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ORIGINAL ARTICLE

Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands

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Abstract
Purpose The main cause of death of colorectal cancer patients is metastatic disease. Approximately 20–25 % of the patients present with metastases at time of diagnosis. The clinical course of patients who develop metachronous metastases, however, is less clear. The aims of this study were to describe the incidence, treatment and survival of patients with metachronous metastases from colorectal cancer and to determine risk factors for developing metachronous metastases.
Methods From the Netherlands Cancer Registry, patients diagnosed with colorectal carcinoma in the period 2002–2003 in North-East Netherlands were selected. Patients were followed for 5 years after diagnosis of the primary tumour. Kaplan-Meier method and Cox regression analyses were used to determine predictors for developing metastases and to analyse overall survival.
Results In total, 333 of 1743 (19 %) patients developed metachronous metastases. The majority (83 %) of these metastases were diagnosed within 3 years, and the most frequent site was the liver. Patients with advanced stage and patients with tumours in the descending colon or in the rectum were more likely to develop metastases. Approximately 10 % of all patients underwent intentionally curative treatment for their metastases, with a 5-year survival rate of 60 %. Treatment of metastases and pathologic N (pN) status were independent prognostic factors for overall survival.
Conclusions Site and stage of the primary tumour were predictors for developing metachronous metastases. A limited number of patients with metastatic disease were treated with a curative intent. These patients had a good prognosis. Therefore, focus should be on identifying more patients who could benefit from curative treatment.

Keywords Colorectal cancer · Metachronous metastases · Population-based study · Treatment · Survival

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Introduction

Colorectal cancer is a major health problem worldwide and the third most common cancer in the Netherlands. In 2012, more than 13,000 new patients were diagnosed with colorectal cancer, while approximately 5000 patients died of this disease [1]. The main cause of death is due to metastatic disease, either discovered at presentation or developed during follow-up.

During the last decades, more patients with metastatic disease are surgically treated with a curative intent. Excellent 5-year overall survival results of above 60 % have been reported in an observational study among patients with solitary liver metastases who underwent complete resection [2]. Patients with multiple liver or lung metastases are currently also increasingly treated with combined modality treatment, including surgery, chemotherapy and/or radiotherapy or radiofrequency ablation techniques.

However, the majority of patients have metastases not amenable for local curative treatment and remain in a palliative setting. During the last decade, survival for these patients has also significantly improved due to the introduction of newly developed chemotherapeutical agents such as irinotecan and oxaliplatin added to 5-FU-based chemotherapy [3, 4]. More recently, the combination of chemotherapy with targeted therapies further improved median survival of patients with advanced disease to 20 months or more [5], compared to approximately 9 months among patients who receive best supportive care [6].

Approximately 20–25 % of the patients already have distant metastases at time of diagnosis of the colorectal tumour, with the liver as the most common site [7]. The number of patients who develop metachronous metastases is not well known. There are only a few population-based studies describing the epidemiology and management of metastases from colorectal cancer [8], often focusing at one site of metastases [9–11]. Therefore, this study aimed to provide insight into the incidence, treatment and survival of all patients with metachronous metastases from colorectal cancer and to identify risk factors for developing metachronous metastases using data from the population-based cancer registry in the Netherlands.

Methods

Netherlands Cancer Registry

All newly diagnosed cancer cases are registered in the nationwide population-based Netherlands Cancer Registry (NCR). Notification is mainly obtained from the automated national pathological archive (PALGA). The National Registry of Hospital Discharge Diagnoses is another important source, accounting for up to 8 % of new cases that were not obtained from PALGA. The completeness of the NCR is estimated to be at least 95 % [12]. Data are collected from hospital records by specially trained registration clerks. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O) [13], and the TNM classification is used for staging of the tumours [14]. The dataset of the NCR includes patient and primary tumour characteristics and information on treatment of these primary tumours. Information on metachronous metastases is not routinely collected in the NCR. This was obtained by retrospectively reviewing the patient files of all patients by the registration clerks of the NCR. Patients were followed for 5 years after diagnosis of the primary tumour, and information on all metastatic sites was collected from hospital records. The vital status of all patients is complete up to 31 December 2011 by linking deaths from the municipal population registries to the cancer registry.

Patients

Patients diagnosed with colorectal carcinoma in 2002–2003 in the region of the Comprehensive Cancer Organisation Stedendriehoek Twente or in 2003 in the region of the Comprehensive Cancer Organisation North Netherlands were selected from the NCR (N=3142).

In the study period, 607 patients (19.3 %) presented with synchronous metastases. They were excluded from the analyses. Patients with another invasive tumour in the medical history (N=373; 11.9 %) were also excluded, because it could not always be identified which primary tumour accounted for the metastatic lesions. Furthermore, patients who did not underwent surgical treatment of the primary tumour (N=236; 7.5 %), patients who underwent their resection in another region (N=12; 0.4 %), patients with a macroscopic irradical resection (N=26; 0.8 %) and those who died within 3 months after diagnosis (N=121; 3.9 %) were excluded. In the remaining group of 1767 patients, 24 (1.4 %) were lost to follow-up.

Detailed information about the follow-up program was not available for all patients, but most patients were followed at least once or twice per year in accordance with the Dutch guidelines. Metastases were defined as metachronous when detected at least 3 months after diagnosing the primary colorectal cancer [9]. Site was categorised into right-sided colon (C18.0–C18.2), transverse colon (C18.3–C18.5), left-sided colon (C18.6–C18.7), overlapping lesions of colon or not otherwise specified (C18.8–C18.9), rectosigmoid (C19.9) and rectum (C20.9).

Treatment after diagnosis of the metastasis was categorised into intentionally curative treatment, palliative treatment (chemotherapy, targeted therapy and/or radiotherapy) and best supportive care.

Statistical analyses

Cumulative metastasis rates were calculated using the Kaplan-Meier method. Differences between variables were tested using the log-rank test. Multivariable Cox proportional hazards regression analysis was performed to determine risk factors for developing metachronous metastases, using variables with a p value <0.1 in univariable analyses. Time to metastases was calculated from the date of diagnosis of the primary tumour to the date of diagnosis of the metastasis. Patients who did not develop a metastasis were censored at time of death or end of follow-up (31 December 2011).

Crude survival rates were analysed using the Kaplan-Meier method and compared by the log-rank test. Survival time was calculated from the date of diagnosis of the metastasis until the date of death or end of follow-up. Cox proportional hazards regression analysis was used to determine prognostic factors for 5-year overall survival after diagnosis of metachronous

metastases. Variables with a p value <0.1 in univariable analysis were incorporated into the multivariable model.

For all analyses, STATA version 12.0 was used. All tests were two-sided and a p value <0.05 was considered statistically significant.

Results

In total, 5-year follow-up data was complete for 1743 of 1767 (99 %) selected patients. Table 1 summarises the characteristics of this study population. Among these patients, 52 % was male and 66 % was aged younger than 75 years. The most common sites of the primary tumour were rectum (27 %) and left-sided colon (26 %). The majority of tumours (68 %) were moderately differentiated and 40 % was diagnosed with stage IIA disease.

Within 5 years after diagnosis of the primary tumour, 333 patients (19 %) were diagnosed with metachronous metastases: 227 (18 %) patients with colon cancer and 106 (22 %) patients with rectal cancer. Half of these metastases were detected at multiple sites (N=158; 47 %), with 31 % at two sites, 12 % at three sites and 4 % more widespread.

Median time between diagnosis of the primary tumour and metastases was 1.5 years (range 0.3–5.0 years). The majority

Table 1 Characteristics of study population, cumulative metastasis rate and multivariable analyses of risk factors associated with developing metachronous metastases

	No. of patients (%)	Cum. metastasis rate		Multivariable analyses
		5 years (95 % CI)	p value	HR (95 % CI)
Total	1743 (100)	20.52 (18.63–22.58)		
Gender			0.87	
Males	911 (52)	20.36 (17.79–23.25)		
Females	832 (48)	20.71 (18.01–23.74)		
Age at time of diagnosis of the primary tumour			0.12	
<75 years	1149 (66)	21.58 (19.25–24.14)		
≥75 years	594 (34)	18.39 (15.31–22.01)		
Site			0.02	
Right-sided colon	426 (24)	15.34 (12.11–19.33)		1.00 (reference)
Transverse colon	190 (11)	17.59 (12.77–23.96)		1.33 (0.87–2.05)
Left-sided colon	456 (26)	24.71 (20.85–29.15)		1.77 (1.29–2.43)
Overlapping lesions and colon NOS	14 (1)	15.38 (4.09–48.78)		1.48 (0.36–6.09)
Rectosigmoid	179 (10)	17.72 (12.65–24.51)		1.16 (0.74–1.81)
Rectum	478 (27)	23.44 (19.79–27.64)		1.81 (1.31–2.50)
Grade			0.16	
Well differentiated	56 (3)	23.44 (14.00–37.69)		
Moderately differentiated	1186 (68)	20.45 (18.19–22.95)		
Poorly differentiated	230 (13)	24.38 (19.09–30.84)		
Unknown	271 (16)	17.01 (12.89–22.26)		
Histology			0.54	
Adenocarcinoma	1475 (85)	20.79 (18.73–23.04)		
Mucinous carcinoma	268 (15)	19.00 (14.61–24.50)		
Stage			<0.001	
I (pT1-2N0)	354 (20)	5.04 (3.16–7.98)		1.00 (reference)
IIA (pT3N0)	690 (40)	15.18 (12.62–18.19)		3.50 (2.09–5.89)
IIB (pT4N0)	58 (3)	17.29 (9.36–30.71)		4.74 (2.10–10.71)
IIIA (pT1-2N1)	59 (3)	24.98 (15.59–38.58)		5.40 (2.66–10.97)
IIIB (pT3-4N1)	320 (18)	32.15 (27.07–37.92)		8.09 (4.81–13.61)
IIIC (pTanyN2)	187 (11)	53.58 (46.14–61.39)		16.52 (9.82–27.79)
Unknown	13 (1)	7.69 (1.12–43.36)		1.41 (0.19–10.58)
pTanyNX + 0 evaluated lymph nodes	62 (4)	19.43 (11.23–32.42)		3.96 (1.85–8.45)

NOS not otherwise specified

of metastases (83 %) were diagnosed within 3 years after diagnosis of the primary tumour. A longer time between diagnosis of the primary tumour and metastases was not associated with a higher number of metachronous metastases.

The 5-year cumulative metastasis rate was 20.5 %. In multivariable analyses, site and stage of the primary tumour were associated with the occurrence of metastases (Table 1). Patients with a tumour in the left-sided colon and patients with a tumour in the rectum had a higher risk of developing metastases compared to patients with a tumour in the right-sided colon (hazard ratio (HR) 1.77, 95 % confidence interval (CI) 1.29–2.43 and HR 1.81, 95 % CI 1.31–2.50, respectively). Patients with a more advanced stage were more likely to develop metastases. The hazard ratio increased up to 16.52 (95 % CI 9.82–27.79) among patients with stage IIIC.

The most frequent site for metachronous metastases was the liver (Table 2). Of all patients with metastases, 215 (65 %) developed liver metastases within 5 years of follow-up. The second most common site was the lung (43 %). Patients with colon cancer developed more often peritoneal metastases compared to patients with rectal cancer (15 and 3 %, respectively, $p=0.001$) and less often lung metastases (34 and 63 %, respectively, $p<0.001$).

Liver-only metastases occurred in 103 (31 %) patients, and 41 (12 %) patients developed lung-only metastases. Thirty-nine (12 %) patients developed both liver and lung metastases, and 55 (17 %) patients had metastases at more than two sites.

In Table 3, the treatment of metachronous metastases is shown by site of metastases. The proportion of all patients with liver metastases who received intentionally curative treatment for their liver metastases was 15 %. Palliative treatment was performed in 47 % of the cases, and 36 % received best supportive care. Of the 103 patients with liver-only metastases, 20 (19 %) received intentionally curative treatment, 45 (44 %) palliative treatment and 35 (34 %) best supportive care. The majority of patients (83 %) who received best supportive care were 75 years or older.

Among the 144 patients with lung metastases, 7 % received intentionally curative treatment, 45 % palliative treatment and 47 % best supportive care for their lung metastases. Seven (17 %) of the 41 patients with lung-only metastases received intentionally curative treatment, 14 (34 %) palliative treatment and 20 (49 %) patients best supportive care. Approximately half of the patients (55 %) who received best supportive care were 75 years or older.

The majority of patients with lymph node metastases and bone metastases received palliative treatment, 60 and 66 %, respectively. Most patients with peritoneal metastases received best supportive care. Among the 27 patients with brain metastases, 11 % underwent intentionally curative treatment and 48 % received palliative treatment.

Overall survival of all patients with metachronous metastases was 50 % at 1 year, 20 % at 3 years and 9 % at 5 years after diagnosis. Patients with single-site metastases had a 5-year survival of 15 %, which dropped to less than 5 % among patients with metastases at two or three sites. There were no 5-year survivors among patients with metastases at more than three sites.

Table 2 Sites of metastases, according to site of the primary tumour

	Total		Colon		Rectum		
	N	%	*N*	%	*N*	%	*p* value
Most common sites							
Liver	215	65	153	67	62	58	0.11
Lung	144	43	77	34	67	63	<0.001
Non-regional lymph nodes	52	16	40	18	12	11	0.14
Peritoneal	37	11	34	15	3	3	0.001
Bones	30	9	19	8	11	10	0.55
Brain	27	8	16	7	11	10	0.30
Combinations of sites							<0.001
Liver only	103	31	79	35	24	23	
Lung only	41	12	18	8	23	22	
Liver and lung	39	12	22	10	17	16	
Liver and all other sites (excl. lung)	30	9	23	10	7	7	
Lung and all other sites (excl. liver)	22	7	12	5	10	9	
All other sites (excl. lung and liver)	43	13	37	16	6	6	
Metastases >2 sites	55	17	36	16	19	18	
Total	333	100	227	100	106	100	

Table 3 Treatment of all patients with metastases, according to site of metastases

	Liver		Lung		Non-regional lymph nodes		Peritoneal		Bones		Brain	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Intentionally curative treatment	33	15	10	7	2	4	4	11	0	0	3	11
Surgery	22	10	8	6	1	2	3	8	–	–	–	–
Surgery and RFA	4	2	–	–	–	–	–	–	–	–	–	–
Surgery and RT	–	–	1	1	–	–	–	–	–	–	3	11
Surgery and CT	4	2	1	1	1	2	1	3	–	–	–	–
RFA	3	1	–	–	–	–	–	–	–	–	–	–
Palliative treatment	101	47	65	45	31	60	10	27	19	63	12	44
CT	96	45	58	40	26	50	10	27	4	13	–	–
CT and RT	2	1	2	1	–	–	–	–	–	–	–	–
CT and RFA	3	1	–	–	–	–	–	–	–	–	–	–
RT	–	–	5	3	5	10	–	–	15	50	12	44
Best supportive care	78	36	68	47	19	37	23	62	10	33	11	41
Unknown	3	1	1	1	–	–	–	–	1	3	1	4
Total	215	100	144	100	52	100	37	100	30	100	27	100

RFA radiofrequency ablation, *RT* radiotherapy, *CT* chemotherapy

Five years after diagnosis of the metachronous metastases, survival was 60 % among patients who received intentionally curative treatment, compared to 6 % among patients who received palliative treatment and 2 % among patients who received best supportive care (Fig. 1). Median survival among these two latter categories was, respectively, 16 and 5 months.

In univariable survival analyses, age, grade, pathologic N (pN) status, number of metastases, site(s) of metastases and treatment of metastases were prognostic factors for 5-year overall survival. In multivariable analysis, only pN status and treatment of metastases remained independent prognostic factors (Table 4). Patients who received palliative treatment or best supportive care had a worse survival (HR 5.01, 95 % CI 2.75–9.11 and HR 10.34, 95 % CI 5.53–19.33, respectively) compared to patients who received intentionally curative treatment. Patients with a pN2 tumour had a worse survival (HR 1.40, 95 % CI 1.03–1.89) compared to patients with a pN0 tumour.

Discussion

The present population-based study provided insight into the incidence, treatment and survival of patients with

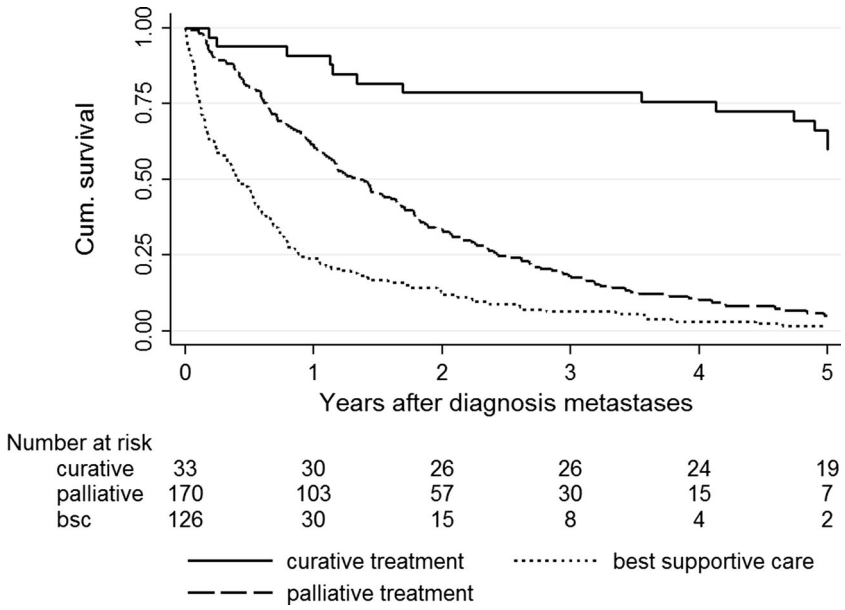

Fig. 1 Survival after diagnosis of metachronous metastases, according to treatment

Table 4 Multivariable survival analysis of prognostic factors for 5-year overall survival after diagnosis of metachronous metastases

	Univariable		Multivariable	
	HR	95 % CI	HR	95 % CI
Gender				
Male	1.00	Reference		
Female	1.01	0.80–1.26		
Age at time of diagnosis of metachronous metastases				
<75 years	1.00	Reference	1.00	Reference
≥75 years	2.03	1.59–2.57	1.30	0.99–1.70
Site of primary tumour				
Right-sided colon	1.00	Reference		
Transverse colon	0.99	0.63–1.56		
Left-sided colon	0.75	0.53–1.05		
Overlapping lesions of colon NOS	2.16	0.52–8.89		
Rectosigmoid	0.86	0.54–1.37		
Rectum	0.80	0.57–1.12		
Grade				
Well differentiated	1.00	Reference	1.00	Reference
Moderately differentiated	1.03	0.54–1.94	0.68	0.36–1.31
Poorly differentiated	1.89	0.95–3.74	1.05	0.52–2.12
Unknown	0.97	0.48–1.94	0.54	0.26–1.10
Histology				
Adenocarcinoma	1.00	Reference		
Mucinous carcinoma	1.05	0.75–1.46		
pT				
1	1.00	Reference		
2	1.12	0.49–2.57		
3	0.96	0.45–2.03		
4	0.84	0.37–1.91		
X	1.04	0.13–8.46		
pN				
0	1.00	Reference	1.00	Reference
1	1.14	0.87–1.49	0.99	0.75–1.32
2	1.54	1.16–2.04	1.40	1.03–1.89
Treatment of metastases				
Intentionally curative treatment	1.00	Reference	1.00	Reference
Palliative treatment	5.50	3.09–9.80	5.01	2.75–9.11
Best supportive care	11.63	6.46–20.94	10.34	5.53–19.33
Number of metastases				
1	1.00	Reference	1.00	Reference
>1	1.53	1.21–1.92	1.10	0.71–1.72
Site(s) of metastases				
Liver only	1.00	Reference	1.00	Reference
Lung only	1.03	0.69–1.53	0.88	0.71–1.72
Liver and lung	1.57	1.07–2.31	1.01	0.56–1.83
Other	1.62	1.23–2.12	1.11	0.70–1.77

metachronous metastases from colorectal cancer. We demonstrated that site and stage of the primary tumour were prognostic factors for developing metastases. The liver was the most common site of metastases for both colon and rectal

cancer patients. Patients who underwent intentionally curative treatment for their metastases had a significant survival benefit compared to patients who did not underwent intentionally curative treatment, irrespective of the number and site of the metastases.

Overall, we found a 5-year cumulative metastasis rate of 20.5 %. This was comparable with the results of a French regional population-based study, which reported a rate of 21.1 % among patients with colon cancer in the period 1996–2000 [8]. Although follow-up data were collected by trained registration clerks, some metachronous metastases may be missed. This could especially occur among patients with metastatic disease in a palliative phase who will not be submitted to examinations for other metastases. This could lead to an underestimation of patients with multiple metastases. However, the metastasis rates in our study are similar to results of a retrospective study which reviewed pathological records of patients diagnosed with colorectal cancer who underwent an autopsy [15].

Advancing stage at diagnosis was associated with an increase in the number of patients with metachronous metastases, up to a 5-year cumulative metastasis rate of 54 % among patients with stage IIIC disease, as was reported before [8, 10].

Similar to a population-based study of Manfredi et al. [8], the majority of metastases were diagnosed within 3 years after diagnoses of the primary tumour and median time between primary tumour and metastases was 1.5 years, reflecting the follow-up regimen in the Netherlands. Detailed information about the follow-up was not available for all patients, but according to the Dutch guidelines, patients will be followed at least once or twice per year with carcinoembryonic antigen (CEA) assessment and hepatic ultrasound [16]. Information about incidence and survival of metachronous metastases should be taken into consideration when determining optimal follow-up programs. Nowadays, the follow-up of colorectal cancer patients is the subject of numerous studies. However, the intensity of follow-up programs after colorectal cancer is still unclear. A review showed a slight survival benefit after a more intensive follow-up schedule compared to minimal follow-up [17]. The cost effectiveness of follow-up schedules also needs to be taken into account. The benefit in survival or quality of life by intensifying follow-up must be weighed against the costs of additional diagnostic tests. A cohort study among patients after intentionally curative resection of colorectal liver metastases revealed that the cost per year per curable recurrence was €2196 for recurrences found with an increase of CEA and €6721 for recurrences detected with routine imaging and CEA [18]. In the present study, only 5 % of the patients with stage I disease developed metastases, which raises the question whether this group should have an intensive follow-up schedule. Furthermore, we observed a higher rate of lung metastases among rectal cancer patients compared to colon cancer patients, whereas the rate of peritoneal metastases was higher among colon cancer patients, as reported before [11, 19]. This information could be important for follow-up strategies focusing on thoracic or abdominal imaging techniques.

Concerning the low percentages of patients with intentionally curative resection of metachronous liver and lung metastases, this study suggests that many patients were not referred for this type of surgery. Hospital series reported higher proportions of patients undergoing surgery for metastases ranging from 25 up to 46 % [6, 19], but this could be an overestimation due to selective referral. Population-based studies eliminate this selection bias, but unfortunately, information on reasons for not performing surgery was not available in the NCR. A Swedish population-based study demonstrated that only 4 % of patients underwent hepatic resection, whereas according to retrospective reviews of CT/MR images, 10 % likely had resectable metastases [20]. Another study, using data from a regional oncology centre, demonstrated that a large proportion of patients with liver-only metastases who underwent palliative treatment were considered potentially resectable after reviewing by liver surgeons [21]. This emphasises the importance of discussing patients in multidisciplinary teams in which liver surgeons participate. However, the decision whether a patients is potentially curable is somewhat subjective, as a multicentre study showed heterogeneity between liver surgeons in their conclusion about the resectability of patients after reviewing the CT or MRI scans [22]. A computer-based decision model could support medical specialists in determining which patients should be referred for surgery [23].

Almost half of all patients with metastases were diagnosed with metastases at one site, especially in the liver and lung. Similar to previous studies [9, 10], patients who underwent surgery had a significant improved survival compared to patients who did not underwent surgery. Furthermore, number and site of the metastases were not independent risk factors for survival. This underlines the importance of evaluating the possibility of resection among all patients with potential resectable metastases, also among patients with metastases at multiple sites who have a lower chance of being referred for curative treatment [24].

However, a limitation of this study is that there was no information available on case-mix factors such as extent of metastatic disease, co-morbidity and performance status. Patients who are selected for surgery may have a better prognosis than other patients who did not underwent surgery, as their metastatic disease was less extended. Furthermore, these patients could have had a better performance status or less co-morbidity.

Another Dutch population-based study previously described an increase over time in the rate of hepatic surgery for synchronous metastases in the period 1995–2007 [7]. In the past, liver resection was only considered in patients with liver-only metastases, but indications for liver resections are currently expanding. Multiple liver metastases or potentially

resectable extrahepatic disease is no longer a contraindication for liver surgery, and therefore, the hepatic resection rate will further increase [25]. Additionally, the possibilities for intentionally curative treatment of liver metastases are growing, due to additional techniques such as neoadjuvant chemotherapy, portal vein embolisation, two-staged resections, radiofrequency ablation or radioembolisation [26].

In conclusion, one fifth of patients who underwent curative surgery for colorectal cancer developed metastases during follow-up. The liver is the most common site, but rectal cancer patients also often developed metastases in the lung. Stage of the primary tumour is the most important predictor for developing metastases. Patients who underwent curative treatment for their metastases have a better prognosis compared to non-curatively treated patients, irrespective of the number and site of metastases. Discussing patients with metastatic disease in multidisciplinary meetings might identify more patients who could benefit from metastasectomy. Furthermore, follow-up schedules should be more individualised based on tumour characteristics, but further research to the intensity of follow-up schedules is necessary.

Conflict of interest The authors declare that they have no conflict of interest.

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