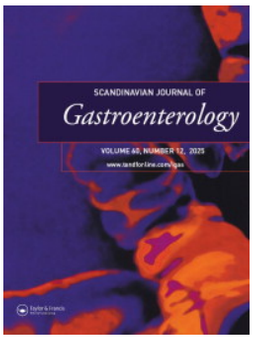

Scandinavian Journal of Gastroenterology

ISSN: 0036-5521 (Print) 1502-7708 (Online) Journal homepage: www.tandfonline.com/journals/igas20

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To cite this article: Joel Kontiainen , Kaisa Lehtomäki , Timo Muhonen , Eetu Heervä , Annika Ålgars , Raija Ristamäki , Hanna Stedt , Annamarja Lamminmäki , Raija Kallio , Tapio Salminen , Teijo Kuopio , Emerik Osterlund , Sonja Aho , Maarit Bärlund , Päivi Halonen , Leena-Maija Soveri , Arno Nordin, Aki Uutela , Bengt Glimelius , Helena Isoniemi & Pia Osterlund (30 Nov 2025): Disease-phase-specific resource utilization and healthcare costs in metastatic colorectal cancer: a subgroup analysis of the finnish RAXO study, Scandinavian Journal of Gastroenterology, DOI: 10.1080/00365521.2025.2594779

To link to this article: https://doi.org/10.1080/00365521.2025.2594779

Published online: 30 Nov 2025.

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY
https://doi.org/10.1080/00365521.2025.2594779

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Disease-phase-specific resource utilization and healthcare costs in metastatic colorectal cancer: a subgroup analysis of the finnish RAXO study

Joel Kontiainen[a], Kaisa Lehtomäki[a], Timo Muhonen[b], Eetu Heervä[c], Annika Ålgars[c], Raija Ristamäki[c], Hanna Stedt[d], Annamarja Lamminmäki[d], Raija Kallio[e], Tapio Salminen[a], Teijo Kuopio[f], Emerik Osterlund[g,h], Sonja Aho[a], Maarit Bärlund[a], Päivi Halonen[b], Leena-Maija Soveri[b,i], Arno Nordin[h], Aki Uutela[h], Bengt Glimelius[g], Helena Isoniemi[h] and Pia Osterlund[a,b,j]

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ABSTRACT

Introduction: Metastatic colorectal cancer (mCRC) represents a growing burden on healthcare, yet comprehensive data on treatment costs across different disease phases remain limited. This study aims to estimate hospital resource utilization and costs of treating mCRC patients according to international up-to-date guidelines.

Materials and methods: The RAXO study aimed at maximising metastasectomy with repeated centralized assessment of resectability (inclusion 2012–2018). Cost data from the six largest Finnish hospital districts ($n=941$) in RAXO were collected from mCRC diagnosis to death or the end of 2021. All patient costs were characterized day-by-day to diagnostic, curative, remission, palliative SACT, treatment break, or end-of-life disease phases. The resource utilization and mean costs, in 2021 euros, were calculated per patient per month (PPPM).

Results: The mean PPPM cost for treating mCRC patients was 2323€, when 37% had curative-intent metastasectomy. On average, each month included 0.7 ward days, 1.9 outpatient and 0.1 emergency visits. Outpatient care accounted for 64% of costs, inpatient care for 34%, and emergency room visits for 2%. The higher costs during disease phases involving active tumour-directed treatments (2963€–3059€/PPPM) were balanced by lower costs during remission and treatment break (453€–560€/PPPM). Pharmacy, ward, operating room, and outpatient costs (39%/18%/15%/15%, respectively) were the main drivers for internal hospital billing.

Conclusions: Resource utilization, costs, and cost drivers varied 8-fold between disease phases. Outpatient care accounted for two-thirds, and inpatient care accounted for one-third of costs.

Abbreviations: CRC: colorectal cancer; mCRC: metastatic colorectal cancer; LAT: local ablative treatment; PPPM: per patient per month; SD: standard deviation

ARTICLE HISTORY
Received 26 August 2025
Revised 15 October 2025
Accepted 23 October 2025

KEYWORDS
Metastatic colorectal cancer; healthcare costs; disease phase; antineoplastic treatment; metastasectomy

Introduction

Colorectal cancer (CRC) imposes a growing burden on healthcare. Globally, it is the third most common cancer and the second leading cause of cancer mortality, responsible for approximately 0.9 million annual deaths [1]. By 2040, the incidence of CRC is expected grow from the current 1.9 million to 3.1 million new cases per year [2]. At diagnosis, 20%–25% of patients have synchronous metastases, and 15%–20% will develop metastases (mCRC) later. Among Nordic patients with mCRC, 28%–30% receive no tumour-directed therapy. Of those who are eligible for tumour-directed therapy, around

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30%–39% undergo curative-intent metastasectomy and/or local ablation, consistent with the 37% reported in the RAXO study, while the remainder receive systemic anticancer therapy (SACT) alone [3–5]. In patients with potentially resectable metastases, repeated reassessment of resectability by a specialised multidisciplinary team (MDT) is recommended in international guidelines [6–8]. While survival has improved, CRC-related healthcare costs are also rising. CRC is projected to impose a financial burden equivalent to 0.06% of the global gross domestic product between 2020 and 2050, ranking second only to tracheal, bronchial, and lung cancer [9,10].

Information on resource utilization and the costs associated with various cancer treatment strategies is essential for informing future healthcare policy and developing robust cost-effectiveness models [11,12]. However, detailed data on the costs and resource use associated with treating mCRC remain limited. A recent systematic review of real-world cost analyses of mCRC from 12 countries reported that average total mCRC treatment costs vary widely between $12,346 and $293,461 [13]. However, these studies varied significantly regarding the treatments that were provided and how medical expenses were reported.

Only a few studies have examined costs by disease phase to better identify key cost drivers. Two American studies on mCRC reported that the diagnostic and end-of-life phases caused higher monthly costs than the actual treatment phase. They defined the diagnostic phase as the first three months post-diagnosis, the end-of-life phase as the final three months before death, and the actual treatment phase as the interval in between. Other studies have used alternative definitions, such as 12-month periods for the diagnostic and end-of-life phases [14–16].

Presently, treatment of mCRC involves distinctly different disease phases, ranging from curative-intent surgical interventions to palliative SACT and treatments without tumour-directed therapy. The differences in resource usage between these phases are not properly captured when categorization into different phases is done using time-based methods and are too crude to provide detailed knowledge. There is a gap in the literature regarding detailed analysis of clinically determined, phase-specific costs, patterns of care in a real-world setting [12,17].

This study aimed to characterize the resource utilization and costs of treating mCRC in different clinically determined disease phases from a specialist healthcare provider perspective, in a setting of national universal health coverage, when cancer treatments and active evaluation of resectability are carried out according to recent international guidelines.

Materials and methods

Study design and population

The RAXO-study was a Finnish nationwide prospective study of mCRC patients with a centralised repeated assessment of resectability by an experienced multidisciplinary team and aimed for high resectability rates. Between June 2012 and October 2018, the study (NCT01531621, EudraCT2011-003158-24) included 1,086 patients from 5 tertiary and 16 secondary referral centres [3]. The study was approved by the Ethics Committee at Helsinki University Hospital (242/13/03/02/2011) and conducted according to the Declaration of Helsinki. All patients provided written informed consent.

In this RAXO subgroup analysis, 952 (88%) patients from six largest oncological centres were included: Helsinki, Tampere, Turku, Oulu, and Kuopio University Hospitals, and Central Finland Central Hospital. Patient characteristics were prospectively collected in the RAXO database during the mCRC disease trajectory (Figure S1). Table S1 shows demographic data for included and excluded patients.

Disease phase definitions

Each day in the trajectory of an individual patient was categorized into six mutually exclusive disease phases according to the aim of the intervention: diagnostic, curative treatment of metastases (denoted curative), remission, palliative SACT, treatment break, and specialist care in end-of-life (denoted end-of-life) (Figure S2). The categorization was based on patient-level clinical information, with dates of all interventions and death. Follow-up started at the beginning of the first disease phase and ended at death or the end of the study period (December 31, 2021). Duration of phases is presented in Table S2 and Figure S3.

Disease phases were defined as follows:

- The diagnostics phase was defined as the time period starting one month before the date of mCRC diagnosis and ending at the start of any subsequent disease phase.
- The curative phase began one month before metastasectomy or LAT, or from the start of neoadjuvant treatment, and ended six months after metastasectomy/LAT or at the completion of adjuvant SACT, whichever occurred later.
- The remission phase is the time period between the end of the curative phase until the initiation of any subsequent disease phase.

- The palliative SACT phase began at the start date of palliative-intent SACT and ended at death or one month after the last administration of SACT, corresponding to the start of the treatment break or end-of-life phase.
- The treatment break phase started if palliative SACT was not administered within two months and ended at death, upon restarting palliative SACT, or at the start of the end-of-life phase.
- The specialist care in end-of-life phase was defined as starting one month SACT was permanently discontinued and extending up to three months, ending at the date of death.

Patients may enter the same disease phase multiple times during their disease trajectory; for example, in the case of repeated recurrences, a patient may undergo several curative treatment phases. A characterization of study design and patient flow into disease phases is provided in Figure S1 and Table S3.

Cost and resource utilization estimations

Cost elements for each disease phase are outlined in Table S1 and included monthly healthcare visits, ward days, outpatient visits, and emergency room visits. Costs were aggregated into total, inpatient, outpatient, and emergency room costs, and further disaggregated by hospital department (wards, operating rooms, intensive care units, hospital pharmacy, outpatient clinics, radiology, laboratory, and other services). To support economic modelling and decision-making, reporting followed recommendations for economic evaluation [18], with all costs adjusted to the 2021 price level using the Finnish Producer Price Index for Health and Social Work Services [19]. The patient-level costs and resource use were retrospectively collected from participating centres until death or the cut-off date. The data covered all secondary and tertiary health care visits at participating centres, independent of the reason for the visit. The costs and resource usage were categorised into a disease phase based on the date of service. Patients with incomplete cost or resource data were excluded from that specific phase (Table S3).

A specialist healthcare provider perspective was adopted, capturing direct costs arising in specialist secondary/tertiary care settings (oncology, inpatient, and outpatient hospital services), excluding primary/community care and patient-incurred costs and non-hospital pharmacy costs for oral agents such as capecitabine, regorafenib, and trifluridine/tipiracil. This should be noted especially regarding the results of the end-of-life disease phase, as a majority of healthcare costs in this disease phase are primary care costs.

During the study period, all direct healthcare costs were charged from the patient's municipality of residence according to the hospital's product price. According to the Finnish Health Care Act (valid until December 2022), the product price was based on the actual costs at the unit. As participating hospitals were not allowed to gain profit, these product prices are accurate estimations of the real-world resource utilization required to manage cancer treatments [20,21].

Inpatient costs comprise all claims where an admission included at least one night's stay in the hospital. Emergency room costs comprise invoices where the unit is an emergency room or an acute care clinic. Outpatient costs include all other visits to health care units, again, independent of the reason for the visit.

The Nordic Medico-Statistical Committee (NOMESCO) codes were used to describe procedures and resources used to treat patients [22]. This patient-level information on treatment procedures and imaging modalities was collected with the claims data. Minor bedside procedures, such as percutaneous ascites drainage, were not systematically noted and therefore excluded from resource analysis.

As oral antineoplastic drugs in home care are distributed *via* non-hospital pharmacies in Finland, we performed a subgroup analysis with individual actual dosing and billing of all antineoplastic drugs, for 436 patients from Helsinki and Tampere University Hospitals. Unless otherwise specified, the cost assessments for these drugs are based on 2021 drug pricing data from Tampere University Hospital.

Statistical analysis

Results for continuous variables are presented as mean values with standard deviation (SD), while some patient descriptive characteristics are reported as median with range. In this study, the mean with SD was reported because cost outcomes are additive and thus suitable for aggregation and economic modelling. Counts and percentages are shown for categorical variables. Time-related outcomes (presented as mean and SD per patient per month, PPPM) are reported as weighted values according to time spent in the disease phase. Times in disease phases are presented as months, i.e., 30 days. The data analyses were purely descriptive, and no a priori hypotheses were tested. Statistical analyses were conducted in R Statistical

Software (Version 4.3.1) [23] and IBM SPSS Statistics (Version 28) [24].

Results

Demographics

Patient data were collected from 952 individuals participating in the RAXO study. Eleven patients lacked complete claims data for all disease phases and were therefore excluded, resulting in a final study population of 941 patients. A comparison of these patients with those from the smaller RAXO hospitals excluded from this subanalysis revealed no major differences (Table S1).

Baseline demographics for the 941 included patients are presented in Table 1. The median age at diagnosis was 67 years (range 24–90), and 60% were men. The primary tumour location was right colon in 29%, left colon in 37%, and rectum in 34% of the patients. Synchronous metastases were observed in 68% and 53% had one metastatic site only. Survival outcomes, key clinical events, quality of life, and follow-up details for this patient cohort have been comprehensively reported in previous RAXO publications [3,25–27].

Table 1. Patient demographics.

		All patients	
		N = 941	%
Length of follow-up, months			
Mean (SD)		36.7 (26.7)	
Median (IQR)		29.5 (10.6–48.4)	
Age, median (Range)		67 (24–90)	
Age	≤70 years	616	65
	>70 years	325	35
Sex	Male	565	60
	Female	376	40
ECOG	PS 0	241	26
	PS 1	531	56
	PS 2–3	169	18
Charlson comorbidity index	No	722	77
	1–2	213	23
	3–5	6	1
Smoking status	Never smoker	362	51
	Ex-smoker	241	34
	Smoker	102	14
BMI	<20	68	7
	20–30	698	74
	≥30	175	19
Primary location	Right colon	277	29
	Left colon	343	36
	Rectum	316	34
	Multiple	5	1
Surgery of primary tumour	Operated upfront	621	66
	Operated later	93	10
	Never operated	227	24
Presentation of metastases	Synchronous	640	68
	Metachronous	301	32
Metastatic sites	1 site	502	53
	2 sites	280	30
	3–6 sites	159	17
Molecular status	RAS ± BRAF wt	360	38
	RAS mt	477	51
	BRAF mt	85	9
	Not tested	19	2
Mismatch repair status	Proficient (MSS)	290	31
	Deficient (MSI-H)	15	2
	Not tested	636	68

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; MSI-H: microsatellite instability high; MSS: microsatellite stable; PS: performance status; SD: standard deviation.

Duration of disease phases

After categorising the claims data into predefined disease phases, 2,940 disease phase episodes were detected for the 941 patients. Study design and patient flow through disease phases and specified phase durations are described in Figures S1–S3 and Table S2–S3.

An average patient participated in 3.1 disease phases. Among all patients, 875 patients (93%) were included in the diagnostic phase, 352 (37%) in the curative phase, and 221 (23%) in the remission phase. Non-curative treatment included the palliative SACT phase in 762 (81%) patients, treatment break in 231 (25%), and specialist care in the end-of-life phase in 501 (53%).

The mean follow-up time was 37 months. The average durations of the disease phases were as follows: 2.5 months for the diagnostic phase, 21 months for the curative phase, 35 months for the remission phase, 21 months for the palliative SACT phase, 8 months for the treatment break phase, and 1.8 months for the end-of-life phase (Table S2).

Monthly costs and healthcare visits

Mean costs and number of healthcare visits PPPM are presented in Table 2. The total average cost for each patient was €85,100. The cost was €9200 for the diagnostic phase, €63,100 for the curative phase, €15,700 for the remission phase, €57,500 for the palliative SACT phase, €4200 for the treatment break phase, and €3100 for the end-of-life phase. Outpatient care was the main cost driver, accounting for 64% of total costs, driven mainly by hospital pharmacy costs in the curative phase and palliative SACT phase (50% and 66%, respectively).

The mean monthly cost across all disease phases was €2323 PPPM. The PPPM costs were highest in the diagnostic phase (€3662), followed by the curative phase (€3059). In the diagnostic and curative phases, costs were driven by surgical procedures. Inpatient services (2.1 and 1.0 ward days PPPM, respectively) and imaging (1.12 and 0.75 PPPM) were also frequent in

Table 2. Costs and resource utilization.

Disease phase	Diagnostic[a] $n=875$			Curative $n=352$			Remission $n=219$			Palliative SACT $n=762$			Treatment break $n=231$			End-of-Life $n=501$			All phases $n=941$		
	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%
Months in phase	2.5	1.0		20.6	16.0		34.6	29.5		19.5	15.5		7.5	15.2		1.8	1.1		36.7	26.7	
Monthly visits to healthcare	4.4	3.6	100	3.3	1.8	100	0.8	1.2	100	3.3	2.0	100	1.2	2.1	100	3.3	4.8	100	2.7	2.4	100
Ward days	2.1	2.9	47	1.0	1.2	31	0.2	0.8	29	0.6	1.0	17	0.3	1.5	29	1.3	3.1	38	0.7	1.4	25
Outpatient visits	2.2	1.6	49	2.2	1.2	67	0.5	0.6	67	2.6	1.3	80	0.8	1.1	65	1.7	2.6	52	1.9	1.5	71
Emergency Room visits	0.2	0.3	4	0.1	0.1	2	0.0	0.1	4	0.1	0.2	4	0.1	0.2	7	0.3	0.6	10	0.1	0.2	4
	Mean, €	SD, €	%	Mean, €	SD, €	%	Mean, €	SD, €	%	Mean, €	SD, €	%	Mean, €	SD, €	%	Mean, €	SD, €	%	Mean, €	SD, €	%
Total costs	9189	12,948		63,054	44,718		15,657	40,481		57,651	45,826		4197	8107		3114	5882		85,148	60,928	
Monthly total costs	3662	6444	100	3059	1732	100	453	1039	100	2963	1641	100	560	1348	100	1695	3011	100	2323	1572	100
Inpatient total costs	2628	6431	72	1516	1305	50	243	903	54	501	1031	17	290	1202	52	1068	2575	63	798	1007	34
Outpatient total costs	950	714	26	1509	922	49	197	266	44	2405	1144	81	239	342	43	498	1090	29	1480	1056	64
Emergency room total costs	83	217	2	34	52	1.1	13	28	3	56	96	2	31	104	5	129	278	8	45	68	2
Monthly total costs by department[b]	3570	6466	100	2772	1522	100	406	816	100	2801	1577	100	489	1208	100	1361	2514	100	2164	1455	100
Wards	1187	1722	33	577	559	21	128	443	32	316	618	11	169	690	35	615	1507	45	386	519	18
Operating room	1060	1286	30	592	411	21	92	198	23	147	277	5	99	295	20	151	531	11	328	270	15
Intensive care units	182	4959	5	56	233	2	5	36	1.2	6	120	0.2	0	0	0.0	0	6	0.0	27	255	1.3
Hospital pharmacy	22	140	0.6	762	712	27	8	60	2	1579	957	56	3	43	0.6	9	116	0.6	842	807	39
Outpatient clinic	325	293	9	343	348	12	68	100	17	479	483	17	113	178	23	303	584	22	328	347	15
Radiology	369	469	10	223	202	8	59	161	15	159	230	6	63	252	13	187	550	14	160	164	7
Laboratory	326	323	9	131	93	5	32	66	8	104	84	4	33	79	7	73	135	5	104	83	5
Other	99	201	3	88	174	3	13	40	3	11	35	0	10	46	2	23	134	2	33	69	2

All costs are presented as unit per patient per month (PPPM), [a]Includes treatment of synchronous primary tumour; [b]Hospital internal invoicing. SD: standard deviation.

Table 3. Surgical procedures and endoscopy by disease phase.

Disease phase	Diagnostic			Curative			Remission			Palliative SACT			Treatment break			End-of-Life			All phases		
	Patients with any use $n=875$	Number of services per patient with any use		Patients with any use $n=352$	Number of services per patient with any use		Patients with any use $n=219$	Number of services per patient with any use		Patients with any use $n=762$	Number of services per patient with any use		Patients with any use $n=231$	Number of services per patient with any use		Patients with any use $n=501$	Number of services per patient with any use		Patients with any use $n=941$	Number of services per patient with any use	
	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD
Months in phase		2.5	1.0		20.6	16.0		34.6	29.5		19.5	15.5		7.5	15.2		1.8	1.1		36.7	26.7
Surgical procedures	49	1.6	0.9	97	2.7	2.1	21	2.1	2.4	20	1.8	1.1	4	1.1	0.3	3	1.3	0.5	76	2.8	2.3
Liver (includes biopsies)	12	1.1	0.3	75	1.4	0.7	2	1.5	1.0	2	1.1	0.3	0.0	0.0	0.0	0.2	1.0	NA	38	1.5	0.8
Lung	0.0	0.0	0.0	18	1.4	0.7	0.0	0.0	0.0	0.1	1.0	NA	0.4	1.0	NA	0.0	0.0	0.0	7	1.4	0.7
Peritoneum	6	1.2	0.4	24	1.7	1.0	4	1.1	0.3	4	1.3	0.5	0.9	1.0	0.0	0.6	1.0	0.0	17	1.5	0.9
Bowel	41	1.3	0.6	39	1.9	1.2	15	1.9	2.8	15	1.4	0.8	3	1.0	0.0	2	1.1	0.4	57	1.8	1.4
Gynaecological organs	2	1.4	0.5	9	1.3	0.5	0.9	2.0	0.0	0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5	1.7	1.3
Other	0.8	1.1	0.4	5	1.6	1.2	5	1.5	0.7	4	1.8	1.4	0.0	0.0	0.0	0.8	1.3	0.5	7	1.3	0.5
Endoscopy	43	1.2	0.6	43	1.7	1.2	43	2.4	5.6	16	1.4	0.9	7	1.8	1.1	1.2	1.2	0.4	61	2.0	2.8
Metastectomies[a]				98	1.6	0.9													37	1.6	0.9
Liver				75	1.3	0.6													28	1.3	0.6
Lung				18	1.4	0.8													7	1.4	0.8
Peritoneum				7	1.2	0.4													3	1.2	0.4
Other				24	1.2	0.5													9	1.2	0.5

[a]Including surgery and definitive treatment with local ablative therapy. SD: standard deviation.

these phases (Tables 2–4). Emergency room visits were infrequent at 0.2 and 0.1 PPPM, for diagnostic and curative phases respectively.

In the palliative SACT phase, the mean costs (€2963 PPPM) were mainly driven by outpatient care, including drugs and drug administration, which made up 81% of the total costs. In this phase, patients had on average, 2.6 outpatient healthcare visits PPPM, accounting for 80% of all healthcare visits. Inpatient care was substantially lower compared with phases that included surgery.

On the contrary, the remission and treatment break phases were modest in costs PPPM (€453 and €560, respectively). In these phases, there were few healthcare visits (0.8 and 1.2 PPPM, respectively) compared with the other phases.

In the end-of-life phase, the costs (€1695 PPPM) were mainly driven by inpatient care. Furthermore, costs from using emergency room services were higher in this phase than in other disease phases, (€129 PPPM), which accounted for 8% of the total costs in this phase. It should be noted, however, that resource use and healthcare costs during the end-of-life treatment phase are predominantly generated in primary care, which was not captured in this analysis. Consequently, the costs reported here should be interpreted as representing only one component of the total expenditures in this phase, rather than a comprehensive estimate.

Radiological and surgical procedures

The utilization of radiological resources was highest during the diagnostic phase (mean 1.12 PPPM) and lowest in the remission phase (0.25 PPPM). The mean number of radiologic procedures per patient was 21.7. The most commonly used modality was computed tomography (CT), with a mean 12.2 per patient (Table 4).

Of all patients, 76% had a surgical procedure during treatment, mean 2.1 procedures per patient. Liver (75% of patients) was the most common target in the curative phase, followed by peritoneum (24%), and lung (18%). The diagnostic phase often included surgery of the primary tumour, but other phases did also (Table 3). Corrective bowel procedures, such as stoma closures, were observed in phases following the curative phase. The mean (SD) cost for a curative-intent metastasectomy, including pre- and postoperative inpatient care, was €15,024 (€11,033). For liver, lung, peritoneum, and other sites costs for metastasectomy were €16,003 (€10,096), €10,262 (€6418), €24,191 (€20,367), and €13,724 (€11,376), respectively.

Table 4. Monthly radiological procedures.

Disease phase	Diagnostic			Curative			Remission			Palliative SACT			Treatment break			End-of-Life			All phases		
	Patients with any use $n=875$	Number of services across all patients per month		Patients with any use $n=352$	Number of services across all patients per month		Patients with any use $n=219$	Number of services across all patients per month		Patients with any use $n=762$	Number of services across all patients per month		Patients with any use $n=231$	Number of services across all patients per month		Patients with any use $n=501$	Number of services across all patients per month		Patients with any use $n=941$	Number of services across all patients per month	
	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD
Months in phase		2.5	1.0		20.6	16.0		34.6	29.5		19.5	15.5		7.5	15.2		1.8	1.1		36.7	26.7
Radiological procedures	90	1.12	0.92	99	0.75	0.43	89	0.25	0.23	95	0.64	0.38	50	0.27	0.44	44	0.75	1.45	99	0.59	0.37
CT	85	0.53	0.36	98	0.36	0.16	87	0.15	0.12	93	0.41	0.16	37	0.14	0.20	29	0.24	0.45	98	0.33	0.17
MRI	21	0.10	0.22	42	0.06	0.09	25	0.01	0.03	25	0.03	0.07	5	0.01	0.09	4	0.03	0.14	47	0.04	0.06
US	21	0.12	0.29	76	0.10	0.10	33	0.03	0.05	43	0.04	0.08	13	0.03	0.11	13	0.10	0.36	68	0.06	0.14
XRay	31	0.22	0.42	81	0.16	0.18	42	0.04	0.08	67	0.11	0.17	20	0.06	0.15	24	0.23	0.59	84	0.11	0.00
PET	8	0.03	0.13	26	0.02	0.04	14	0.01	0.03	9	0.01	0.04	2	0.00	0.03	0.8	0.00	0.05	21	0.01	0.03
Other[a]	21	0.11	0.23	46	0.05	0.09	20	0.02	0.06	32	0.03	0.10	13	0.03	0.16	15	0.14	0.44	58	0.04	0.07

[a]Includes interventional radiology and special imaging. CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; SD: standard deviation.

Medical treatments

Hospital pharmacy costs accounted for approximately 39% of the total costs of treating mCRC (Table 2). Hospital pharmacy costs were significant cost drivers in phases with tumour-directed treatments, such as in the curative phase (762€PPPM) and in the palliative SACT phase (1579€PPPM). These costs include all medical agents distributed by hospital pharmacies, mostly antineoplastic agents. One line of SACT was administered to 39%, two lines to 25%, and three or more lines to 34%, while 2% received no tumour-directed therapy. Cetuximab or panitumumab in any line of treatment were given to 75% (218/290) of patients with *RAS±BRAF* wildtype left-sided primaries and in 2+ line of treatment to 83% (29/35) of patients with right-sided primaries. Bevacizumab was given to 64% (231/360) of *RAS±BRAF* wildtype, 77% (371/480) of *RAS* mutant, and 76% (68/89) of *BRAF* mutant.

The dosing and costs of antineoplastic drugs in mg, intravenous and/or oral, was separately analysed for a subpopulation of 436 patients from Helsinki and Tampere and priced according to the Tampere university pharmacy costs in 2021 (Table 5). During the curative and palliative SACT phases, most patients (95% and 98%, respectively), received SACT, and 78% and 88%, respectively, received biologic agents. The most common cytotoxics were capecitabine, oxaliplatin, and irinotecan. The most frequently used biologic agents were bevacizumab, panitumumab, or cetuximab. The costs for non-hospital drugs, not included in hospital pharmacy costs, were 4% and 10% of the curative and palliative SACT phases, respectively.

Discussion

Based on data from this large cohort of mCRC patients, the estimated costs from a specialist healthcare provider perspective were €2,300 PPPM under a treatment strategy that included active metastasectomy/LAT with curative intent whenever clinically appropriate, as recommended by current guidelines [6–8]. This real-life study was able to quantify, day-by-day, the resource usage in different phases.

Cost drivers in inpatient and outpatient care

Earlier studies have reported a wide range of lifetime costs (from $12,346 to $293,461) and overall resource usage on a general level [13–15,28–32]. The total costs of €85,000 or $92,600 reported in this study are in the middle of this range, with the caveat that this does not cover all lifetime costs. In studies that were mainly

Table 5. Medical treatments among subgroups treated at helsinki or tampere university hospitals.

Disease phase	Curative-intent SACT $n = 148$						Palliative SACT $n = 360$					
	Patients with any use	Cycles per patient with any use		Cost for medical treatment per treated patient		Of total medical costs	Patients with any use	Cycles per patient with any use		Cost for medical treatment per treated patient		Of total medical costs
	%	Mean, n	SD	Mean, €	SD	%	%	Mean, n	SD, €	Mean, €	SD	%
Chemotherapy	95	24.9	17.9	932	1162	21	98	37.5	33.5	3027	5634	25
Fluorouracil (bolus and infused)	13	10.3	4.5	286	168	0.9	17	16.8	17.1	432	427	0.6
Calcium folinate	13	10.3	4.5	478	297	1.5	17	16.8	17.1	759	774	1.1
Capecitabine[a]	86	12.0	8.6	391	312	8	87	17.1	13.9	529	464	4
Tegafur, Gimeracil, Oteracil[a]	6	11.9	8.7	3211	2368	5	6	11.2	8.2	2600	1983	1.3
Oxaliplatin	69	6.9	3.9	246	134	4	71	6.8	4.5	230	165	1.4
Irinotecan	58	9.6	4.4	134	347	2	76	13.2	12.1	191	598	2
Trifluridine, Tipiracil[a]							10	3.0	1.7	7346	4058	6
Regorafenib[a]							21	3.0	3.4	5181	5936	9
Biological agents	78	8.2	7.6	4241	6864	79	88	17.9	14.7	10,225	15,398	75
Bevacizumab[b]	72	7.3	7.2	1950	1938	34	84	15.1	12.8	4029	3742	28
Aflibercept	1	2.0	NA	1747	NA	0.3	2	27.2	25.3	46,333	48,417	6
Cetuximab	4	10.2	5.9	17,273	10,622	17	9	10.5	11.2	17,534	18,342	14
Panitumumab	7	9.0	5.7	15,790	10,091	28	20	8.0	6.0	15,761	13,643	27

SD: Standard Deviation.
Drug costs are determined based on the actual usage of the medication and the prices listed in the TAUH 2021 price index if not stated otherwise.
[a]Outpatient pharmacy drug. Drug price according to outpatient Pharmaceuticals Pricing Boards Reference price system 2021.
[b]2022 Drug Price, 2021 drug price not available.

published before 2015, inpatient care and hospitalization costs were the main cost drivers, ranging between 45% and 60% of total costs [13,28–30]. In this study, the main cost driver was outpatient care (64% of total costs). The lower impact of inpatient costs, at 34% of total costs, was slightly surprising as surgery of metastases was actively sought, and three-quarters of patients underwent surgery with a mean 2.1 procedures per patient, mostly for synchronous primary tumours (in line with previously published resection rates) [33,34]. Metastasectomy/LAT was performed in 37% of all patients (in the higher range compared with the literature, Osterlund et al. 2021), with a mean 1.6 procedures per patient [3]. These lower inpatient costs may be explained by shortened hospitalisations after adoption of minimally invasive surgery and enhanced recovery protocols [35]. Another reason may be the longer time spent, and thus higher outpatient healthcare costs, in the palliative SACT phase as more lines of therapy are available [35,36], emphasized by 34% receiving 3+ lines of SACT in this study.

Costs and resources based on accurate clinical disease phases

Phases with diagnostic procedures or tumour-directed therapies had a cost of around €3,000 PPPM. However, higher-cost disease phases are balanced by less expensive phases with no tumour-directed therapies, such as treatment breaks and remission phase. For example, a patient undergoing curative intent treatment spends a mean of 21 months in the resource-intensive curative phase with metastasectomy, LAT, perioperative medical treatment, etc (€3,059 PPPM) and then in follow-up for 35 months in the low-cost remission phase (€453 PPPM). The mean number of hospital visits were 94 during these 56 months, with 28 in-hospital days, 63 outpatient visits, 3 ER visits, and 3 surgical and 23 radiologic procedures performed. To the best of our knowledge, detailed disease phase-specific costs and resource consumption have not been presented before, only for specific treatments such as liver resections [37,38].

Costs per time-period-based categorization of disease phases have previously been investigated in some American studies, typically using three-month intervals to define diagnostics and end-of-life phases. Using this method [13,17], Song et al. estimated monthly costs in 2009 US dollars to be $16,895 (€17,703 PPPM if adjusted to 2021 euro) in the diagnostic phase, $27,554 (€28,872) in the end-of-life phase, and $8891 (€9316) in the active treatment phase [17]. Had we applied similarly rigorous three-month time intervals instead of clinically determined disease phases, the cost estimations would be €4900 PPPM (SD €4028) for the diagnostic phase, €3454 (SD €3720) for the end-of-life phase, and €2034 PPPM (SD €1478) for the active treatment phase. When comparing with American studies, the cost levels in this study reflect the lower healthcare prices and expenditures outside the USA,

although the relative distribution across time-period–based phases is broadly similar. The high costs in the end-of-life phase in the American studies may be attributed to ongoing chemotherapy and biological agents [13], as these studies did not, contrary to our study, use clinical events to define disease phases and used only time-based approach.

Medical treatment as a cost driver

Treatment with medical agents is one of the most significant cost drivers in the management of mCRC, accounting for 39% of internal billing in this study. Changes in drug prices and the introduction of new agents can quickly change the costs of cancer care, as with the introduction of bevacizumab (used in 73% of eligible patients in this study), cetuximab/panitumumab (75%–83%), aflibercept (11%), trifluridine/tipiracil (34%), regorafenib (42%), and pembrolizumab (25%) [39,40]. Now, some of the patents for these biologic agents have expired or are due to expire [41,42]. This has already led to a remarkable decrease in the price of bevacizumab biosimilars and generic capecitabine during the time period of this study. If all antineoplastic treatments in this study had been carried out at the 2021 price level, the cost for antineoplastic treatment would have been cut by half in the curative phase (€350 PPPM vs €762 PPPM) and by 30% in the palliative SACT phase (€1100 PPPM vs €1579 PPPM).

Strengths

Although some data exist on the costs and resource use of mCRC patients, including a Finnish study by Färkkilä et al. that also considered societal costs, there remains limited knowledge about disease-phase-specific costs within the most resource-intensive treatments provided in specialist healthcare settings [14]. The strengths of this study include the use of detailed clinical data, during the entire disease trajectory, as the basis for categorising every patient day-to-day into disease phases to avoid many common challenges related to the use of claims data for cost analysis [43]. For example, this analysis used precise index dates for the diagnosis, resections of primary and metastases, exact dosing chemotherapy and biologics, and death/end-of-follow-up instead of using proxy measures to determine these endpoints, as done previously [17,28]. Furthermore, internal billing information was available for all secondary and tertiary health care visits. Precise real-world cost data is needed, for example, when making economic analyses of mCRC treatment costs and utilities. So far, cost assumptions in many economic models have relied on expert opinions and/or standardized cost multipliers [11,44]. These outcomes from the RAXO prospective study are also in line with nationwide Finnish population-based data for metastasectomy, LAT, and systemic therapy only, although with slightly higher resection and/or LAT rates (37% vs 30% of actively treated patients) [5]. These findings are also comparable to the 39% resection rate reported in the Uppsala region, Sweden [4].

Limitations

This was an analysis of treatable Finnish patients in the prospective RAXO dataset. Although healthcare prices and health expenditure in Finland are close to the OECD mean [45], costs and resource use should be generalised cautiously beyond countries where specialised MDT meetings and metastasectomy are routinely implemented [45]. In addition, the categorization into different disease phases used here is open for discussion, especially between curative and remission disease phases. The curative disease phase includes a six-month postoperative period, as the aim was to capture all curative-intent care activities within this phase, not just surgical interventions, especially since the majority of patients received adjuvant chemotherapy. We acknowledge that this may lead to a 'Will-Rogers' phenomenon' with patients having no adjuvant chemotherapy. There is also a risk of this bias in other delineations, e.g., between the palliative SACT, treatment break, and specialist care in end-of-life phases. However, alternative delineations were not feasible, as we sought to avoid the risk of attributing SACT or tumour-directed surgery costs to disease phases without tumour-directed therapy. Such misclassification would likely create greater distortions, particularly if the data were later used as a basis for modelling studies. Our chosen categorisation therefore represents a pragmatic compromise, acknowledging some risk of misclassification but minimising the likelihood of more substantial errors in cost attribution. Also, the separation between the curative phase and the palliative SACT phase may not reflect the intention of the treatment but rather the end result. Therefore, patients in the palliative SACT phase may have been treated more intensively than the general mCRC patient. Furthermore, primary care costs were not available for this analysis, and the analyses were therefore conducted from a specialist healthcare provider perspective. For treatment phases with tumour-directed therapies, the use of primary care services is probably

low, as shown by Färkkilä et al. who reported that primary care accounts for approximately 3% of total costs in patients with mCRC [14]. In contrast, during the end-of-life phase, the use of primary care and hospice services increases substantially, accounting for up to 47% of total costs [14]. As a result, costs and resource use in the end-of-life phase are likely underestimated in our study, and the reported figures mainly reflect hospital-based specialist services [16]. Finally, non-hospital pharmacy costs are not included in the general cost analysis. When analysed at the 2021 price level, these agents accounted for approximately 12% of the total medical costs in the curative phase and 20% in the palliative SACT phase (Table 5).

Conclusions

Resource utilization, costs, and cost drivers varied 8-fold between disease phases. Outpatient care, accounted for two-thirds of costs while inpatient care accounted for one-third of overall costs during the mCRC disease trajectory. The mean overall cost for treating mCRC with maximised metastasectomies was €2,323 PPPM. This study provides a new perspective on resource utilization and costs during clinically determined disease phases.

Acknowledgements

The authors would like to thank the patients and their families, the investigators, study personnel, and the hospitals that participated in this study. Additionally, we extend our thanks to Jarmo Hahl and Iiro Toppila from Medaffcon Ltd, and Professor Harri Sintonen from Health Economics at Helsinki University for their invaluable expertise. Special appreciation is also due to Kaisa Kinnari from the Pharmacy of Tampere University Hospital for her assistance in providing drug cost data. The authors also acknowledge the contribution of a medical writer, Sandy Field, PhD, for English language editing and formatting of this manuscript. J.K., K.L., H.I., T.M., B.G., and P.O. developed the analysis plan, interpreted the data, and drafted the original manuscript.

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki and protocol and amendments approved by the Regional Scientific Ethical Board at Helsinki University Hospital (number 242/13/03/02/2011 and HUS/1288/2016).

Consent to participate

An informed consent statement was obtained from all patients included in the study.

Authors contributions

CRediT: **Joel Kontiainen**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing; **Kaisa Lehtomäki**: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing; **Timo Muhonen**: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing; **Eetu Heervä**: Investigation, Writing – review & editing; **Annika Ålgars**: Investigation, Writing – review & editing; **Raija Ristamäki**: Investigation, Writing – review & editing; **Hanna Stedt**: Investigation, Writing – review & editing; **Annamarja Lamminmäki**: Investigation, Writing – review & editing; **Raija Kallio**: Investigation, Writing – review & editing; **Tapio Salminen**: Investigation, Writing – review & editing; **Teijo Kuopio**: Investigation, Writing – review & editing; **Emerik Osterlund**: Investigation, Writing – review & editing; **Sonja Aho**: Investigation, Writing – review & editing; **Maarit Bärlund**: Investigation, Writing – review & editing; **Päivi Halonen**: Investigation, Writing – review & editing; **Leena-Maija Soveri**: Investigation, Writing – review & editing; **Aki Uutela**: Investigation, Writing – review & editing; **Bengt Glimelius**: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing; **Helena Isoniemi**: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing; **Pia Osterlund**: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Disclosure statement

All authors report institutional research funding from Eli Lilly, Merck KGaA, Roche Finland, Sanofi and unrestricted grants from Amgen and Servier, during the conduct of the study. J.K., K.L., T.M., E.H., A.Å., R.R., H.S., am, R.K., T.S., T.K., E.O., S.A., M.B., P.H., L-M.S., A.N., A.U., B.G., H.I., and P.O. report grants, personal fees or non-financial support from Abbvie, Amgen, Astellas, Astra- Zeneca, Baxalta/Shire, Bayer, BMS, Celgene, Eisai/Ewopharma, Eli Lilly, Erythech Pharma, Fresenius, Incyte, Jansen-Cilag, Medicom, Merck, MSD, Nordic Drugs/Pharma, Novartis, Nutricia/Danone, Pierre-Fabre, Roche, Sanofi, Servier, Sobi, Takeda, and/or Varian.

Trial registration

The RAXO study is registered at ClinicalTrials.gov NCT01531621 (date of registration February 3, 2012) and EudraCT 2011 003158-24 (date of registration September 22, 2011).

Funding

This investigator-initiated study was supported by Finska Läkaresällskapet (2016, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025), The Finnish Cancer Foundation (2019–2020, 2021, 2022–2023, 2025), Relander's foundation (2020–2022), The Competitive State Research Financing of the Expert

Responsibility Area of Tampere, Helsinki, Turku, Kuopio, Oulu, and Satakunta Hospitals (2012, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025), Tampere University Hospital Fund (Tukisäätiö 2019, 2020, 2023, 2024 and OOO-project 2020, 2022), Helsinki University Hospital research fund (2019, 2020, 2021, 2022, 2023, 2024), Mary and Georg C. Ehrnrooth Foundation (2023), Liv & Hälsa (2023), Radiumhemmets fonder (2022–2023, 2025–2026), Cancerfonden (2023–2024); and the infrastructure with the database and study nurses partly supported by pharmaceutical companies: Amgen—unrestricted grant (2012–2024), Eli Lilly and Company (2012–2017), Merck KGaA (2012–2020), Roche Oy (2012–2020), Sanofi (2012–2017), and Servier—unrestricted grant (2016–2024). J.K. report personal grants from Suomen Lääketieteen Säätiö [2025] and Juhani Ahon Lääketieteen Tutkimussäätiö [2025]. The funders had no role in the study design, analysis, interpretation of the data or decision to publish.

Data availability statement

The data collected for this study can be made available to others in a de-identified form after all primary and secondary endpoints have been published, in the presence of a data transfer agreement, and if the purpose of use complies with Finnish legislation. Requests for data sharing can be made to the corresponding author, including a proposal that must be approved by the steering committee.

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