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CLINICAL

Multiple treatment lines and prognosis in metastatic colorectal cancer patients

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Abstract
The proportion of patients with metastatic colorectal cancer (mCRC) receiving second or further lines of treatment has not been widely studied. To shed light on this issue, we retrospectively analysed the treatments administered for metastatic disease, and investigated prognostic factors after a diagnosis of metastases, in a consecutive cohort of mCRC patients. Three hundred forty-six mCRC patients were enrolled: 173 were stage II or III (metachronous group), and 173 stage IV (synchronous group) at diagnosis. Survival was calculated between the date of metastatic disease and the date of death or last follow-up. Patients with synchronous lesions more frequently had multiple disease sites, peritoneal carcinomatosis and massive liver deposits, whereas significantly more patients with metachronous lesions developed lung metastases as the sole disease site. 97.4% patients received at least one, 62.4% two, 41.9% three and 23.7% four treatment lines. Patients with metachronous metastases more frequently underwent surgery of metastases in first-line treatment (48.5 *versus* 24.8%), and more of them were progression-free at the time of the analysis (44 *versus* 34.9%). At univariate analysis, age > 70 years, multiple disease sites and peritoneal carcinomatosis were associated with significantly decreased survival, whereas surgery of metastases and isolated lung metastases predicted better survival. At multivariate analysis, only peritoneal carcinomatosis and surgery of metastases independently affected survival. The percentage of patients who received an active treatment decreased going from first- to fourth-line treatment. However, the proportion of patients who received efficacious treatment in advanced line remained high. Surgery of metastases was the most important prognostic factors.

Keywords Metastatic colorectal cancer · Multiple treatment lines · Prognostic factors · Continuum of care

1 Introduction

Colorectal adenocarcinoma remains a leading cause of cancer death worldwide: it is second to lung cancer in man and third after lung and breast cancer in women in developed countries [1]. In Italy, 53,000 new cases were estimated in 2017, and 18,670 deaths in 2014 [2]. The overall survival in colorectal cancer patients depends on the stage at diagnosis [3]. It is excellent for initial lesions (*in situ* or TNM I stage tumours), intermediate for localised operable stage II or III disease and poor for metastatic disease [4]. Colorectal cancer mortality has decreased considerably during recent decades in many developed countries [1] due to a combination of factors. Indeed, the increasing coverage of the target population (men and women aged ≥ 50 years) in terms of screening programmes, faecal occult blood sampling and endoscopic procedures, has resulted in a diagnosis of early stage, and thus curable, tumours [5, 6]. Moreover, adjuvant chemotherapy after radical surgery for stage II or III colon cancer [7, 8], and the optimal combination of chemotherapy and/or radiotherapy with total mesorectal excision for rectal cancer [9, 10] have significantly reduced the incidence of relapses, thereby prolonging the survival of patients with localised colorectal tumours.

Also the overall survival from the diagnosis of metastasis has increased significantly from the 1980s to the present, thanks to new cytotoxic molecules (irinotecan and oxaliplatin), the addition of targeted drugs (antiangiogenic and anti-EGFR) to chemotherapy [11–15], effective palliative treatment in advanced lines [16, 17] and the radical resection

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of metastases [18, 19]. It was reported that overall survival significantly correlated with exposure to all three active chemotherapeutics (fluorouracil, oxaliplatin and irinotecan), irrespective of their combination or sequence [20, 21].

The aim of this retrospective analysis was to describe the lines of treatment administered in a consecutive "real-life" cohort of metastatic colorectal cancer (mCRC) patients treated at a university hospital, and to evaluate factors that may predict survival from the diagnosis of metastatic disease.

2 Methods

2.1 Patients

Consecutive patients with a diagnosis of metastatic colorectal cancer treated at the Oncology Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II, from 2001 to 2016 and recorded in the institutional database were enrolled in this study. The minimum follow-up period was 6 months. All treatments administered were registered: chemotherapy ± targeted drugs, surgery, radiotherapy or other local treatment for metastases. A maximum of four subsequent lines of treatment for metastatic disease were analysed, even though a small subgroup of patients received five or more treatments.

The passage from a treatment line to the subsequent one was considered only for documented disease progression. Maintenance or partial schedule modification (for example, oxaliplatin or irinotecan discontinuation due to toxicity) was not considered a "new" line of treatment. Upfront surgery of liver/lung metastases (± perioperative or postoperative adjuvant chemotherapy) was considered one treatment line. If a patient experienced disease progression after complete resection of liver/lung metastases, the treatment for these new metastases was considered a subsequent treatment line.

2.1.1 Statistical methods

Survival was considered as the time between the date of diagnosis of mCRC and the date of death due to disease or any other cause or last known follow-up. For OS, HRs and 95% CIs for variable comparisons were calculated using univariate Cox proportional hazards models. Median survival times were estimated using the Kaplan-Meier method (product limit estimates), and *P* values were calculated using log-rank tests. The Chi-square test of independence was used to evaluate relationships between the sites of metastases (one or multiple locations) and pathologic stages of patients at the time of diagnosis (stages II–III or stage IV subjects). For all analyses, statistical significance was set at $p < 0.05$ for a bilateral test.

3 Results

A total of 346 patients with mCRC were enrolled in the study. Half ($n = 173$) were diagnosed at stage IV ("synchronous" group), and the other half ($n = 173$) were diagnosed when they were at stage II or III, and experienced distant and/or local relapse during follow-up ("metachronous" group). The characteristics of patients are reported in Table 1. Metastatic disease was diagnosed at a median age of 64 years, and 91 patients were 71 years old or above. The primary tumour had been resected in all the 173 patients of the metachronous group and in most cases of the synchronous group; about two-thirds of the stage II or III patients had received adjuvant chemotherapy after radical surgery.

More than one-third of patients had multiple sites of disease at the time metastases were diagnosed (Table 1). Notably, the pattern of metastatic lesions differed between patients with synchronous and those with metachronous metastases. In fact, as shown in Table 2, the patients whose colorectal cancer was diagnosed when they were at stage IV of the disease more frequently (< 0.001) had multiple sites of disease, peritoneal carcinomatosis and massive liver deposits as the sole site of metastasis *versus* patients who received a diagnosis of metastatic disease during follow-up after radical surgery (± adjuvant chemotherapy or radiotherapy). Moreover, significantly, more patients in the metachronous group had lung metastases as the only site of disease ($p < 0.001$) (Table 2).

The rate of primary rectal cancer did not differ significantly between the two groups: 39 (25.5%) in the synchronous, and 63 (36.4%) in the metachronous cohort of patients. There was no correlation between primary site (right colon, left colon, rectum) and stage at diagnosis ($p = 0.07$). The percentage of patients with a normal CEA level (≤ 5 ng/ml) was two-fold higher in the metachronous patients than in patients with synchronous metastases at diagnosis (28.9 *versus* 14.5%).

Overall, 337/346 patients (97.4%) received at least one treatment line, 62.4% received two treatment lines, 41.9% received three treatment lines and 23.7% received four treatment lines. Among the synchronous subgroup of patients, 98.8% received at least one treatment, 70.5% two, 45.7 three and 32.4% four treatment lines. In the metachronous group, fewer patients received two or more treatment lines: 95.9% received at least one treatment, 54.3% two, 38.1% three and 15.0% four treatments (Fig. 1). Notably, the proportion of patients who received surgery of metastases as part of first-line treatment was about two-fold higher in the metachronous group (48.5%) than in subjects diagnosed at stage IV (24.8%). Furthermore, fewer patients progressed after the first treatment line if surgery had been part of the treatment, especially in the metachronous group (55.9% yes-surgery *versus* 92.7% no-surgery) with respect to patients diagnosed at stage IV

Table 1 Patients' characteristics ($N = 346$)

	N	%
Age		
70 years	255	73.7%
> 71 years	91	26.3%
Median age (range)	64.08	(27.1–90.1)
Gender		
Male	214	61.8
Female	132	38.2
Stage at diagnosis		
Stage II or III	173	50.0
Stage IV	173	50.0
Primary tumour site		
Right colon	92	26.5
Transversum	12	3.5
Left colon (sigma included)	140	40.5
Rectum	102	29.5
Surgery of primary tumour		
Resected	321	92.8
Not resected	25	7.2
Adjuvant chemotherapy ($N = 173$)		
Yes (any)	117/173	67.6
Fluoropyrimidine alone	50/117	42.7
Fluoropyrimidine + oxaliplatin	63/117	53.9
Other	4/117	3.4
N. metastatic sites		
1	222	64.2
> 1	124	35.8
Site(s) of metastases		
Liver only	118	34.1
Lung only	39	11.2
Multiple	124	35.8
Peritoneal carcinomatosis (alone or multiple)	41	11.8
Local/pelvic	34	9.8
Other	6	1.7
(K)RAS status		
KRAS wild type[a]	128	37.0
Mutated	92	26.6
Unknown	126	36.4
CEA level at diagnosis of stage IV		
≤ 5	75	21.7
5.1–100	83	24.0
101–200	14	4.0
> 200	18	5.2
Unknown	156	45.1

[a] 44/128 KRAS wild-type cases were also tested for NRAS mutations: 40 all wild type (90.9%) and 4 mutated (9.1%)

(65.1% yes-surgery *versus* 73.4% no-surgery). Thus, of the patients who had progressed after each line of treatment, 210/245 (85.7%) received a second line, 145/184 (78.8%) a third line and 82/134 (61.2%) a fourth line of treatment.

Table 3 shows the chemotherapy regimens administered in 286/346 patients, excluding 60 patients who received, as first-line treatment, surgery and/or local treatment ± adjuvant chemotherapy, and either remained free from relapse or experienced disease progression, but did not receive any further systemic treatment for metastatic disease. As first line, 57.7% of patients received chemotherapy plus bevacizumab, 18.5% chemotherapy plus anti-EGFR and 21.3% chemotherapy alone. Bevacizumab was the most frequently administered biological drug in first and second treatment lines. The proportion of patients who received an anti-EGFR drug increased going from first (19.6%) to second (24.5%) and third treatment lines (33.6%), whereas the proportion of patients receiving bevacizumab decreased after second-line treatment. Chemotherapy alone was the most frequently administered treatment in third- (50.8%) and fourth-line treatments (51.5%), because regorafenib became available and refundable in Italy in September 2015.

The median follow-up time after the diagnosis of metastatic disease was 66.8 months (range 6.7–183.8 months). Overall, 215/346 (62.1%) patients died, and the median survival was 31.9 months (range 27.7–36.2). As shown in Table 4, the following covariates negatively affected survival: age above 70 years ($p = 0.019$), multiple sites of disease $p < 0.0001$) and peritoneal carcinomatosis ($p < 0.0001$). Surgery for metastases ($p < 0.0001$) and isolated lung metastases ($p = 0.042$) predicted a significantly longer survival. The median survival after the diagnosis of metastatic disease was longer for patients with metachronous metastases, but the difference was not statistically significant. Among patients who did not undergo surgery for metastases, median survival was longer for those receiving ≥ 3 lines of treatment than for those receiving ≤ 2 lines (34 *versus* 22 months), but the difference was not statistically significant.

At multivariate analysis (Table 5), only two covariates included in the model independently affected survival: the presence of peritoneal carcinomatosis nearly doubled the risk of death (HR = 1.98; $p < 0.0001$), whereas radical surgery of metastases predicted a significantly better survival (HR = 0.30; $p < 0.0001$).

4 Discussion

In this retrospective real-life study, we report the systemic and local treatments received by patients with mCRC, and the prognostic factors for survival after the diagnosis of

Table 2 Pattern of first metastasis according to stage at diagnosis of colorectal cancer

	Sinchronous group ($N = 173$)		Metachronous group ($N = 173$)		p value*
Site of metastasis	*N*	%	N	%	
Liver only	74	42.8	44	25.4	< 0.001
Lung only	6	3.5	33	19.1	< 0.001
LFN only	4	2.3	5	2.9	n.s.
Peritoneal carcinomatosis only	8	4.6	8	4.6	n.s.
Other	3	1.7	3	1.7	n.s.
Local/pelvis	0	0	34	19.7	n.s.
Multiple	78	45.1	46	26.6	< 0.001
Peritoneal carcinomatosis (± other)	24	13.9	17	9.8	< 0.001

*RxC test of independence

metastasis. Almost 3% of patients did not receive any treatment for metastatic disease due to their very poor condition. Surgery of metastases was part of first-line therapy in about one-third of patients, and favourably affected survival. Stage at original diagnosis did not significantly affect survival; however, patients with metachronous metastases had a more favourable metastatic pattern *versus* patients with synchronous lesions. The proportion of patients who received further treatment after the first-line therapy progressively declined, but about one-quarter of patients underwent a fourth line of treatment. Overall, even in the era of molecular selection and of targeted drugs, the greater the number of treatment lines, the longer the survival.

Most previous studies of patients who received multiple lines of treatment for metastatic disease were based on data from cancer registries or insurance databases [22–25]. Consequently, the reason for changing therapy and factors related to disease progression were not always available, and most studies focused on drug usage patterns in a given region or in a community of medical oncologists. The proportion of patients receiving second-line or third-line treatment was low in US databases: 44.8 [24], 51.5 [22] and 53% [23] in the case of second-line treatment, and 19.2 [24], 26.9 [22] and 28% [23] in the case of third-line treatment. In addition, Seal et al. [22], whose source was a US health insurance database, reported that 15.7% of patients did not receive any treatment for metastatic disease. Similar to our findings, a double-regimen (fluoropyrimidine + oxaliplatin) was the most frequently used chemotherapy, and bevacizumab the most frequently used biologic drug in first-line treatment in the three North-American studies [22–24]. Academic and high volume centres were more prone to prescribe combination regimens, and biologics in first- and second-line treatment [23], and, indeed, 77.3 and 65.8% of our patients received a targeted drug in first and second line, respectively. The results of a Canadian single-institution retrospective study [25] are more similar to our findings: 74.4% of patients received a second line, 36% a third line and 16.3% a fourth line of therapy. None of the North-American studies reported survival data.

The prospective study by Tampellini et al. [26] of data from a single-institution database in Italy was very similar to our results, the median follow-up times being 60 and 66 months, respectively, and the median survival of the entire population being 24.5 and 31.9 months, respectively. Furthermore, as both studies were based on institutional databases that contained information about disease progression at each

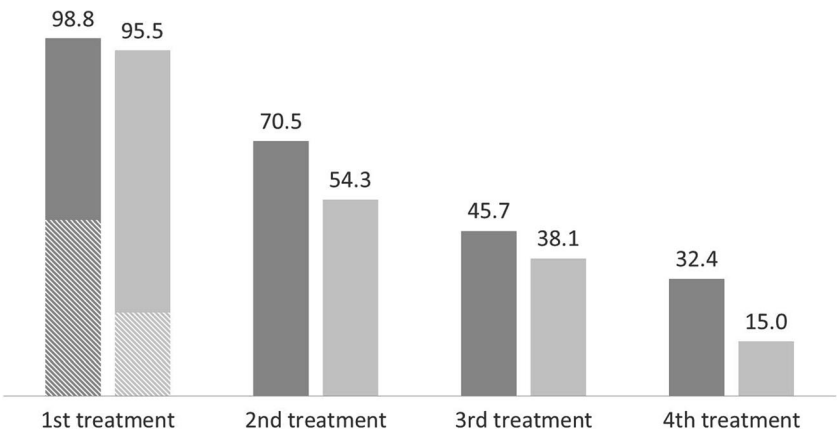

Fig. 1 Percentage of patients treated at each treatment line by stage at diagnosis: synchronous (dark grey), metachronous (light grey); hatching represents the proportion of patients receiving surgery as part of first line treatment

Table 3 Therapy by treatment line ($N = 286$*)

	1st line	2nd line	3rd line	4th line
Fluoropymidine alone	5 (1.7%)	2 (1.0%)	0	3 (4.5%)
Doublet-chemo alone	56 (19.5%)	60 (30.6%)	27 (21.0%)	7 (10.6%)
Fluoropymidine + bevacizumab	6 (2%)	5 (2.5%)	1 (0.7%)	1 (1.5%)
Fluoropurimidine + anti-EGFR	1 (0.3%)	2 (1.0%)	1 (0.7%)	0
Doublet-chemo + bevacizumab	146 (51.0%)	64 (32.6%)	13 (10.1%)	2 (3.0%)
Doublet-chemo + anti-EGFR	53 (18.5%)	45 (22.9%)	17 (13.2%)	6 (9.0%)
Anti-EGFR alone	2 (0.6%)	1 (0.5%)	5 (3.9%)	4 (6.0%)
Triplet + bevacizumab	13 (4.5%)	0	0	0
Regorafenib	0	0	6 (4.6%)	7 (10.6%)
Other	4 (1.3%)	17[a] (8.6%)	58[b] (45.3%)	36[c] (54.5%)
Total	286	196	128	66

*Excluding the 60 patients who received as first-line surgery and/or local treatment ± adjuvant chemotherapy, and remain free from relapse or did not receive systemic treatment

[a] Mitomycin C + fluoropyrimidine ($N = 5$); irinotecan + cetuximab (N = 12)

[b] Mitomycin C + fluoropyrimidine ($N = 38$); irinotecan + cetuximab ($N = 8$); other drugs/combinations ($N = 12$): irinotecan; gemcitabine + oxaliplatin/capecitabine

[c] Mitomycin C + fluoropyrimidine ($N = 24$); irinotecan + cetuximab ($N = 2$); other drugs/combinations ($N = 10$): irinotecan; gemcitabine + oxaliplatin/capecitabine; irinotecan + oxaliplatin

treatment line, we were able to determine the proportion of patients who received a further line of treatment for disease progression. The latter way to analyse the treated population is net of the proportion of cases who are "cured" or have a very long progression-free period after each line of therapy. This could explain why the relative number of patients treated at each treatment line is much higher in the Italian studies than in the US/Canadian studies [22–25]. Indeed, we found that about

Table 4 Univariate analysis for survival

Covariate	Categories	Median OS (months)	HR (95%CI)	*p*
Age at diagnosis	≤ 70 years	36.3		0.019
	> 71 years	26.2	1.4	
			(1.06–1.97)	
Stage at diagnosis	Stage II or III	36.6		0.16
	Stage IV	30.5	1.21	
			(0.92–1.58)	
Primary site	Left + sigma + rectum	34.0		0.58
	Right (+ transversum)	29.0	1.09	
			(0.80–1.47)	
N. metastatic sites	1	39.3		< 0.0001
	> 1	25.6	2.08	
			(1.57–2.75)	
CEA level ($N = 190$)	Normal (≤ 5)	40.3		0.31
	Abnormal (> 5)	29.3	1.23	
			(0.82–1.82)	
Surgery of metastases	No	23.7		< 0.0001
	Yes	60.9	0.276	
			(0.20–0.379)	
Peritoneal carcinomatosis	No	36.5		< 0.0001
	Yes	18.7	2.33	
			(1.66–3.27)	
Lung only	Yes	50.0		0.042
	No	30.5	1.56	
			(1.01–2.41)	

OS overall survival, *HR* hazard ratio

Table 5 Multivariate analysis for survival

Covariate	Categories	HR (95%CI)	*p*
Age at diagnosis	≤ 70 years		0.30
	> 71 years	1.19 (0.86–1.64)	
Stage at diagnosis	Stage II or III		0.34
	Stage IV	1.15 (0.86–1.52)	
N. metastatic sites	1		0.15
	> 1	1.26 (0.92–1.72)	
Surgery of metastases	No		< 0.0001
	Yes	0.30 (0.21–0.41)	
Peritoneal carcinomatosis	No		< 0.0001
	Yes	1.98 (1.36–2.88)	
Lung only	Yes		0.28
	No	1.29 (0.81–2.08)	

two-thirds of patients who progressed after the second line received a third line, and about half of those who progressed after the third line were given a fourth treatment. Thus, medical oncologists should be aware that advanced line therapies can be effective in a large proportion of metastatic patients, and carefully consider them in the continuum of care of mCRC patients.

Age > 70 years negatively affected the possibility of receiving additional lines of treatment in the Tampellini study [26], and it was a negative prognostic factor for survival in our univariate analysis. These findings suggest that older patients are less likely to receive multiple lines of chemotherapy and other intensive treatments (i.e. surgery) for metastases.

In our series, as in other studies, 50 to 75% of patients [22–26] were metastatic at the time of colorectal cancer diagnosis, which suggests that screening programmes are not widely applied. Although in our study and in those of Seal et al. [22] and Tampellini et al. [26], disease stage at diagnosis did not significantly affect survival, we found that, compared to patients initially diagnosed with synchronous metastases, patients with an early diagnosis who progressed during follow-up had a lighter metastatic tumour burden, and their metastases were more frequently operable, and consequently, they had a 6-month longer survival (although the difference was not statistically significant). These observations reinforce the importance of secondary prevention, the benefit of early discovery of metastases and the role of surgery as part of the treatment of metastatic disease.

The proportion of patients receiving second or further lines of treatment may be overestimated in clinical trials due to stringent eligibility criteria. In fact, second-line therapy was administered to about 60% of patients enrolled in the PEAK trial [27], 69% in the FIRE3 study [28] and 76% of patients enrolled in the TRIBE study [29]. Only the FIRE3 study [28] reported the proportion of patients receiving a third-line treatment (41.7 and 44.8% in the two arms, respectively), which is the same as our finding (41.9%).

Although retrospective, the strength of our research lies in the prospective collection of data, namely, information about disease progression throughout all lines of treatment, and about surgery/local therapies for metastases besides chemotherapy.

5 Conclusions

In conclusion, the proportion of patients who receive an active treatment progressively declines after the first line; however, roughly 40% of the initial metastatic population receive third-line therapy [25, 26, 28] and about 20% fourth-line therapy [25, 26], and these figures are similar in clinical trials and in real-life scenarios. The prognosis of mCRC depends on the type of metastatic sites, on the possibility of radically resecting them and on whether multiple active treatments are administered.

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Compliance with ethical standards

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

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