Synchronous and metachronous liver metastases in patients with colorectal cancer

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ABSTRACT

INTRODUCTION: Liver metastases are the most common complication to colorectal cancer, and the presence of metastatic disease severely impacts the overall prognosis of the disease. Since the diagnostic work-up of metastasised colorectal cancer has undergone tremendous changes in past decades, an impact on the incidence of metastatic disease is anticipated. The aim of this study was to evaluate the incidence and prognosis of liver metastasis in patients with colorectal cancer.

METHODS: From 1 January 2005 to 31 December 2011, all patients with a primary diagnosis of colorectal cancer were identified. Data on metastatic dissemination to the liver were collected from medical charts. Patients were followed until death or the end of the study period (31 December 2016).

RESULTS: Among the total study population of 1,672 patients, 23.6% of patients were diagnosed with liver metastases. The incidence of synchronous and metachronous metastases was 16% and 7.7%, respectively. Patients with synchronous and metachronous metastases had a median survival of ten (95% confidence interval (CI): 7.5-12.5) and 43 (95% CI: 35.8-50.2) months, respectively, compared with a median survival of 86 (95% CI: 73.5-98.5) months for patients without liver metastases.

CONCLUSIONS: The incidence of synchronous metastases has remained high despite improved diagnostic technology. Patient survival remains significantly lower when metastatic disease is present, even though treatment options for liver metastases have improved.

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Colorectal cancer (CRC) is the fourth leading cause of cancer-related death worldwide [1]. In Denmark, colonic cancer is the third most common cancer among men and women alike [2]. The incidence of CRC has slowly increased in Denmark, and the introduction of a national screening programme in 2014 has led to a rapid increase in the recorded incidence of CRC [3].

The liver is the first and most common site of dissemination in patients with CRC [4]. Presence of colorectal liver metastases (CRLM) at the time of diagnosis (synchronous) or further along the disease pathway (metachronous) is an important prognostic factor for patients with CRC [5, 6]. Studies having investigated the natural history of CRC with metastatic disease to the liver have found a median survival time from seven to eleven months [5, 7]. In addition, a poor survival outcome was related to the presence of synchronous metastases (SM) [8]. Previously, it was a common understanding that up to 25% of patients with CRC would have SM at the time of diagnosis and that another 25% would develop liver metastases in the course of their disease [4, 9]. However, more recent studies of patients with CRC and metastatic disease have shown a much lower incidence of both synchronous (15-19%) and metachronous liver metastases (MM) (13-14%) [4, 10, 11].

The aim of this study was to investigate the incidence, survival and prognosis of CRLM in a population of patients with CRC treated at a colorectal cancer centre in eastern Denmark. Furthermore, we sought to investigate the significance of distant metastases in addition to CRLM.

METHODS

A retrospective search was conducted using the International Classification of Disease (ICD)-10 codes for cancers of the colon and rectum to identify all patients referred with a verified diagnosis of CRC (codes DC18 and DC20). Another group of patients was identified through a national database including information about all patients registered with verified CRC. Data were retrieved after achieving the relevant approval from the local administrator of the database and was approved by the Danish Data Protection Agency. Patients were included from a high-volume CRC treatment centre, Herlev and Gentofte University Hospitals, covering an admission area of nearly 425,000 inhabitants in eastern Denmark. Data collection was limited to a seven-year period from 1 January 2005 to 31 December 2011 with follow-up until 31 December 2016.

All information was extracted manually from medical records by the authors. The information included: date of diagnosis, tumour location, tumour stage and presence or absence of liver metastases at the time of the primary cancer diagnosis. Moreover, the following information was obtained during the follow-up period

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for patients with CRLM: extent of hepatic involvement, type of imaging used for diagnosis and treatment; and the presence of lung and peritoneal metastases was registered as distant metastases for patients with CRLM. Liver metastases were considered synchronous if metastatic disease was present within six months of the primary CRC diagnosis, and metachronous if present more than six months after the primary diagnosis. For patients without SM or MM at the end of 2011, the 5-year follow-up included information only regarding the incidence of liver metastases.

The tumour-node-metastasis (TNMV) stage of the primary CRC was obtained from the pathologist's report and/or from diagnostic images such as CT, MRI or PET-CT. We excluded patients with recurrent disease or a diagnosis of CRC prior to 1 January 2005 along with patients who had liver metastases of unknown origin. A large number of patients was omitted due to duplicates in the ICD10 codes and in the database. Most of the excluded cases were excluded due to incomplete medical records and a smaller part of the cases were inaccessible since the patients were primarily diagnosed at other hospitals.

The vital status of the patients was obtained from the Danish Civil Registration database. The register contains updated data such as, e.g., the date of birth and death and the status of emigration of every Danish resident. Patients were followed until death, immigration, or until the end of the study whichever came first.

Statistics

The statistical analyses were conducted using SPSS version 22.0 (IBM SPSS, Armonk, NY, USA).

Survival time was calculated from the time of the CRC diagnosis until death or the end of the follow-up period. Survival for patients with SM and MM was calculated by the Kaplan-Meier method, and survival curves were constructed with data presented as medians with 95% confidence intervals (CIs). To evaluate baseline characteristics, the chi-squared test or Fisher's exact test was applied for dichotomous variables. To evaluate prognostic variables for overall survival, a multivariate analysis was applied using Cox's proportional hazards model with data presented as hazard ratios (HRs) with 95% CI. A two-sided p-value ≤ 0.05 was considered statistically significant.

Trial registration: not relevant.

RESULTS

A total of 2,193 patients with a CRC diagnosis were registered during the seven-year study period. After exclusion, a total of 1,672 patients were eligible for further analyses. Patient characteristics are summarised in **Table 1**. A total of 395 (23.7%) patients were diagnosed with CRLM. The overall incidence of SM was 16.0%, and the incidence of MM was 7.7%. Of patients with SM and MM, distant metastases to the peritoneum and lungs were present in 39% and 32% of cases, respectively (Table 1).

Survival and mortality

Overall, patients with CRLM had a median survival of 52 months (95% CI: 44.8-59.1 months). Patients with SM and MM had a median survival of 11 months (95% CI: 6.3-15.7 months) and 36 months (95% CI: 26.7-45.3 months), respectively, compared with a median survival of 86 months (95% CI: 73.5-98.5 months) for patients without CRLM at the end of follow-up. Patients without CRLM had a significantly better survival than patients with SM ($p < 0.001$) and MM ($p < 0.001$). Survival analyses showed a lower survival for patients with SM than for patients with MM and without CRLM (**Figure 1**). Cases with presence of distant metastases in addition to CRLM showed a median survival of 12 months (8.7-15.3) for patients with SM and 41 months (95% CI: 33.2-48.8 months) for MM patients.

Of the total population of 1,672 patients, 801 patients were eligible for five-year survival analyses. For patients with SM the five-year survival rate was 6.6%, and for patients with MM it was 32.4% compared with 56.9% for patients without CRLM.

Management and treatment

A total of 66% of the patients with CRLM underwent surgery for their primary tumour (Table 1). A greater number of patients with SM received symptomatic treatment (32.6%), by e.g. colonic stenting, compared with patients with MM (3.1%) ($p < 0.001$).

A total of 10.6% of the 395 patients with CRLM underwent liver resection as treatment for CRLM. Radio frequency ablation (RFA) was the selected treatment option in 9.4%, and 31.4% of the patients were treated with chemotherapy alone. Survival analyses (unadjusted) showed that patients treated with liver resection or RFA had a survival that was superior to that of patients treated with chemotherapy only or patients receiving non-curative treatment ($p < 0.001$) (**Figure 2**). Multivariate analyses evaluating the impact of CRLM treatment and overall survival found an equal HR for liver resection and chemotherapy only ($p = 0.102$), whereas the prognosis for no treatment was significantly poorer ($p < 0.001$) (**Table 2**). Further sub-analyses were not conducted due to missing data (Table 1).

DISCUSSION

In the present study, a total of 395 (23.5%) patients were diagnosed with CRLM. The incidence of SM was

TABLE 1

Patient characteristics.

	All patients (N = 1,658[a])	Cancer coli (n_{subtot} = 1,123)	Cancer recti (n_{subtot} = 535)	Synchronous liver metastases (n_{subtot} = 267)	Metachronous liver metastases (n_{subtot} = 128[d])
Sex, n (%)					
Male	817 (49.3)	505 (45.0)	312 (58.3)	135 (50.6)	78 (61.0)
Female	841 (50.7)	618 (55.0)	223 (41.7)	132 (49.4)	50 (39.0)
Age, yrs, mean (± SD)	73.9 (± 11.2)	74.5 (± 11.2)	72.6 (± 11.2)	70.3 (± 11.8)	73.2 (11.9)
Primary tumour classification, n (%)					
T-stage:					
T0	9 (0.5)	3 (0.3)	6 (1.1)	1 (0.4)	0 (0.0)
T1	58 (3.5)	39 (3.5)	19 (3.6)	2 (0.8)	2 (1.6)
T2	159 (9.6)	57 (5.1)	102 (19.1)	6 (2.3)	12 (9.4)
T3	787 (47.5)	542 (48.3)	245 (45.8)	89 (33.3)	69 (53.9)
T4	300 (18.1)	255 (22.7)	45 (8.4)	65 (24.3)	31 (24.2)
N/A[b]	345 (20.8)	227 (20.2)	118 (22.1)	104 (39.0)	14 (10.9)
N-stage:					
N0	694 (41.9)	462 (41.1)	232 (43.4)	43 (16.1)	41 (32.0)
N1	356 (21.4)	246 (21.9)	110 (20.6)	60 (22.5)	40 (31.3)
N2	248 (15.0)	182 (16.2)	66 (12.3)	57 (21.3)	31 (24.2)
N/A[b]	360 (21.7)	233 (20.7)	127 (23.7)	107 (40.1)	16 (12.5)
V-stage:					
V0	673 (40.6)	452 (40.2)	221 (41.3)	52 (19.5)	43 (33.6)
V1	325 (19.6)	255 (22.7)	70 (13.1)	67 (25.1)	42 (32.8)
V2	11 (0.7)	8 (0.7)	3 (0.6)	2 (0.7)	2 (1.6)
N/A[b]	649 (39.1)	408 (36.3)	241 (45.0)	146 (54.7)	41 (32.0)
Location of CRLM, n (%)					
Left liver lobe	-	-	-	17 (6.4)	4 (3.1)
Right liver lobe	-	-	-	64 (24.0)	17 (13.3)
Both	-	-	-	180 (67.4)	11 (8.6)
N/A	-	-	-	6 (2.3)	96 (75.0)
Number of CRLM, n (%)					
Solitary	-	-	-	44 (16.5)	12 (9.4)
Multiple	-	-	-	188 (70.4)	16 (12.5)
N/A	-	-	-	35 (13.1)	100 (78.1)
Means of diagnoses, n (%)					
Abdominal CT	-	-	-	180 (67.4)	89 (69.5)
Ultrasound	-	-	-	100 (37.5)	22 (17.2)
PET/CT	-	-	-	32 (12.0)	13 (10.2)
Operative findings	-	-	-	54 (20.2)	4 (3.1)
Treatment for primary tumour, n (%)					
Resection	-	-	-	143 (53.6)	118 (92.2)
Palliative surgery[c]	-	-	-	37 (13.9)	6 (4.7)
Symptomatic treatment	-	-	-	87 (32.6)	4 (3.1)
Treatment for CRLM, n (%)					
Liver resection	-	-	-	31 (11.6)	11 (8.6)
Radio frequency ablation	-	-	-	29 (10.9)	8 (6.3)
Chemotherapy	-	-	-	100 (37.5)	24 (18.8)
N/A	-	-	-	107 (40.1)	85 (66.4)
Distant metastases to other organs, n (%)					
Pulmonary	-	-	-	75 (28.1)	33 (25.8)
Peritoneum	-	-	-	30 (11.2)	8 (6.3)
N/A	-	-	-	0 (0.0)	23 (18.0)

CRLM = colorectal liver metastases; N/A = not applicable; SD = standard deviation.

a) 14 patients with simultaneous colonic and rectal cancer are not included in baseline characteristics. b) Stage not available or tumour was not resected.

c) Includes endoscopic insertion of colonic stents.d) Missing data from 12 patients.

16.0%, which is in line with other studies which have reported an incidence in the 14.5-18.9% range [4, 10, 11], but also remarkably lower than Bengmark et al who found a much higher incidence (24.5%) in 1968 [9]. These ambiguities may have been caused by differences in the definition of liver metastases, which varies among countries. Some studies defined CRLM as synchronous when metastases were present within the first three months from the primary diagnosis; others considered CRLM to be synchronous when present until one year after diagnosis; and others failed to report the definition used [4, 8, 11-13]. In the present study, metastases were considered synchronous until six months after the primary CRC diagnosis and metachronous when detected later than six months after the primary diagnosis. Other factors influencing the incidence may be related to the improvement of the diagnostic work-up, including imaging techniques which have yielded a better and more accurate diagnostic work-up earlier in the disease process. This would lead to an anticipated increase in the incidence of SM, while more aggressive treatment strategies, such as early surgical intervention combined with more potent chemotherapy, may decrease the incidence of SM, contributing to a steady SM incidence.

The incidence of MM demonstrated in the present study was 7.7%. In comparison, other studies have reported the MM incidence to be 12.8-14% [4, 10, 11]. However, the discrepancy in the definition of MM in the literature affects the incidence and may partly explain our results. Furthermore, as this was a retrospective study, a certain degree of selection bias must be considered as not all patients with recurrent disease or MM were diagnosed or registered.

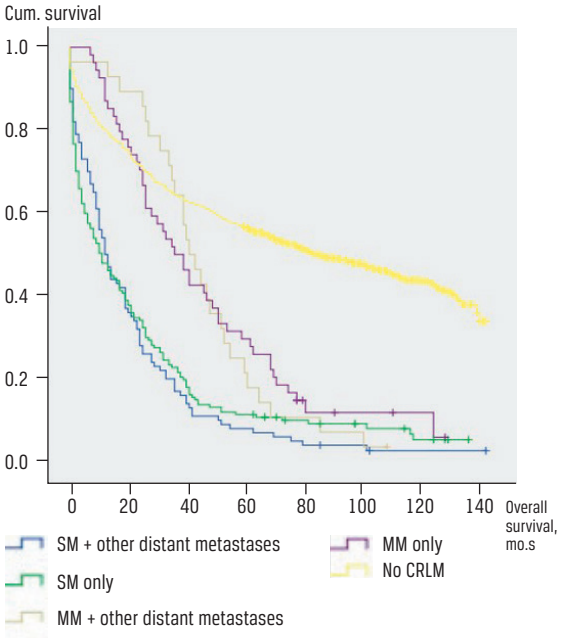
The five-year survival for patients with SM in this study was 6.6%, which is in line with the literature (3-11%) [11, 14]. Also, the five-year survival rate for patients with MM was 32.4%, which is higher than reported by other studies (12.8-20%) [4, 11, 14]. These differences may be caused by the differences in the MM definition but also by the above-mentioned risk of bias. However, it may also be a question of lead-time bias, meaning that the survival may be similar to those reported in the literature, but that the metastases were detected earlier than in other studies.

The survival and prognosis for patients with CRLM depend on multiple factors. The extent of liver involvement represents an important factor; yet, the prognosis may also depend on the total extent of metastatic disease like extra-hepatic metastases and multiple liver lesions [7, 15]. This may reflect that patients with multiple liver metastases often have a larger tumour burden, corresponding to more advanced disease. Our study found a similar overall survival for patients with CRLM with and without distant metastases. However, our data on liver lesions were limited, and interpretation should be done with caution (Figure 1).

Surgical resection of CRLM has shown to improve survival substantially with a reported three-year survival rate of 63-70% [10, 16]. Furthermore, a recent study investigating unresectable CRLM found a super-

FIGURE 1

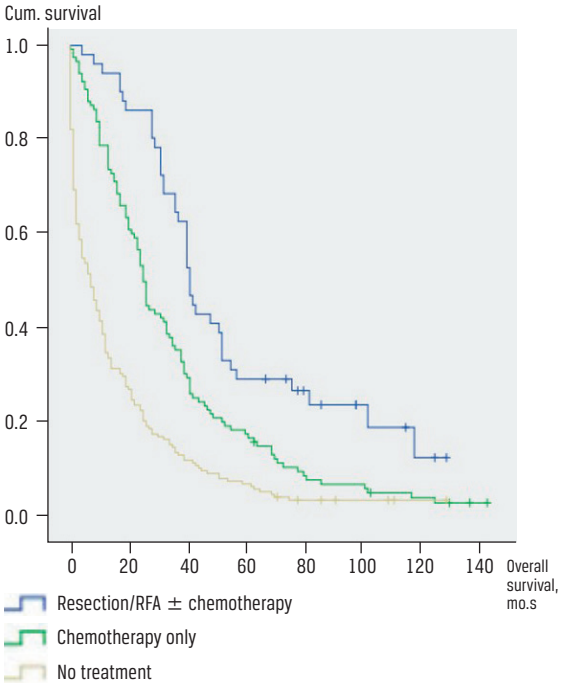
Overall survival of colorectal cancer patients with and without liver metastases.



CRLM = colorectal liver metastases; MM = metachronous liver metastases; SM = synchronous liver metastases.

FIGURE 2

Overall survival by treatment for colorectal cancer patients with liver metastases.



RFA = radio frequency ablation.

ior survival in patients randomised to standard practice in addition to local treatment (surgical or RFA) compared with patients receiving standard care (chemotherapy) [17]. In our study, adjusted multivariate analyses showed that overall survival was similar regardless of treatment with surgery/RFA or chemotherapy. However, once again, our results must be interpreted with caution due to the extent of missing data. Another interesting topic is whether the implementation of CRC screening will have an impact on the number of patients detected with metastatic disease, including CRLM. A recent study found that screening detects an increase of CRC in earlier stages [18], which is evidently linked to a better prognosis owing to earlier treatment and an anticipated reduction in the incidence of metastatic disease, including liver metastases. On the other hand, a screening programme is costly and may entail a risk of over-diagnosing colonic adenomas with no obvious malignant potential. Thus, patients may be enrolled in screening programmes with little benefit. Yet, hard evidence is lacking, and further investigations should be considered [19].

The present study has considerable limitations caused by its retrospective design. Operation notes, medical charts, missing data and registrations can leave room for ambiguous interpretation. In the present study, each chart was studied only by one of the authors, without crosschecking, all of which may result in selection bias since the information retrieved relies on correct record keeping by health providers. The ICD10 disease coding system was applied to identify patients with CRC, and inaccurate coding cannot be ruled out. Hence, some patients with CRC may have been missed, adding to the risk of selection bias. Moreover, changes in the histological classification of the primary tumour from Dukes to TNMV may generate problems with comparing results throughout the study period. Some patients were excluded due to difficulties in accessing their medical charts because of a merging of hospital departments where patients were enrolled in 2007. Furthermore, as some patients in our cohort received parts of their treatments at other hospitals, their medical records were not available to the authors. In addition, some patients may never have received treatment and may therefore not have been registered. Also, in some cases, it was difficult to determine the exact time of diagnosis for SM and MM due to a delay in imaging interpretation from other hospital departments. Nevertheless, this study represents a large cohort of patients with CRLM and owing to the Danish Civil Registration, the follow up is considered highly accurate.

CONCLUSIONS

In this study population, a total of 23.6% patients with CRC were diagnosed with liver metastases, and the incidence of patients with SM was 16.0% and the incidence of patients with MM was 7.7%. The incidence of SM remains high with poor survival outcomes compared with MM patients. An interesting question for future research is whether the national screening programme for CRC will have a positive impact on this matter.

TABLE 2

Multivariate overall survival analysis. Results of Cox regression analysis for all patients[a] or patients with colorectal cancer liver metastases[b].

	HR, median (95% CI)	p-value
All patients (n = 1,295)		
T-stage:		
T0-T2	1 (ref.)	
T3-T4	1.46 (1.13-1.78)	0.003
N-stage:		
N0-N1	1 (ref.)	
N2	1.52 (1.27-1.81)	0.001
SM:		
No	1 (ref.)	
Yes	3.41 (2.79-4.16)	< 0.001
MM:		
No	1 (ref.)	
Yes	1.38 (1.12-1.71)	0.004
Patients with CRLM (n = 141)		
Treatment:		
Surgical	1 (ref.)	
Chemotherapy only	1.55 (0.92-2.62)	0.102
No treatment	3.37 (1.98-5.73)	< 0.001

CI = confidence interval; CRLM = colorectal cancer liver metastases; HR = hazard ratio; MM = metachronous liver metastases; ref. = reference; SM = synchronous liver metastases.
a) Adjusted for tumour location, age, sex.
b) Adjusted for tumour-node-stage, age, number of liver metastases, distant metastases to other organs.

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