical and pathological data on all newly diagnosed malignancies in the Netherlands are registered in the NCR. Main sources of notification are the automated pathology archive (PALGA) and the National Registry of Hospital Discharge Diagnoses. Following the notification, trained registrars collect patient, tumor and treatment characteristics from medical records. Likewise, for all CRC patients with incidence date of the primary tumor between January and June 2015, additional data on the development of metachronous metastasis were collected between February and October 2019 by these registrars from medical records and added to the NCR. The NCR contains a binomial categorical variable on whether the primary CRC diagnosis was established after a positive faecal immunochemical test (FIT) as part of the national population screening (detection mode).

Staging and TNM classification is registered according to the 7th edition of the AJCC cancer staging manual [8]. Topography and morphology is coded according to the International Classification of Diseases for Oncology (ICD-O-3). Tumor location is categorized as right-sided colon (C18.0, C18.1, C18.2, C18.3 or C18.4), left-sided colon (C18.5, 18.6, 18.7), rectum (C19.9, C20.9) or unknown (C18.8 or C18.9). Data on vital status is obtained by annual linkage between the NCR and the Dutch Personal Records Database, and updated until 1 February 2022. Surviving patients were censored at this date.

2.3. The Dutch CRC population screening program; characteristics of patients with screen-detected versus non-screen-detected tumors

The Dutch population screening program for CRC was launched in 2014 with a stepwise introduction by birth cohorts, until all eligible birth cohorts were invited in 2019 [3]. The aim was to eventually screen all individuals between the ages of 55 and 75 years once every two years by a FIT. In 2015, the incidence year of our study population, the following birth cohorts were meant to be invited for screening: 1940, 1946, 1948, 1950, 1952, and 1954 [9]. The birth cohorts (target groups) for 2014 were: 1938, 1939, 1947, 1949, and 1951. Of the 2014 intended target group, 18.7% was not invited in 2014 [9]. The remainder of the 2014 target group was invited in 2015, implying that the individuals who were invited to participate in the screening program in 2015 were between 60 and 77 years old. Of all individuals aged 55–75 years old in 2015 (n = 1,963,873), 59.7% was invited in 2015 [3]. The proportion of invited individuals who participated (participation rate) was 72.4% [3].

Screening was performed using FIT to detect hemoglobin (occult blood) in feces. If the FIT was positive, screening participants were referred for colonoscopy if considered eligible. Of the individuals with a positive FIT in 2015, 79.4% underwent colonoscopy [9].

Patients whose tumor was non-screen-detected could be any age ≥ 18 years old at CRC diagnosis. The non-screen-detected group consists of patients who were not yet invited to participate in the screening program, patients who were invited but did not participate (non-participants), and/or patients who had a false-negative FIT. To which of these three groups non-screen-detected patients belonged to is unknown.

2.4. Statistical analysis

Patient and tumor characteristics were described for the total study population, and for patients with screen-detected versus non-screen-detected primary tumors separately.

OS was calculated from date of first metachronous metastasis until date of death. Surviving patients were censored at 1 February 2022. OS after metachronous metastases of patients with screen-detected versus non-screen-detected primary tumors were compared using the Kaplan-Meier method and log-rank tests for the total study population, and per tumor stage. One-year and five-year OS rates were calculated for the total study population and separately per stage at diagnosis.

We investigated whether detection-mode was associated with OS after metachronous metastasis using multivariable Cox proportional hazards (PH) regression modeling adjusted for potential confounders. A directed acyclic graph (DAG) was created to deduce for which variables should be adjusted in this multivariable analysis [10]. The following potential confounders were selected based on literature [7,11,12] and entered in the Cox PH model in addition to the detection mode variable: age at primary tumor diagnosis, gender, pathological T stage (pT), pathological N stage (pN), differentiation grade, histologic classification, and primary tumor location (right-sided colon, left-sided colon, rectal). We reported results for unadjusted (univariable) Cox PH models, for Cox PH models adjusted for age at diagnosis primary tumor and sex, and for fully adjusted models. Hazard ratios (HRs) with 95% confidence intervals (CI) were obtained from the Cox PH models. The PH assumption was assessed for detection mode, our variable of interest, using Schoenfeld residuals and by visual assessment of a log-log transformation of the survival curve. The PH assumption was met.

To avoid loss of information and selection bias, we used multiple imputation using Multivariate Imputation by Chained Equations (MICE) [13] for variables with missing data that we entered in the multivariable Cox PH model, assuming missingness at random. The imputation model contained the variables of the substantive analysis model, the survival outcome (the event indicator and the Nelson-Aalen estimate of the cumulative hazard of death [14]), and the following auxiliary variables: number of metastatic sites at mCRC diagnosis, location of metastasis at mCRC diagnosis, age at mCRC diagnosis, time interval between diagnosis primary tumor and diagnosis metachronous metastasis, primary tumor resection, adjuvant chemotherapy, neoadjuvant (chemo)radiation, antitumor treatment after mCRC diagnosis (systemic treatment, HIPEC, surgical metastasectomy, radiotherapy, non-surgical local treatment of liver metastasis). Continuous variables (age at primary tumor diagnosis, age at mCRC diagnosis, and time interval between diagnosis primary tumor and diagnosis metachronous metastasis) were modeled using restricted cubic splines. We generated 14 imputed datasets (with 25 iterations each), based on the percentage of patients with at least one missing variable. Regression analysis was performed on each imputed dataset and results were pooled according to Rubin's rules [15].

P values < 0.05 were considered statistically significant and all tests were two-sided. Analyses were carried out using SPSS version 26.0, R version 4.0.3 [16] (packages "survival", "mice", "survminer", "ggplot2") and GraphPad Prism 9.0.

Table 1
Characteristics of study population.

	Screen-detected	Not screen-detected	Total
	(N = 152)	(N = 642)	(N = 794)
Sex			
Male	99 (65.1%)	382 (59.5%)	481 (60.6%)
Female	53 (34.9%)	260 (40.5%)	313 (39.4%)
Age at diagnosis primary tumor (years)			
Mean (SD)	66.1 (4.48)	68.4 (11.1)	67.9 (10.2)
Median [Min, Max]	65.0 [45.0, 76.0]	70.0 [23.0, 93.0]	68.0 [23.0, 93.0]
Age at diagnosis metastasis (years)			
Mean (SD)	67.8 (4.54)	69.9 (11.0)	69.5 (10.2)
Median [Min, Max]	67.0 [46.0, 78.0]	71.0 [25.0, 95.0]	70.0 [25.0, 95.0]
Interval between diagnosis primary tumor and diagnosis metachronous metastasis (months)			
Mean (SD)	20.9 (11.7)	18.2 (11.0)	18.7 (11.2)
Median [Min, Max]	18.6 [2.14, 52.3]	15.9 [1.05, 56.4]	16.4 [1.05, 56.4]
Stage at diagnosis CRC[a]			
Stage I[b]	24 (15.8%)	31 (4.8%)	55 (6.9%)
pT1	15 (62.5%)	6 (19.4%)	21 (38.2%)
pT2	9 (37.5%)	23 (74.2%)	32 (58.2%)
pT missing	0 (0%)	2 (6.5%)	2 (3.6%)
pN0	19 (79.2%)	26 (83.9%)	45 (81.8%)
pN missing	5 (20.8%)	5 (16.1%)	10 (18.2%)
Stage II[b]	42 (27.6%)	159 (24.8%)	201 (25.3%)
pT0	0 (0%)	1 (0.6%)	1 (0.5%)
pT2	1 (2.4%)	3 (1.9%)	4 (2.0%)
pT3 (IIA)	38 (90.5%)	113 (71.1%)	151 (75.1%)
pT4a (IIB)	2 (4.8%)	25 (15.7%)	27 (13.4%)
pT4b (IIC)	0 (0%)	15 (9.4%)	15 (7.5%)
pT missing	1 (2.4%)	2 (1.3%)	3 (1.5%)
pN0	41 (97.6%)	155 (97.5%)	196 (97.5%)
pN missing	1 (2.4%)	4 (2.5%)	5 (2.5%)
Stage III[b]	86 (56.6%)	452 (70.4%)	538 (67.8%)
pT0	0 (0%)	8 (1.8%)	8 (1.5%)
pT1	2 (2.3%)	6 (1.3%)	8 (1.5%)
pT2	10 (11.6%)	40 (8.8%)	50 (9.3%)
pT3	49 (57.0%)	277 (61.3%)	326 (60.6%)
pT4a	24 (27.9%)	75 (16.6%)	99 (18.4%)
pT4b	1 (1.2%)	43 (9.5%)	44 (8.2%)
pT missing	0 (0%)	3 (0.7%)	3 (0.6%)
pN0	8 (9.3%)	48 (10.6%)	56 (10.4%)
pN1	46 (53.5%)	206 (45.6%)	252 (46.8%)
pN2	31 (36.0%)	195 (43.1%)	226 (42.0%)
pN missing	1 (1.2%)	3 (0.7%)	4 (0.7%)
Primary tumor location			
Right-sided colon tumor	33 (21.7%)	213 (33.2%)	246 (31.0%)
Left-sided colon tumor	65 (42.8%)	185 (28.8%)	250 (31.5%)
Rectal tumor	53 (34.9%)	242 (37.7%)	295 (37.2%)
Location primary tumor unknown	1 (0.7%)	2 (0.3%)	3 (0.4%)
Differentiation grade			
Well	3 (2.0%)	15 (2.3%)	18 (2.3%)
Moderate	126 (82.9%)	449 (69.9%)	575 (72.4%)
Poor	11 (7.2%)	95 (14.8%)	106 (13.4%)
Missing	12 (7.9%)	83 (12.9%)	95 (12.0%)
Histology			
Adenocarcinoma	141 (92.8%)	567 (88.3%)	708 (89.2%)
Mucinous adenocarcinoma	10 (6.6%)	55 (8.6%)	65 (8.2%)
Signet ring cell carcinoma	0 (0%)	15 (2.3%)	15 (1.9%)
Other	1 (0.7%)	5 (0.8%)	6 (0.8%)
> 1 Primary tumor	0 (0%)	2 (0.3%)	2 (0.3%)
Molecular pathology[c]			
No BRAF mutation	34 (22.4%)	148 (23.1%)	182 (22.9%)
BRAF mutation	2 (1.3%)	14 (2.2%)	16 (2.0%)
BRAF status unknown	116 (76.3%)	480 (74.8%)	596 (75.1%)
No RAS mutation	15 (9.9%)	76 (11.8%)	91 (11.5%)
RAS mutation	22 (14.5%)	93 (14.5%)	115 (14.5%)
RAS status unknown	115 (75.7%)	473 (73.7%)	588 (74.1%)
MSS	41 (27.0%)	146 (22.7%)	187 (23.6%)
MSI	1 (0.7%)	14 (2.2%)	15 (1.9%)
MS status unknown	110 (72.4%)	482 (75.1%)	592 (74.6%)
Year of diagnosis first metastasis			
2015	21 (13.8%)	145 (22.6%)	166 (20.9%)
2016	68 (44.7%)	275 (42.8%)	343 (43.2%)
2017	38 (25.0%)	150 (23.4%)	188 (23.7%)
2018	19 (12.5%)	57 (8.9%)	76 (9.6%)
2019	6 (3.9%)	15 (2.3%)	21 (2.6%)
Number of metastatic sites at mCRC diagnosis			
1	110 (72.4%)	432 (67.3%)	542 (68.3%)
2	28 (18.4%)	129 (20.1%)	157 (19.8%)
3	9 (5.9%)	56 (8.7%)	65 (8.2%)
> =4	5 (3.3%)	25 (3.9%)	30 (3.8%)
Location of metastasis at mCRC diagnosis			
Liver	78 (51.3%)	319 (49.7%)	397 (50.0%)
Liver only	59 (38.8%)	188 (29.3%)	247 (31.1%)
Lung	46 (30.3%)	210 (32.7%)	256 (32.2%)
Lung only	21 (13.8%)	89 (13.9%)	110 (13.9%)
Peritoneal	33 (21.7%)	144 (22.4%)	177 (22.3%)
Peritoneal only	18 (11.8%)	61 (9.5%)	79 (9.9%)
Bone	6 (3.9%)	28 (4.4%)	34 (4.3%)
Brain	3 (2.0%)	14 (2.2%)	17 (2.1%)
Treatment after diagnosis mCRC			
No antitumor treatment	20 (13.2%)	160 (24.9%)	180 (22.7%)

(continued on next page)

Table 1 (*continued*)

	Screen-detected (N = 152)	Not screen-detected (N = 642)	Total (N = 794)
Systemic treatment (palliative/ induction)	72 (47.4%)	317 (49.4%)	389 (49.0%)
Local treatment of metastases			
- HIPEC/CRS	17 (3.4%)	37 (5.8%)	54 (6.8%)
- Surgical resection of metastases	63 (41.4%)	201 (31.3%)	264 (33.2%)
- Radiotherapy of metastases	35 (23.0%)	127 (19.8%)	162 (20.4%)
- Nonsurgical local treatment of liver metastases[d]	15 (9.9%)	42 (6.5%)	57 (7.2%)

SD: standard deviation, CRC: colorectal cancer, mCRC: metastatic colorectal cancer, HIPEC: hyperthermic intraperitoneal chemotherapy, CRS: cytoreductive surgery.
a. Stage based on pTNM supplemented with cTNM, according to AJCC 7th edition cancer staging manual. In case of neoadjuvant treatment, cTNM was used to determine stage.
b. pT and pN percentages calculated with number of patients per stage as the denominator.
c. We assumed that RAS and BRAF mutations are mutually exclusive.
d. Radiofrequent ablation (RFA), microwave ablation (MWA), radio-embolisation, nanoknife-IRE.

2.5. Sensitivity analyses

Since individuals are invited for participation in the population screening based on their year of birth, age at diagnosis of the primary tumor is an important potential confounder for the association between detection mode and OS after metachronous metastasis. We adjusted for age in our multivariable analyses. Additionally, we performed a sensitivity analysis in which we restricted our analysis to patients aged 60–77 years at diagnosis to asses potential variation of results because of age differences. Furthermore, we conducted another sensitivity analysis in which we excluded all patients who did not receive any antitumor treatment after the development of metachronous metastasis.

3. Results

3.1. Study population

Of all adult patients who were diagnosed with stage I-III CRC between January and June 2015 in the Netherlands, 814 (14.9%) developed metachronous metastases before October 2019. After exclusion of 7 patients who underwent endoscopic instead of surgical resection of the primary tumor and 13 patients with rectal cancer who opted for a wait-and-see approach after neoadjuvant chemoradiation, our total study population consisted of 794 patients with metachronous mCRC.

In 19% of the patients with metachronous mCRC (n = 152), CRC was diagnosed after a positive FIT, performed in the context of the national CRC population screening program. Patients with screen-detected tumors were on average younger, more often had lower tumor stage, and more favorable differentiation grade (Table 1). pT4b tumors (i.e. tumors which directly invade or adhere to other adjacent organs or structures) that led to metachronous metastasis were almost always non-screen-detected. Screen-detected tumors were more often localized in the left-side of the colon. At diagnosis of the first distant metastases, they were more often limited to the liver in patients with screen-detected primary tumors. Patients with screen-detected primary tumors more

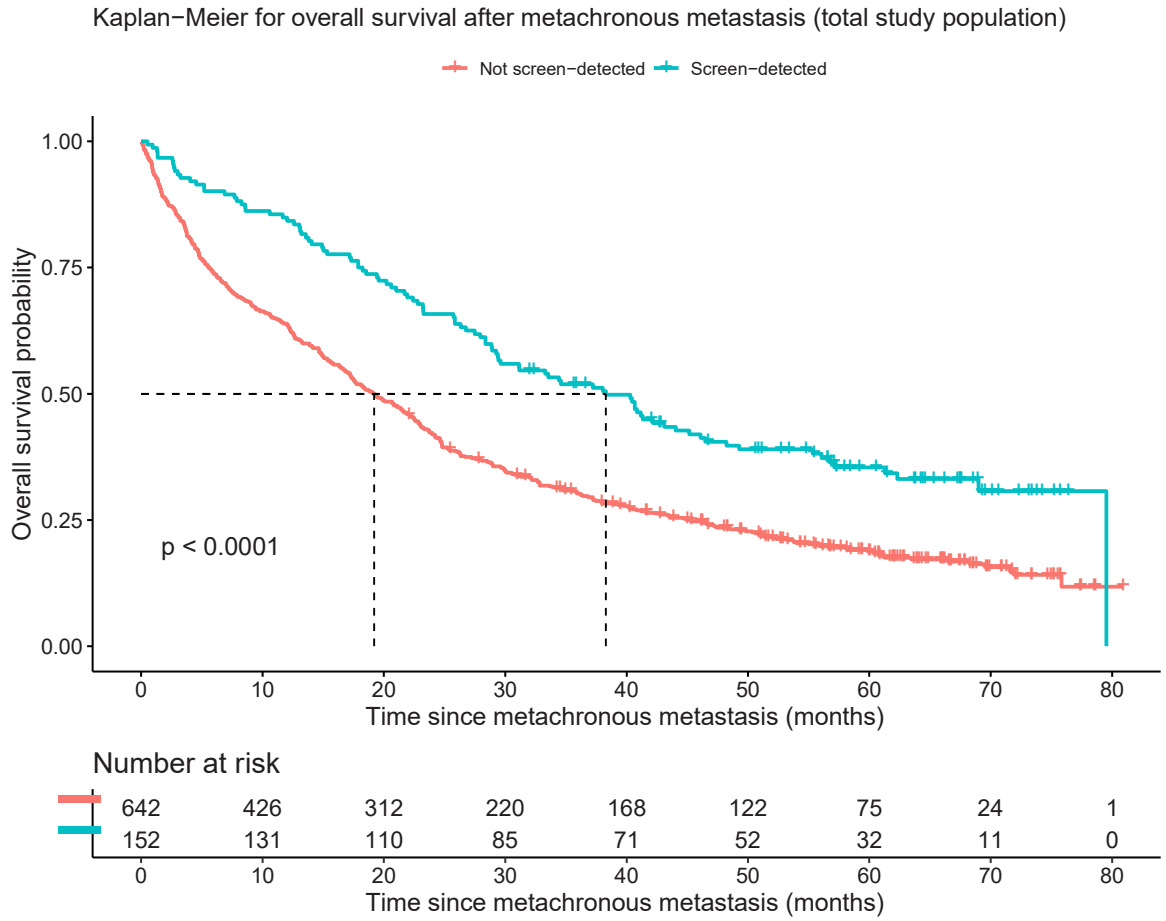

Fig. 1. Kaplan-Meier curve for overall survival after metachronous metastasis (total study population).

Table 2
OS after metachronous metastasis of patients with screen-detected versus non-screen-detected primary tumors, for the total study population, and stratified per stage at CRC diagnosis.

	Screen-detected	Not screen-detected	P value (log-rank)
Overall			
n	152	642	
Median OS, months (95% CI)	38.3 (29.4–46.5)	19.2 (17.3–21.9)	< 0.0001
One-year OS rate, % (95% CI)	85.9 (79.4–90.8)	63.9 (60.3–67.7)	
Five-year OS rate, % (95% CI)	35.4 (28.3–44.3)	18.8 (15.9–22.3)	
Stage I			
n	24	31	
Median OS, months (95% CI)	41.8 (28.9-NR)	34.6 (23.7–63.5)	0.15
One-year OS rate, % (95% CI)	79.2 (64.5–97.2)	87.1 (76.1–99.7)	
Five-year OS rate, % (95% CI)	37.0 (21.9–62.7)	25.8 (13.3–50.2)	
Stage II			
n	42	159	
Median OS, months (95% CI)	69.0 (41.3-NR)	21.9 (16.8–29.0)	0.00033
One-year OS rate, % (95% CI)	100%	66.7 (59.7–74.4)	
Five-year OS rate, % (95% CI)	52.9 (39.4–71.0)	26.5 (20.3–34.6)	
Stage III			
n	86	452	
Median OS, months (95% CI)	27.6 (20.6–38.0)	17.5 (15.1–20.7)	0.0037
One-year OS rate, % (95% CI)	79.1 (70.9–88.2)	61.3 (57.0–65.9)	
Five-year OS rate, % (95% CI)	26.4 (18.1–38.5)	15.7 (12.5–19.7)	

NR: not reached.

often received antitumor treatment for metastatic disease. Specifically, they more often received (potentially curative) surgical resection of metastases compared to patients with non-screen-detected primary tumors: 41.4% vs. 31.3% within the total study population (n = 794), 71.2% vs. 55.9% within the subgroup of patients with liver-only metastatic disease (n = 247).

3.2. Univariable analysis

For the total study population of 794 patients, median OS after metachronous metastasis was 22.3 [95% CI 19.9–24.2] months, with one- and five-year survival rates after metachronous metastasis of 67.9% [64.7–71.2] and 22.0% [19.2–25.2], respectively. Median OS after metachronous metastasis was significantly longer for patients with a screen-detected primary tumor (n = 152, 19%) compared to patients with a non-screen-detected primary tumor (n = 642, 81%) (Fig. 1 and Table 2): 38.3 [29.4–46.5] versus 19.2 [17.3–21.9] months (p < 0.0001). One- and five-year survival rates after metachronous metastasis were higher for patients with a screen-detected primary tumor compared to patients with a non-screen-detected primary tumor: 85.9% [79.4–90.8] versus 63.9% [60.3–67.7] and 35.4% [28.3–44.3] versus 18.8% [15.9–22.3], respectively. The superior survival outcomes for patients with screen-detected primary tumors remained after stratification per stage (Fig. 2 and Table 2), although sample size was insufficient for stage I to demonstrate a statistically significant difference.

3.3. Multivariable analysis

Four of the variables that we entered in the multivariable Cox PH model had missing data (Table 1): pT (n = 8, 1.0%), pN (n = 19, 2.4%), differentiation grade (n = 95, 12.0%), and primary tumor location (n = 3, 0.4%). Patients with missing data were compared to patients with complete data (Table S1).

Screen-detection of the primary tumor was independently associated with OS after metachronous metastasis (HR 0.70 [0.56–0.89])(Table 3 and Fig. 3) in multivariable Cox PH regression analysis. The association between screen-detection and longer OS after metachronous metastases (HR <1.0) was present in all subgroups, although statistical significance could not be demonstrated in most subgroups due to small sample sizes resulting in broad 95% CI's crossing 1.0.

3.4. Sensitivity analyses

After exclusion of patients < 60 and > 77 years (n = 287), changes in median OS, one-year survival rate, and five-year survival rate after metachronous metastasis were negligible compared to results for the total study population (Tables S2 and 2). HR for the association between screen-detection of the primary tumor and OS after metachronous

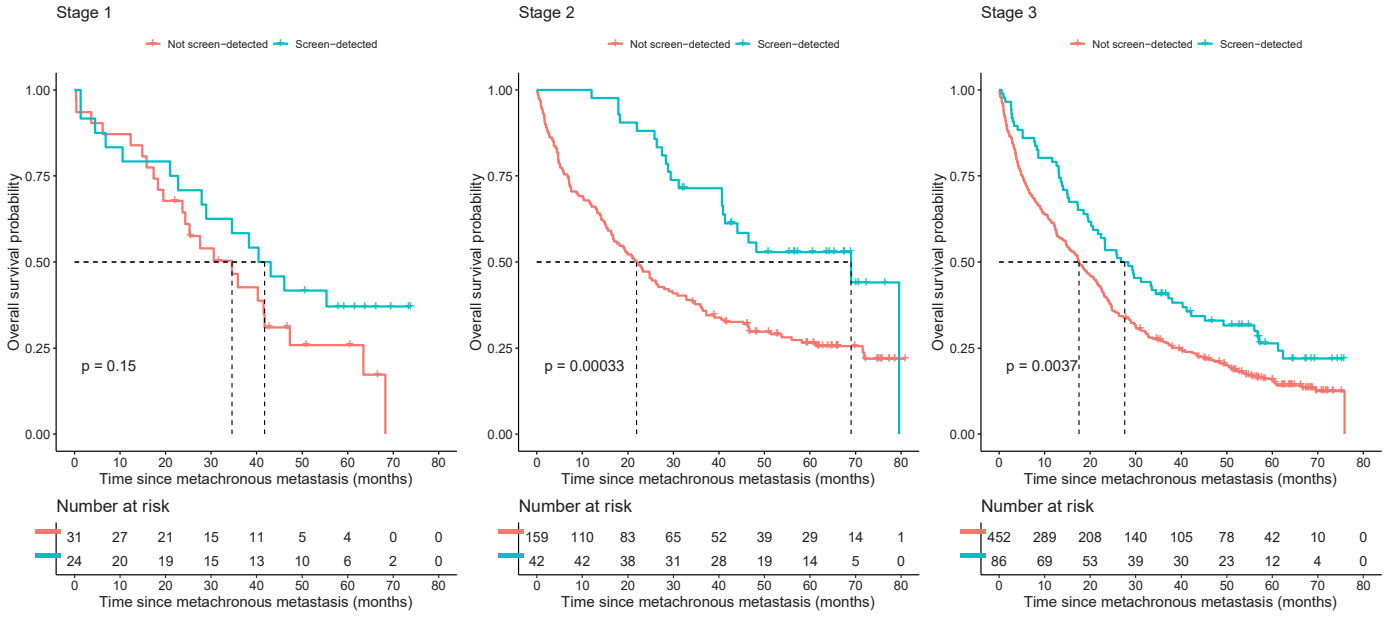

Fig. 2. Kaplan-Meier curves for overall survival after metachronous metastasis, stratified per stage at CRC diagnosis.

Table 3
Association between method of detection, and OS after metachronous metastasis, adjusted for potential confounders, stratified by stage and primary tumor location.

	Unadjusted		Adjusted for age and sex[a]		Fully adjusted[b]	
	HR	95% CI	HR	95% CI	HR	95% CI
Overall						
Not screen detected	1.00	Ref.	1.00	Ref.	1.00	Ref.
Screen detected	0.57	0.46–0.71	0.66	0.52–0.83	0.70	0.56–0.89
Stage I						
Not screen detected	1.00	Ref.	1.00	Ref.	1.00	Ref.
Screen detected	0.62	0.32–1.20	0.62	0.29–1.33	¶	¶
Stage II						
Not screen detected	1.00	Ref.	1.00	Ref.	1.00	Ref.
Screen detected	0.44	0.27–0.69	0.49	0.30–0.81	0.55	0.33–0.92
Stage III						
Not screen detected	1.00	Ref.	1.00	Ref.	1.00	Ref.
Screen detected	0.67	0.52–0.88	0.79	0.60–1.04	0.79	0.60–1.06
Right-sided colon						
Not screen detected	1.00	Ref.	1.00	Ref.	1.00	Ref.
Screen detected	0.59	0.39–0.89	0.71	0.46–1.09	0.81	0.51–1.28
Left-sided colon						
Not screen detected	1.00	Ref.	1.00	Ref.	1.00	Ref.
Screen detected	0.52	0.36–0.75	0.65	0.44–0.97	0.77	0.50–1.18
Rectum						
Not screen detected	1.00	Ref.	1.00	Ref.	1.00	Ref.
Screen detected	0.67	0.47–0.97	0.68	0.47–0.99	0.62	0.42–0.92

OS: overall survival, CRC: colorectal cancer, HR: hazard ratio, CI: confidence interval.
a. Adjusted for age at diagnosis primary tumor, and sex.
b. Adjusted for age at diagnosis primary tumor, sex, differentiation grade, histology, pT, pN, and location of primary tumor.
Full adjustment not possible for stage I due to insufficient sample size.

metastasis in multivariable analysis was also retained (HR 0.67 [0.52–0.86], Table S2). After exclusion of patients who did not receive any antitumor treatment after mCRC diagnosis (n = 180), survival estimates were higher for both patients with screen-detected and patients with non-screen-detected tumors (Table S3). The independent association between detection mode and OS after metachronous metastasis was retained (HR 0.67 [0.51–0.87], Table S3).

4. Discussion

In this registry-based cohort of patients with metachronous mCRC, median OS after metachronous metastasis was 19.1 months longer for patients with a screen-detected primary tumor compared to patients with a non-screen-detected primary tumor. The higher proportion of long-term survivors (5-year OS rate 35.4% versus 18.8%) is of particular interest since it seems to indicate that early detection of the primary tumor, and therefore early resection, increases the chance of cure once mCRC is diagnosed. The association between detection mode of the primary tumor and OS after metachronous metastasis remained after adjustment for potential confounders and in both sensitivity analyses.

A possible explanation for our findings is that early resection of the primary tumor might be favorable for the behavior of micrometastases. This hypothesis is supported by the higher proportion of liver-only metastasis in patients with screen-detected primary tumors, which can more often be treated with local, potentially curative, treatment [17, 18]. On the other hand, residual confounding by factors both related to screening participation and outcome, such as educational level, socio-economic status (SES), ECOG performance status, comorbidity, and lifestyle, may partly explain the better survival after the development of metachronous metastases for screening participants [19–26]. Our observation that patients with screen-detected primary tumors more often underwent antitumor treatment for metastatic disease, likely reflects that these patients were in better physical condition and/or had a higher SES [24]. We addressed this by conducting a sensitivity analysis in which we excluded all patients who did not undergo antitumor treatment after mCRC diagnosis, after which the independent association between detection mode and OS after metachronous metastasis was retained. Also, as described in the methods section, we expect that a significant proportion of the non-screen-detected patients within the 55–75 year target population in our study were not yet invited to participate given the stepwise implementation of the Dutch screening program as from 2014. Consequently, our non-screen-detected group includes patients who were not yet invited to participate in the screening program, patients who were invited but declined participation (non-participants), and/or patients who had a false-negative FIT. The 'not yet invited' individuals consist of a combination of individuals who are and are not inclined to participate in population screening. Hence, the characteristics of the 'not yet invited' individuals are more comparable to the screening participants than a group of exclusively non-participants would be. This benefits the comparability of the screen-detected and non-screen-detected group and decreases healthy-user bias.

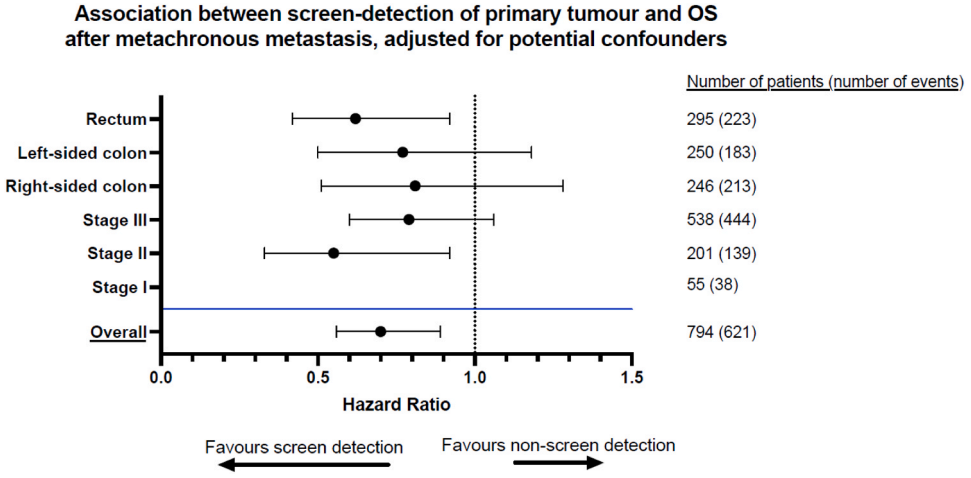

Fig. 3. Hazard ratios with 95% CI for the association between screen-detection of the primary tumour and OS after metachronous metastasis, for the overall study population and stratified for subgroups. Adjusted for potential confounders. HR not displayed for stage I since adjustment for potential confounders was not possible due to insufficient sample size.

Prior studies on the effect of CRC screening programs have found a decreased CRC incidence, and a shift towards detection at earlier stages [1–3]. A decrease in CRC mortality due to CRC screening has not (yet) been demonstrated [3,27]. Previous comparisons of survival between patients with screen-detected and non-screen-detected CRC were hampered by lead-time bias [4,28,29]. The main strength of our study lies in the focus on survival after metachronous metastasis, so lead-time bias did not influence our results. Furthermore, we used nationwide population-based data, corrected for potential confounders in multivariable analyses, and performed sensitivity analyses to asses potential variation of results because of age differences and/or antitumor treatment after mCRC diagnosis.

The potential residual confounding in our study by abovementioned factors (e.g. educational level, lifestyle) reveals the difficulty of working with real-world data from nationwide cancer registries in which a limited number of variables is collected. Large-scale cohort studies, such as the Prospective Dutch CRC cohort (PLCRC) [30,31], which collect additional (patient-reported) data on included patients may enable more extensive adjustment for potential confounders in future research. In addition, our sample size was insufficient to draw conclusions on the association between screen-detection of the primary tumor and OS after metachronous metastasis in certain subgroups (patients with stage I disease, subgroups based on primary tumor location). Also, this study lacks information on cause of death which prevented us from reporting cancer-specific survival. However, we expect the impact of competing risks to be limited in this population of patients with mCRC since almost all patients with mCRC die as a result of their metastatic disease [32,33]. RAS/BRAF mutational status is missing in approximately 75% of our study population, but we assume that this does not influence our results since RAS/BRAF status is likely not prognostic in stage I-III CRC [34,35] and therefore is not associated with detection method.

Our results have two main implications for clinicians, researchers and policy makers. First, the independent association between screen-detection of the primary tumor and longer OS after metachronous metastasis may support the clinical utility of CRC population screening. Second, even if the association between screen-detection of the primary tumor and longer OS after metachronous metastasis would be partly explained by residual confounding and therefore cannot be used to quantify screening effects, our results can be used to inform patients, physicians and the general population about the prognosis of patients with metachronous mCRC who were initially diagnosed by screening [4]. Until now, available survival probabilities for patients with metachronous mCRC were reported irrespective of detection mode and therefore are too grim for patients with screen-detected primary tumors. Medical oncologists should become aware of the change in their patient population in daily clinical practice as a consequence of the introduction of CRC population screening. Likewise, detection mode of the primary tumor should be taken into account in the design and analysis of clinical trials for new therapies for recurrent CRC, since the median survival difference of 19.1 months found between patients with screen-detected versus non-screen-detected cancer is larger than any survival benefit that has been shown in prospective randomized studies in mCRC.

In conclusion, we found an independent association between screen-detection of the primary tumor and considerably longer OS after metachronous metastases in patients with CRC. This may support the clinical utility of the population screening program and it shows the prognostic value of detection mode of the primary tumor once distant recurrence is diagnosed.

Ethics

According to the Central Committee on Research involving Human Subjects, this type of registry-based study does not require approval from an ethics committee in the Netherlands. The study was approved by the Privacy Review Board and the scientific council of the Netherlands Comprehensive Cancer Organisation (IKNL) which collects and guards the data for the Netherlands Cancer Registry (NCR). All data were pseudonymised prior to the transfer from IKNL to the researchers. The NCR uses an opt-out approach to consent.

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CRediT authorship contribution statement

Patricia A.H. Hamers: Conceptualization, Data curation, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Geraldine R. Vink**: Conceptualization, Writing – review & editing, Supervision. **Marloes A.G. Elferink**: Writing – review & editing. **Leon M.G. Moons**: Writing – review & editing. **Cornelis J.A. Punt**: Writing – review & editing. **Anne M. May**: Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision. **Miriam Koopman**: Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

GRV reports research grants/funding paid to her institution by Servier, BMS, Bayer, Merck, PGDx, Delfi Diagnostics, Lilly, Pierre Fabre and Sirtex. GRV reports travel/accommodation fees from Servier. CP reports an advisory role for Nordic Pharma. MK reports personal travel/accommodation fees from Congress Care-Dutch oncology society (NVMO). MK reports research grants/funding paid to her institution by Amgen, Bayer, BMS, Merck-Serono, Nordic Pharma, Roche, Servier, Sirtex, and Sanofi-Aventis. MK reports honoraria paid to her institution by BMS, Nordic Pharma, and Servier. PH reports honoraria paid to her institution by Servier. All remaining authors have declared no conflicts of interest.

Data availability

The data that support the findings of our study are available from the NCR. Restrictions apply to the availability of these data, which were used under license for our study.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113429.

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